Immunogenetic Determinants of Therapeutic Resistance in Glanzmann Thrombasthenia

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Abstract

Background: Glanzmann thrombasthenia (GT) is a rare inherited platelet function disorder characterized by qualitative or quantitative defects in the platelet glycoprotein IIb/IIIa (αIIbβ3) integrin, leading to impaired platelet aggregation and a lifelong bleeding tendency. Despite advances in supportive management, including platelet transfusions and recombinant activated factor VII (rFVIIa), a subset of patients demonstrates poor or diminishing therapeutic response. Increasing evidence suggests that immunogenetic factors play a pivotal role in modulating treatment outcomes in GT, particularly through mechanisms involving alloimmunization and immune-mediated platelet refractoriness.

The aim of this review is to critically evaluate the role of immune gene polymorphisms in determining therapeutic resistance in patients with Glanzmann thrombasthenia. Specific focus is placed on genetic variations in human leukocyte antigen (HLA) loci, cytokine genes, Fc gamma receptor (FcγR) polymorphisms, and other immune regulatory pathways that influence antigen presentation, antibody production, and immune effector responses. These polymorphisms may predispose patients to heightened immune reactivity against transfused platelets or therapeutic agents, ultimately leading to reduced efficacy and increased clinical complications.

Emerging studies highlight that certain HLA class I and II alleles are associated with an increased risk of anti-platelet antibody formation, while polymorphisms in cytokine genes such as TNF-α, IL-6, and IL-10 may alter inflammatory responses and immune tolerance. Additionally, Fcγ receptor genetic variants can influence antibody-mediated clearance of platelets, further contributing to treatment failure. Understanding these immunogenetic interactions provides valuable insight into the heterogeneity of treatment response observed in GT patients.

In conclusion, immunogenetic variability represents a critical but underexplored determinant of therapeutic resistance in Glanzmann thrombasthenia. Integrating genetic profiling into clinical practice may enable risk stratification, guide individualized therapeutic strategies, and improve long-term outcomes. Future research should focus on large-scale, multicenter studies to validate these associations and facilitate the development of precision medicine approaches in the management of this rare but clinically significant disorder.

Keywords: *Immunogenetic Determinants, Therapeutic Resistance, Glanzmann Thrombasthenia*

Introduction

Glanzmann thrombasthenia (GT) is a rare autosomal recessive inherited platelet function disorder caused by qualitative or quantitative defects in the platelet integrin αIIbβ3, which is essential for fibrinogen binding and platelet aggregation. The disorder was first described by Eduard Glanzmann in 1918 and remains a significant cause of mucocutaneous bleeding, particularly in populations with high rates of consanguinity. Clinically, patients present with epistaxis, gingival bleeding, menorrhagia, and excessive bleeding following trauma or surgical procedures. Although the molecular basis of GT has been extensively characterized at the level of platelet glycoproteins, variability in clinical severity and response to therapy remains poorly understood, suggesting the involvement of additional modifying factors beyond the primary genetic defect [1].

The cornerstone of GT management includes local hemostatic measures, antifibrinolytic agents, platelet transfusions, and the use of recombinant activated factor VII (rFVIIa) in refractory cases. While platelet transfusion is highly effective in controlling bleeding episodes, repeated exposure often leads to the development of alloantibodies against platelet glycoproteins or human leukocyte antigens (HLA), resulting in platelet refractoriness. This immune-mediated complication significantly limits treatment efficacy and poses a major clinical challenge. Notably, not all patients develop alloimmunization despite similar transfusion exposure, indicating that host-related immunogenetic factors may influence susceptibility to immune responses [2].

Recent advances in immunogenetics have highlighted the critical role of genetic variability in immune response pathways in determining individual differences in disease progression and therapeutic outcomes. Polymorphisms in genes encoding HLA molecules, cytokines, and Fc gamma receptors have been implicated in modulating antigen presentation, antibody production, and immune complex clearance. These genetic variations can alter both innate and adaptive immune responses, potentially predisposing certain GT patients to heightened immune reactivity against transfused platelets or therapeutic proteins such as rFVIIa [3].

