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# GENETIC AND MOLECULAR DETERMINANTS OF PEMPHIGUS VULGARIS AND THEIR THERAPEUTIC IMPLICATIONS

**Marius IRIMIE**[1]

***Abstract:*** *Pemphigus vulgaris (PV) is a rare, potentially life-threatening autoimmune blistering disease driven by pathogenic IgG autoantibodies targeting desmosomal cadherins (primarily desmoglein-3 and desmoglein-1), leading to loss of keratinocyte adhesion (acantholysis). Beyond antibody-mediated mechanisms, convergent evidence supports a strong genetic contribution to disease susceptibility, phenotype, and therapeutic response. This expanded narrative review synthesizes classical and emerging genetic determinants of PV including HLA class II associations, non-HLA immune modifiers, desmosomal/epithelial susceptibility genes, genome-wide association study (GWAS) loci, epigenetic and transcriptomic signals and integrates contemporary therapeutic advances (rituximab, FcRn inhibitors, BTK inhibition, and antigen-specific cell therapies). We highlight genotype-phenotype relationships, ethnic differences in risk alleles, translational biomarkers, and future directions for precision medicine in PV.*

***Key words:*** *pemphigus vulgaris, immunogenetics, HLA, desmoglein, ST18, FcRn inhibitors, rituximab*

## 1. Introduction

Pemphigus vulgaris (PV) is the most common form of pemphigus and is characterized by mucosal and/or cutaneous blistering that rapidly evolves into painful erosions. Prior to immunosuppressive therapy, pemphigus was frequently fatal; contemporary treatment has reduced mortality but at the cost of significant morbidity from chronic disease, infections, and long-term corticosteroid exposure. The epidemiology of PV exhibits striking geographic and ethnic variation, with consistently higher incidence in certain populations (e.g., individuals of Jewish, Mediterranean, Middle Eastern, South Asian, and some East Asian ancestries), supporting a strong inherited component [1-3]. In recent years, an increase in the number of cases of pemphigus vulgaris has been observed in Romania, with personal observations indicating a higher prevalence in ethnic groups of Asian origin.

The canonical model of PV pathogenesis centers on circulating IgG autoantibodies against desmogleins. However, several

[1] Faculty of Medicine, *Transilvania* University of Braşov

observations cannot be fully explained by humoral autoimmunity alone: (i) variability in age of onset and clinical phenotype, (ii) differences in autoantibody specificity and subclass distribution, (iii) heterogeneity in relapse risk and response to rituximab, and (iv) population-specific allele associations. Over the last two decades, immunogenetic and genomic studies have provided a richer, polygenic view of PV that implicates antigen presentation, immune checkpoints, cytokine networks, B-cell biology, and keratinocyte-intrinsic susceptibility pathways [4-6].

## 2. Clinical Spectrum, Diagnosis, and Outcome Measures

PV may present as mucosal-dominant disease (often oral erosions preceding skin lesions), cutaneous-dominant disease, or mucocutaneous disease. The desmoglein compensation hypothesis provides a biologic explanation for mucosal predilection: DSG3 is highly expressed in the basal and suprabasal layers of mucosa, whereas DSG1 is more abundant in superficial epidermis. Accordingly, patients with predominant anti-DSG3 reactivity may exhibit mucosal-dominant disease, while additional anti-DSG1 reactivity is associated with cutaneous involvement [2, 3].

Diagnosis relies on clinicopathologic correlation. Histopathology typically reveals suprabasal acantholysis (“row of tombstones”) and direct immunofluorescence demonstrates intercellular IgG/C3 deposition in the epithelium. Serologic assays (ELISA for anti-DSG1/3) support diagnosis and longitudinal monitoring. Standardized outcome measures such as the Pemphigus Disease Area Index (PDAI) facilitate assessment of severity and response across clinical trials and real-world cohorts [2].