Among these, HLA class I and class II polymorphisms are of particular interest due to their central role in antigen presentation and T-cell activation. Specific HLA alleles have been associated with increased risk of alloantibody formation in transfusion-dependent conditions. Similarly, cytokine gene polymorphisms, including those affecting tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10), may influence the balance between pro-inflammatory and anti-inflammatory responses, thereby modulating immune tolerance versus sensitization. Variations in Fc gamma receptor genes can further affect the efficiency of antibody-mediated phagocytosis and clearance of opsonized platelets [4].

Despite these emerging insights, the role of immunogenetic determinants in Glanzmann thrombasthenia remains insufficiently explored, with most studies limited by small sample sizes and heterogeneous methodologies. There is a clear gap in the literature regarding the integration of immune genetic profiling with clinical outcomes in GT, particularly in relation to therapeutic resistance and alloimmunization risk. Addressing this gap is crucial for advancing toward personalized medicine approaches that can optimize treatment strategies based on individual genetic risk profiles [5].

The aim of this review is to comprehensively evaluate the current evidence on immunogenetic factors contributing to therapeutic resistance in Glanzmann thrombasthenia. By synthesizing data on HLA polymorphisms, cytokine gene variants, Fc receptor genetics, and other immune regulatory mechanisms, this article seeks to provide a cohesive framework for understanding variability in treatment response. Furthermore, it aims to identify potential biomarkers for predicting poor therapeutic outcomes and to highlight future research directions that may facilitate the development of targeted and individualized therapeutic interventions in GT [6].

Pathophysiology of Glanzmann Thrombasthenia and Basis of Standard Therapies

Glanzmann thrombasthenia (GT) is fundamentally a disorder of platelet aggregation resulting from defects in the integrin αIIbβ3 complex, a transmembrane receptor critical for platelet–platelet interactions. This integrin, composed of glycoprotein IIb (CD41) and glycoprotein IIIa (CD61), mediates fibrinogen binding and cross-linking of activated platelets, which is essential for stable clot formation. Mutations in the *ITGA2B* and *ITGB3* genes disrupt either the expression or function of this receptor, leading to absent or defective platelet aggregation despite normal platelet count and morphology. The inability to form a proper platelet plug explains the characteristic mucocutaneous bleeding phenotype observed in GT patients [7].

At the molecular level, GT is classified into different subtypes based on the level and functionality of αIIbβ3 expression. Type I GT is characterized by less than 5% of normal receptor expression, while Type II exhibits 5–20%, and variant forms may have near-normal expression but dysfunctional receptors. These variations can influence the severity of bleeding symptoms but do not fully account for differences in therapeutic response, suggesting that additional factors, including immune mechanisms, contribute to clinical heterogeneity. Importantly, even patients with similar genotypes can exhibit markedly different bleeding profiles and treatment outcomes [8].

Platelet activation in normal physiology involves a cascade of intracellular signaling events triggered by agonists such as ADP, thrombin, and collagen. These signals induce a conformational change in αIIbβ3, enabling high-affinity binding to fibrinogen and von Willebrand factor. In GT, this “inside-out” signaling may remain intact, but the defective receptor prevents effective ligand binding, thereby impairing aggregation. Furthermore, “outside-in” signaling, which stabilizes thrombus formation and supports clot retraction, is also compromised, leading to unstable hemostatic plugs and prolonged bleeding episodes [9].

The standard therapeutic approach in GT primarily targets the correction of defective platelet aggregation. Platelet transfusion remains the most effective treatment for controlling moderate to severe bleeding and for perioperative management. Transfused platelets provide functional αIIbβ3 receptors, temporarily restoring aggregation capacity. However, repeated transfusions expose patients to alloantigens, particularly HLA and platelet-specific glycoproteins, increasing the risk of alloimmunization. This immune response can result in the production of antibodies that rapidly clear transfused platelets, leading to refractoriness and reduced therapeutic efficacy [10].

Recombinant activated factor VII (rFVIIa), such as Eptacog alfa, has emerged as an important alternative therapy, particularly in patients who are refractory to platelet transfusions or have developed alloantibodies. rFVIIa enhances thrombin generation on activated platelet surfaces independently of αIIbβ3 function, thereby promoting fibrin formation and improving hemostasis. Clinical studies have demonstrated its efficacy in controlling bleeding episodes and during surgical interventions, although variability in response persists, again pointing toward underlying host-related factors [11].

Adjunctive therapies, including antifibrinolytic agents such as Tranexamic acid, play a supportive role by stabilizing formed clots and reducing bleeding, particularly in mucosal tissues. Local hemostatic measures and hormonal therapy for menorrhagia are also commonly employed. While these approaches can be effective in mild cases, they do not address the underlying defect and are insufficient in severe bleeding scenarios. Moreover, their effectiveness is not significantly influenced by immunogenetic factors, unlike transfusion-based therapies [12].

Bone marrow transplantation and, more recently, gene therapy have been explored as curative options for GT. Hematopoietic stem cell transplantation can restore normal platelet function by replacing defective megakaryocytes with donor-derived cells. However, this approach carries significant risks, including graft-versus-host disease and transplant-related mortality, limiting its use to severe cases. Experimental gene therapy strategies aim to correct the underlying genetic defect in hematopoietic stem cells, offering a promising future direction, although these remain largely investigational [13].

Despite the availability of multiple therapeutic options, treatment outcomes in GT remain highly variable. A critical limitation of current management strategies is the lack of predictive markers for therapeutic response and the inability to identify patients at high risk for developing alloimmunization or refractoriness. This variability underscores the importance of exploring immunogenetic determinants that may influence how patients respond to therapies such as platelet transfusions and rFVIIa. Understanding these factors is essential for optimizing treatment strategies and minimizing complications in this rare but clinically challenging disorder [14].

Mechanisms of Therapeutic Resistance in Glanzmann Thrombasthenia

Therapeutic resistance in Glanzmann thrombasthenia (GT) is a multifactorial phenomenon that significantly complicates clinical management and contributes to increased morbidity. The most prominent mechanism underlying treatment failure is immune-mediated refractoriness to platelet transfusion, which arises following repeated exposure to allogeneic platelet antigens. Patients develop antibodies directed against human leukocyte antigens (HLA) and, more specifically, against platelet glycoproteins such as αIIbβ3. These antibodies bind to transfused platelets, leading to their rapid clearance from circulation and rendering transfusion therapy ineffective. However, the onset and severity of this response vary widely among patients, indicating that host immunogenetic variability plays a critical role in determining susceptibility [15].

Alloimmunization is driven by antigen presentation and adaptive immune activation, processes that are tightly regulated by genetic factors. Antigen-presenting cells process donor-derived platelet antigens and present them via HLA class II molecules to CD4+ T lymphocytes, initiating a cascade that leads to B-cell activation and antibody production. The efficiency of this process depends on the individual's HLA genotype, which influences peptide binding affinity and T-cell receptor recognition. Certain HLA alleles may enhance the immunogenicity of platelet antigens, predisposing patients to a more robust alloimmune response. This variability provides a key mechanistic link between immunogenetics and therapeutic resistance in GT [16].

In addition to alloantibody formation, immune-mediated platelet destruction is influenced by Fc gamma receptor (FcγR) pathways. These receptors, expressed on macrophages and other immune effector cells, bind to the Fc portion of IgG antibodies coating transfused platelets, facilitating their phagocytosis. Genetic polymorphisms in FcγR genes can alter receptor affinity for IgG subclasses, thereby modulating the efficiency of antibody-mediated clearance. Patients with high-affinity FcγR variants may experience more rapid destruction of transfused platelets, contributing to poor clinical response despite adequate transfusion support [17].

Another important mechanism contributing to therapeutic resistance involves cytokine-mediated modulation of immune responses. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) enhance antigen presentation, T-cell activation, and B-cell differentiation, thereby promoting alloantibody production. Conversely, anti-inflammatory cytokines like interleukin-10 (IL-10) play a role in maintaining immune tolerance. Polymorphisms in cytokine genes can shift this balance, resulting in either heightened immune reactivity or relative tolerance. Patients with genotypes favoring a pro-inflammatory profile may be at increased risk of developing refractoriness to platelet transfusion [18].