## 3. Immunopathogenesis: beyond autoantibodies

PV is driven by pathogenic IgG autoantibodies, but multiple immune pathways converge to sustain autoimmunity. Antigen presentation by HLA class II molecules activates autoreactive $CD4^+$ T cells that provide B-cell help via costimulation and cytokine support, promoting class switching and differentiation into antibody-secreting cells. Autoantibody binding to desmogleins triggers signaling cascades (p38 MAPK, Src-family kinases, EGFR pathways) and cytoskeletal reorganization, resulting in desmosome disassembly and keratinocyte detachment (figure 1) [7, 8].

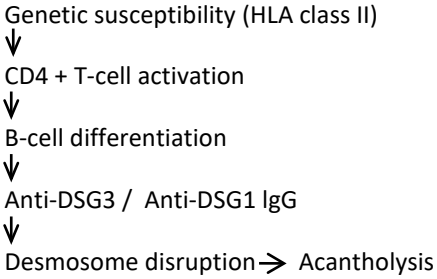


Fig. 1. *Immunopathogenic cascade in pemphigus vulgaris (PV)*

Recent mechanistic work reinforces that keratinocytes are not passive targets: they respond to immune injury by altering adhesion, stress-response, and inflammatory gene expression programs. This provides a rationale for therapies targeting signaling pathways (e.g., EGFR and downstream kinases) and for integrating epithelial biology into genetic models of PV [7, 8].

## 4. HLA Class II Susceptibility and Genotype-Phenotype Links

The most robust genetic associations in PV reside in the HLA class II locus on chromosome 6p21. Across diverse populations, HLA-DRB1*04:02 and HLA-DQB1*05:03 are repeatedly associated with increased risk. These alleles are thought to present immunodominant desmoglein peptides to $CD4^+$ T cells with high efficiency, lowering the threshold for loss of tolerance. Importantly, HLA risk alleles vary in frequency across ancestries, which shapes both susceptibility and the landscape of autoimmune specificity [9].

Genotype-phenotype correlations have increasingly been documented: DRB1*04:02 has been associated with higher anti-DSG3 levels and mucosal-only disease, while DQB1*05:03 may correlate with anti-DSG1 reactivity and higher rates of mucocutaneous disease. Emerging data further identify population-specific signals such as DRB1*08:04 in patients of African ancestry, emphasizing the need for inclusive cohorts and careful interpretation of linkage disequilibrium (table 1) [9].

*Selected HLA alleles associated with PV across populations (representative examples)* Table 1

| HLA allele | Populations frequently reported | Typical phenotype association (reported) | Notes |
|---|---|---|---|
| DRB1*04:02 | Ashkenazi Jewish; non-Jewish Caucasian; Hispanic; others | Higher anti-DSG3; mucosal-dominant disease | Strongest and most replicated PV risk allele |
| DQB1*05:03 | South Asian; East Asian; many non-Jewish cohorts | Higher anti-DSG1; mucocutaneous disease | Often co-occurs with specific DRB1 alleles |
| DRB1*14:01 / 14:04 | Mediterranean; Middle Eastern; Asian cohorts | Susceptibility signal; variable phenotype | May represent multiple related risk haplotypes |
| DRB1*08:04 | Patients of African ancestry (reported in US cohorts) | Elevated anti-DSG3; phenotype variable | Highlights underrepresented genetic architecture |

## 5. Non-HLA Immune Genetic Modifiers

Candidate-gene studies and GWAS-informed analyses implicate non-HLA immune genes as modifiers of PV risk and disease expression. Variants in cytokine genes (e.g., TNF, IL6, IL10) may influence inflammatory tone, B-cell differentiation, and persistence of antibody-secreting cells. Polymorphisms in immune checkpoint and costimulatory pathways (e.g., CTLA4, ICOS, CD40/CD40L) may modulate T-cell activation thresholds and germinal-center responses. Fc gamma receptor variants (FCGR2A/FCGR3A) can alter immune-complex handling and effector functions [10].