Therapeutic resistance is not limited to platelet transfusions but can also affect response to recombinant activated factor VII, such as Eptacog alfa. Although rFVIIa acts independently of platelet αIIbβ3, its efficacy depends on adequate thrombin generation and the presence of functional platelet surfaces. Variability in response to rFVIIa may be influenced by underlying inflammatory states, endothelial activation, and genetic factors affecting coagulation and immune pathways. Additionally, the development of neutralizing antibodies, although rare, has been reported and may further contribute to reduced therapeutic efficacy in certain patients [19].

Non-immune factors also contribute to therapeutic resistance, including the severity of the underlying genetic defect, the presence of residual αIIbβ3 function, and clinical variables such as infection or systemic inflammation. However, these factors alone do not fully explain the observed heterogeneity in treatment

outcomes. Increasing evidence supports the notion that immune-related genetic differences are key modulators that interact with clinical and molecular factors to shape individual responses to therapy [20].

The concept of immune tolerance versus sensitization is central to understanding why some GT patients remain responsive to platelet transfusions while others rapidly develop refractoriness. Regulatory T cells (Tregs) and immune checkpoint pathways play essential roles in maintaining tolerance to transfused antigens. Genetic variations affecting these regulatory mechanisms may impair tolerance induction, leading to enhanced alloimmune responses. Although this area remains underexplored in GT, parallels from other transfusion-dependent conditions suggest that these pathways are likely to be highly relevant [21].

Collectively, these mechanisms highlight the complex interplay between immune activation, genetic predisposition, and therapeutic interventions in determining treatment outcomes in Glanzmann thrombasthenia. A deeper understanding of these processes is essential for identifying patients at risk of therapeutic resistance and for developing targeted strategies to prevent or mitigate alloimmunization. This sets the stage for a detailed exploration of specific immunogenetic polymorphisms, particularly within HLA systems, cytokine networks, and Fc receptor genes, which will be discussed in the subsequent sections [22].

HLA Polymorphisms and Their Role in Alloimmunization and Treatment Resistance in Glanzmann Thrombasthenia

Human leukocyte antigen (HLA) polymorphisms represent one of the most critical immunogenetic determinants influencing alloimmunization and therapeutic resistance in Glanzmann thrombasthenia (GT). The HLA system, located on chromosome 6, encodes highly polymorphic molecules responsible for antigen presentation to T lymphocytes. In the context of platelet transfusion, donor-derived antigens—including platelet glycoproteins and HLA molecules—are processed and presented by recipient antigen-presenting cells. The efficiency and specificity of this process depend heavily on the recipient's HLA genotype, which determines peptide-binding affinity and the subsequent activation of adaptive immune responses [23].

HLA class I molecules (HLA-A, HLA-B, and HLA-C) are expressed on the surface of platelets and play a direct role in transfusion immunogenicity. Mismatches between donor and recipient HLA class I antigens can trigger the formation of anti-HLA antibodies, which are a major cause of platelet transfusion refractoriness. Studies in transfusion medicine have consistently demonstrated that patients exposed to multiple HLA-mismatched platelet units are at significantly higher risk of developing alloantibodies. However, not all individuals with similar exposure develop such responses, suggesting that specific HLA alleles may confer either susceptibility or protection against alloimmunization [24].

HLA class II molecules, particularly HLA-DR and HLA-DQ, are central to initiating immune responses through their role in presenting exogenous antigens to CD4+ T helper cells. Certain HLA class II alleles have been associated with increased immune responsiveness due to their higher binding affinity for immunogenic peptides derived from platelet glycoproteins such as αIIbβ3. This enhanced antigen presentation facilitates T-cell activation and subsequent B-cell differentiation into antibody-producing plasma cells. In GT patients, this mechanism is particularly relevant, as the absence of native αIIbβ3 may render the transfused protein more immunogenic, especially in individuals with permissive HLA backgrounds [25].

Evidence from related hematologic and transfusion-dependent disorders indicates that specific HLA haplotypes are associated with an increased risk of alloantibody formation. For example, certain HLA-DRB1 alleles have been linked to heightened immune responses against therapeutic proteins and transfused cells. Although data specific to GT remain limited, extrapolation from these conditions supports the hypothesis that HLA polymorphisms significantly influence alloimmunization risk. Preliminary studies in GT cohorts have identified associations between particular HLA alleles and the development of anti-platelet antibodies, though larger studies are needed for validation [26].

The concept of "epitope matching" has emerged as an important refinement in understanding HLA-related immunogenicity. Rather than considering only broad HLA antigen mismatches, epitope-level

differences—specific amino acid variations within HLA molecules—may more accurately predict immune responses. Patients with greater epitope disparity between donor and recipient are more likely to develop alloantibodies. Incorporating epitope matching into transfusion strategies has shown promise in reducing alloimmunization in other clinical settings and may be particularly beneficial in GT patients requiring repeated platelet support [27].

Another layer of complexity is introduced by linkage disequilibrium within the HLA region, where certain alleles are inherited together with other immune-related genes. This genetic clustering can amplify or modulate immune responses beyond the effect of individual HLA alleles. For instance, HLA haplotypes may be associated with specific cytokine gene variants that collectively influence the magnitude and quality of immune activation. Such interactions highlight the need to consider the broader immunogenetic landscape rather than isolated polymorphisms when evaluating therapeutic resistance [28].

HLA typing has already been incorporated into clinical practice for managing platelet refractoriness, particularly through the use of HLA-matched or crossmatch-compatible platelet transfusions. These strategies aim to minimize antigenic disparity and reduce the likelihood of alloimmune reactions. However, their effectiveness varies, and not all patients benefit equally. Understanding the underlying HLA polymorphisms that predispose to alloimmunization could enhance the precision of these approaches, enabling more targeted donor selection and improved clinical outcomes [29].

Despite the recognized importance of HLA in transfusion immunology, its specific role in Glanzmann thrombasthenia remains underexplored. Most available data are derived from small case series or extrapolated from broader transfusion populations. There is a pressing need for large-scale, genotype-phenotype correlation studies in GT to identify high-risk HLA profiles and to integrate this knowledge into clinical decision-making. Such efforts could pave the way for personalized transfusion strategies and reduce the burden of therapeutic resistance in this vulnerable patient population [30].

Cytokine Gene Polymorphisms and Immune Modulation in Glanzmann Thrombasthenia

Cytokine gene polymorphisms represent a biologically plausible but still under-investigated contributor to therapeutic resistance in Glanzmann thrombasthenia (GT). Although the primary defect in GT is platelet integrin αIIbβ3 dysfunction, poor response to platelet therapy is often mediated by immune complications, especially anti-HLA and anti-platelet glycoprotein alloimmunization. Registry and review data confirm that platelet transfusion remains standard therapy in severe GT bleeding, but repeated exposure may lead to alloimmunization and refractoriness, creating the clinical setting in which cytokine-mediated immune regulation becomes highly relevant [31,32].

Interleukin-6 (IL-6) is particularly important because it promotes B-cell maturation, plasma-cell differentiation, and antibody production. In a GT patient repeatedly exposed to platelet antigens, genetically determined high IL-6 expression may theoretically amplify alloantibody formation against HLA class I or αIIbβ3 epitopes. This is especially relevant because anti-HLA and anti-HPA antibodies are documented in GT cohorts, although reported frequencies vary according to testing method, transfusion exposure, and population characteristics [33]. Therefore, IL-6 polymorphisms should be viewed as candidate modifiers of alloimmunization risk rather than proven independent predictors in GT [33,34].

Tumor necrosis factor-alpha (TNF-α) polymorphisms may also influence treatment resistance by regulating inflammation, antigen presentation, endothelial activation, and immune-cell recruitment. A pro-inflammatory TNF-α genetic profile could enhance dendritic-cell activation and increase the likelihood that transfused platelet antigens are presented effectively to helper T cells. In children with chronic immune thrombocytopenia, TNF-α, IL-6, IL-10, and related cytokine polymorphisms have been investigated in relation to disease susceptibility and treatment response, supporting their relevance in pediatric platelet-immune disorders, although this evidence cannot be directly equated with GT [35].