A recurring limitation is population size: PV is rare, and many association studies have modest cohorts and heterogeneous ancestry, yielding variable replication. Nevertheless, convergent biology supports a polygenic model in which HLA risk enables pathogenic antigen presentation

while a background of immune regulatory variation shapes magnitude, chronicity, and treatment responsiveness of the autoantibody response [10].

## 6. Non-HLA Immune Genetic Modifiers

Genome-wide Association Studies (GWAS) have broadened PV genetics beyond classical immune loci. A prominent and repeatedly discussed locus is ST18 (suppression of tumorigenicity 18), encoding a transcription factor implicated in inflammation and apoptosis. Risk variants near ST18 have been associated with increased expression in keratinocytes, potentially amplifying cytokine responses and sensitizing epithelium to antibody-mediated injury. Population-specific association studies continue to explore ST18 polymorphisms and their functional impact [11].

Other GWAS-linked or fine-mapped signals implicate genes in interferon and antigen-presentation pathways (e.g., STAT4, IRF8, TAP2), pointing to cross-talk between innate cues and adaptive autoimmunity. Integrating GWAS with transcriptomics and epigenetic datasets is increasingly viewed as necessary to prioritize causal genes and mechanisms [11].

## 7. Desmosomal Genes, Barrier Biology, and Epitope Spreading

Although PV is defined by autoimmunity against desmosomal proteins, genetic variation within epithelial adhesion molecules may influence antigenicity and mechanical resilience. Polymorphisms in DSG3/DSG1 or in desmosomal partners (desmocollins, plakophilins) could affect expression, conformation, or exposure of epitopes, thereby shaping susceptibility to autoantibody binding or promoting tissue damage under stress. Such variants may also facilitate epitope spreading broadening the autoimmune response to additional junctional targets over time [12].

This epithelial dimension aligns with experimental data showing that keratinocyte signaling and stress pathways strongly modulate acantholysis. Targeting keratinocyte-intrinsic pathways (e.g., EGFR signaling) has shown promise in ex vivo human skin models, supporting the concept of combining immunomodulation with barrier-stabilizing strategies [7].

## 8. Epigenetics, Transcriptomics, and Systems-level Signals

Epigenetic dysregulation may contribute to PV by altering immune cell differentiation programs and keratinocyte inflammatory responses. Studies have reported aberrant DNA methylation patterns and histone modifications in peripheral blood mononuclear cells, although causal relationships remain to be established. Transcriptomic profiling of blood and lesional tissues has identified immune activation signatures and potential transcriptional “hot spots,” suggesting that gene-expression changes could help distinguish PV from other autoimmune diseases and may yield biomarkers for disease activity or relapse risk [5].

Future work integrating genomics (GWAS/WES/WGS), epigenomics, proteomics, and single-cell immune profiling is expected to refine PV endotypes molecularly defined subgroups that may respond differently to B-cell depletion, FcRn blockade, or targeted pathway inhibition [13, 14].

## 9. Therapeutic Implications and Precision Medicine

Rituximab (anti-CD20) has transformed PV management and is widely recommended as first-line therapy for moderate-to-severe disease in contemporary guidelines (table 2, figure 2). Long-term follow-up studies of rituximab-based first-line regimens suggest durable remission with reduced reliance on prolonged corticosteroids in many patients. However, relapses still occur and may reflect incomplete depletion of autoreactive memory B cells and long-lived plasma cells, or rapid immune reconstitution in genetically predisposed individuals [15-20].

FcRn inhibitors (e.g., efgartigimod) represent a mechanistically distinct approach that accelerates IgG clearance and can rapidly reduce pathogenic anti-DSG titers. Early-phase clinical trials in pemphigus demonstrate rapid disease control and improvements in PDAI alongside reductions in total IgG and anti-desmoglein autoantibodies. Because FcRn blockade does not directly target B-cell production, combination or sequencing strategies with B-cell–directed agents are being explored [15, 16], [21, 22].