Interleukin-10 (IL-10) has an opposing but equally important role because it regulates excessive inflammation and contributes to immune tolerance. Reduced IL-10 activity may favor persistent immune activation, while higher IL-10 expression may suppress antigen-presenting-cell function and reduce inflammatory amplification. In GT, insufficient anti-inflammatory regulation could permit stronger alloimmune responses after platelet transfusion, whereas protective IL-10 genotypes may theoretically

reduce antibody formation. This hypothesis is consistent with broader immunology literature, but GT-specific validation remains limited and should be highlighted as a research gap rather than overstated as established fact [36].

Transforming growth factor-beta 1 (TGF-β1) and interferon-gamma (IFN-γ) polymorphisms may further modify alloimmune behavior by affecting regulatory T-cell differentiation and Th1 polarization. IFN-γ can promote macrophage activation and enhance antigen presentation, while TGF-β1 supports immune regulation and tolerance under selected conditions. Studies in autoimmune cytopenias have examined cytokine SNPs including TNF-α, TGF-β1, IL-10, IL-6, and IFN-γ, showing that cytokine genetics may correlate with immune phenotype and clinical behavior. These findings support using cytokine SNPs as candidate biomarkers in GT research, especially in patients with recurrent refractoriness [37].

A major challenge is that cytokine polymorphisms are unlikely to act alone. Their effect probably depends on interaction with HLA alleles, transfusion burden, leukoreduction practices, infection, inflammatory status, and the severity of the underlying αIIbβ3 defect. Modern reviews of platelet transfusion refractoriness emphasize that alloimmune refractoriness is driven mainly by anti-HLA class I antibodies, but clinical refractoriness reflects both immune and non-immune mechanisms. Thus, cytokine variants may function as "immune amplifiers" that shape the probability and intensity of antibody development rather than directly causing treatment failure [38].

From a pediatric perspective, cytokine gene polymorphisms are especially relevant because many GT patients begin transfusion exposure early in life. Early immune priming may influence long-term transfusion responsiveness, surgical safety, and future reproductive risks in adolescent girls. Identifying children with high-risk inflammatory genotypes could eventually support preventive strategies, such as minimizing unnecessary platelet exposure, prioritizing leukoreduced and HLA-compatible components, and considering rFVIIa earlier in selected cases. However, such precision strategies require prospective GT-specific studies before routine clinical implementation [31,39].

Overall, cytokine gene polymorphisms provide a compelling explanatory bridge between inherited immune variability and heterogeneous treatment outcomes in GT. Current evidence supports their biological plausibility, but direct clinical evidence in GT remains sparse. Future studies should evaluate IL6, TNF, IL10, TGFB1, and IFNG variants alongside HLA typing, anti-HLA/anti-αIIbβ3 antibody screening, platelet increment data, and rFVIIa response. This integrated model would move GT management beyond reactive treatment of bleeding toward anticipatory risk stratification and individualized hemostatic planning [40].

Fc Gamma Receptor Polymorphisms and Antibody-Mediated Platelet Clearance

Fc gamma receptors (FcγRs) are central mediators of antibody-dependent platelet clearance and therefore represent a key immunogenetic pathway in therapeutic resistance among patients with Glanzmann thrombasthenia (GT). Once anti-HLA or anti-αIIbβ3 antibodies bind to transfused platelets, the Fc region of IgG can engage FcγRs on macrophages, monocytes, neutrophils, and other immune effector cells. This interaction promotes phagocytosis, inflammatory activation, and rapid platelet removal from circulation. Importantly, GT registry data confirm that anti-HLA and/or anti-GPIIb/IIIa antibodies may cause platelet ineffectiveness, but also show that antibody presence does not always translate into clinical refractoriness, implying that effector pathways such as FcγR biology may modify outcome [41].

The most clinically relevant polymorphisms include **FCGR2A H131R** and **FCGR3A V158F**, which influence IgG subclass binding affinity and downstream immune activation. FCGR2A encodes FcγRIIa, the only Fcγ receptor expressed on human platelets and an important receptor on myeloid cells, while FCGR3A encodes FcγRIIIa on natural killer cells and macrophage subsets. Higher-affinity variants may increase the ability of immune cells to recognize antibody-coated platelets, potentially accelerating post-transfusion platelet clearance. This mechanism is well established in immune-mediated platelet disorders, although direct GT-specific genotype-response evidence remains limited [42].

Evidence from platelet transfusion refractoriness studies suggests that FcγR-mediated mechanisms are biologically important but genetically complex. A study evaluating FcγR genetic variation in alloimmunized patients with platelet refractoriness reported that tested FcγR variants were not clearly

associated with severe platelet refractoriness, contrasting with stronger associations seen in autoimmune thrombocytopenia. This negative finding is important because it cautions against overinterpreting FcγR polymorphisms as isolated predictors. In GT, FcγR variants are more likely to function as modifiers within a broader network involving antibody specificity, antibody titer, IgG subclass, Fc glycosylation, complement activation, and inflammatory state [43].

Anti-HLA antibody pathogenicity also varies according to Fc-dependent effector function. Experimental work has shown that only a subset of anti-HLA antibodies can induce FcγRIIa-dependent platelet activation, helping explain why some antibody-positive patients remain clinically responsive while others develop severe refractoriness. This concept is highly relevant to GT because patients may develop anti-HLA antibodies after repeated platelet exposure, yet the clinical consequences differ markedly. Therefore, antibody testing alone may be insufficient; functional assessment of antibody behavior and host FcγR background may provide deeper prediction of therapeutic failure [44].

Fc glycosylation adds another important layer to antibody-mediated platelet clearance. Altered Fc glycosylation of anti-HLA alloantibodies has been described in patients receiving platelet transfusions, and these structural differences may influence FcγR binding and effector-cell activation. In practical terms, two GT patients with similar anti-HLA antibody titers may experience different platelet increments if their antibodies differ in Fc glycan composition or ability to engage FcγRs. This supports a modern view of refractoriness as a functional immune phenotype rather than simply the presence or absence of alloantibodies [45].

Anti-αIIbβ3 antibodies are especially important in GT because the deficient or absent native integrin can make transfused normal αIIbβ3 appear immunogenic to the recipient. Literature on anti-αIIbβ3 immunization in GT indicates that these antibodies can interfere with transfused platelet function and contribute to treatment ineffectiveness. FcγR pathways may amplify this process by clearing antibody-coated platelets before they can participate in hemostasis. This mechanism is clinically concerning in children and adolescents who require repeated platelet support over many years, as immune memory and repeated antigen exposure may progressively reduce transfusion benefit [46].

The pediatric relevance of FcγR polymorphisms is supported by studies in childhood immune thrombocytopenia, where FCGR2A and FCGR3A variants have been investigated as determinants of susceptibility, chronicity, and treatment response. Although immune thrombocytopenia differs from GT because it is autoimmune rather than alloimmune, both conditions involve IgG-coated platelet clearance through Fc receptor-bearing cells. Thus, ITP data provide mechanistic support for studying FcγR variants in pediatric GT, but they should not be used as direct evidence of causality in GT without disease-specific validation [47].

Overall, Fcγ receptor polymorphisms provide a plausible explanation for why some alloimmunized GT patients develop severe clinical refractoriness while others retain partial response to platelet transfusion. Future GT studies should combine FCGR2A and FCGR3A genotyping with anti-HLA and anti-αIIbβ3 antibody specificity, IgG subclass, Fc glycosylation, corrected count increment, bleeding outcomes, and response to rFVIIa. Such integrated immune profiling may help distinguish patients who are merely antibody-positive from those at true risk of clinically meaningful therapeutic resistance [48].

Platelet-Specific Alloantibodies and Anti-αIIbβ3–Mediated Treatment Failure

Platelet-specific alloantibodies are particularly important in Glanzmann thrombasthenia (GT) because the disease itself involves deficiency or dysfunction of αIIbβ3, the same receptor complex supplied by transfused normal platelets. In patients with severe quantitative deficiency, especially type I GT, transfused αIIbβ3 may be recognized as a foreign antigen, leading to anti-GPIIb/IIIa antibody formation. These antibodies can bind donor platelets, interfere with their function, and promote rapid immune clearance, thereby reducing or abolishing the hemostatic benefit of platelet transfusion. This mechanism makes anti-αIIbβ3 alloimmunization more disease-specific than general anti-HLA refractoriness [49].