Table 2

*Emerging and established targeted therapeutic strategies in PV (mechanism-oriented overview)*

| **Strategy** | **Examples** | **Primary target** | **Rationale in PV** | **Evidence type (recent)** |
|---|---|---|---|---|
| B-cell depletion | Rituximab; other anti-CD20 | CD20+ B cells | Reduce autoantibody generation | Guidelines; RCTs; long-term follow-up; real-world |
| IgG recycling blockade | Efgartigimod (Fc fragment); other FcRn inhibitors | FcRn | Rapidly lower pathogenic IgG | Phase II trial; translational studies |
| BCR signaling inhibition | Rilzabrutinib | BTK | Suppress B-cell activation & innate signaling | Phase II data; program updates |
| Antigen-specific B-cell elimination | DSG3-CAAR T cells | Autoreactive anti-DSG3 B cells | Precision removal of pathogenic clones | Early-phase clinical trial |
| Keratinocyte pathway modulation | EGFR pathway inhibitors (experimental) | EGFR/kinase signaling | Reduce acantholysis signaling cascades | Ex vivo / translational studies |

Small-molecule pathway inhibitors (e.g., BTK inhibition with rilzabrutinib) aim to suppress B-cell receptor signaling and innate immune activation while potentially reducing corticosteroid exposure. Early phase results showed clinical activity and acceptable safety, although trial outcomes have been mixed across programs [23]. Additional targeted strategies include inhibition of CD40-

CD40L interactions, blockade of inflammatory kinases, and approaches to modulate keratinocyte signaling [8].

Antigen-specific cellular therapies, including DSG3 chimeric autoantibody receptor (CAAR) T cells, represent a precision concept: selectively eliminating autoreactive B cells while sparing protective humoral immunity. Ongoing early-phase trials are evaluating feasibility and safety in mucosal-dominant PV [24-26]. If successful, such strategies could offer durable, drug-free remission in carefully selected patients.

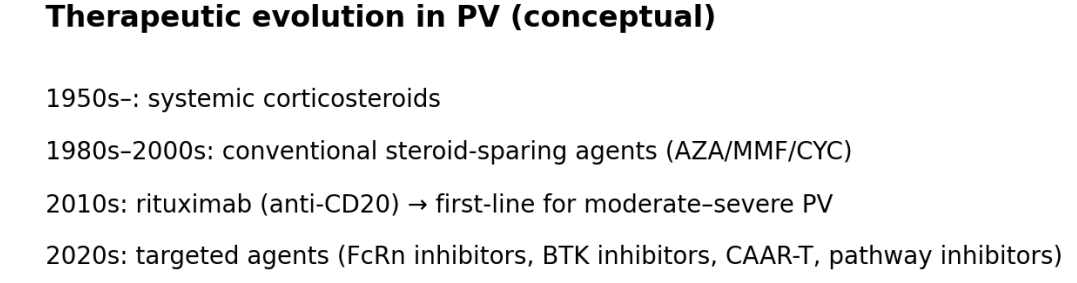


Fig.2. *Conceptual timeline of therapeutic milestones in pemphigus vulgaris (PV).*

**10. Limitations and Future Directions**

Despite major progress, several gaps persist. Genetic studies remain uneven across global populations, and many cohorts are underpowered for fine-mapping or multi-omic integration. Heterogeneity in clinical phenotype definitions (mucosal vs mucocutaneous) and treatment exposure can obscure genotype–phenotype relationships. Future studies should prioritize: (i) multinational consortia with harmonized phenotyping, (ii) ancestry-aware fine-mapping and functional validation, (iii) single-cell immune profiling of blood and lesional tissues before and after targeted therapies, and (iv) development of predictive biomarkers integrating genetics, autoantibody kinetics, and immune reconstitution dynamics.

From a translational perspective, a realistic near-term goal is to define clinically useful endotypes: for example, patients with rapid relapse after rituximab versus those with sustained remission; patients with predominant mucosal disease and high anti-DSG3 titers versus those with broader antigen spreading. Such endotypes could guide early combination therapy (e.g., rituximab + FcRn inhibitor), maintenance strategies, and monitoring intensity.

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