Anti-HLA antibodies remain the most frequent immune cause of platelet refractoriness in transfusion practice, but anti-αIIbβ3 antibodies carry special clinical significance in GT. Unlike anti-HLA antibodies, which mainly accelerate platelet destruction, anti-αIIbβ3 antibodies may both clear donor platelets and

directly block the receptor needed for aggregation. This dual mechanism can result in poor clinical response even when platelet products are available and appropriately administered. Registry data emphasize that anti-HLA and/or anti-GPIIb/IIIa antibodies may cause platelet ineffectiveness, although antibody positivity does not always perfectly predict clinical failure [50].

The development of anti-αIIbβ3 antibodies is influenced by the patient's underlying molecular phenotype. Individuals with absent or markedly reduced αIIbβ3 expression may have limited immune tolerance to the normal protein complex, increasing the likelihood of recognizing transfused αIIbβ3 as non-self. In contrast, variant GT patients with residual receptor expression may retain partial immunologic tolerance, although this protection is not absolute. This phenotype-dependent risk provides a strong rationale for integrating platelet receptor expression, mutation type, and immune antibody screening when estimating future transfusion risk [51].

Detection of platelet-specific alloantibodies requires careful laboratory strategy because antibody profiles may be complex and may include both anti-HLA and anti-HPA or anti-GPIIb/IIIa reactivity. A recent study in inherited platelet disorders highlighted the importance of structured alloantibody detection in GT and Bernard–Soulier syndrome, conditions in which transfusion exposure is common and alloimmunization may compromise management. For GT patients, antibody testing should ideally distinguish anti-HLA from anti-αIIbβ3 antibodies because their clinical implications and transfusion strategies may differ [52].

The clinical impact of anti-αIIbβ3 antibodies becomes especially evident during severe bleeding, surgery, trauma, or childbirth, when rapid and reliable hemostasis is essential. Patients with these antibodies may fail to respond to conventional platelet transfusion, requiring alternative strategies such as recombinant activated factor VII, HLA-compatible or crossmatch-compatible platelets, antifibrinolytics, and intensive local hemostatic measures. International registry data support the use of rFVIIa in GT patients with platelet antibodies and/or refractoriness, making it a critical therapeutic option when alloantibody-mediated resistance develops [53].

Anti-αIIbβ3 alloimmunization also has important implications for pediatric and adolescent care. Children diagnosed early may accumulate multiple transfusion exposures across childhood, increasing the probability of immune sensitization before adulthood. In adolescent girls, antibody development may complicate management of menorrhagia, future pregnancy, delivery, and neonatal risk if maternal antibodies cross the placenta. Therefore, prevention of unnecessary platelet exposure and early recognition of antibody formation are particularly important in pediatric GT practice [54].

From an immunogenetic perspective, anti-αIIbβ3 antibody formation likely reflects interaction between the absent platelet antigen, recipient HLA class II peptide presentation, cytokine-driven B-cell activation, and FcγR-mediated clearance. This means that anti-αIIbβ3 alloimmunization should not be treated simply as a transfusion complication but as the final clinical expression of several immune genetic pathways. Future studies should evaluate whether specific HLA-DR/DQ alleles, inflammatory cytokine polymorphisms, and Fc receptor variants predict which GT patients are most likely to form clinically significant anti-αIIbβ3 antibodies [55].

Overall, platelet-specific alloantibodies represent one of the most direct mechanisms linking immunogenetics to therapeutic resistance in GT. Their presence may explain why patients with similar bleeding phenotype and similar transfusion exposure show very different responses to platelet therapy. A precision approach should combine baseline GT molecular classification, platelet αIIbβ3 expression level, transfusion history, anti-HLA and anti-GPIIb/IIIa antibody testing, and clinical response measures such as corrected count increment and bleeding control. This integrated model would allow clinicians to identify high-risk patients before emergency treatment failure occurs [56].

Complement Pathways, Innate Immunity, and Platelet Refractoriness in Glanzmann Thrombasthenia

Complement activation is an increasingly recognized mechanism in immune platelet refractoriness, although direct data in Glanzmann thrombasthenia (GT) remain limited. In alloimmunized patients, anti-HLA or anti-platelet antibodies may not only engage Fcγ receptors but also activate the classical

complement pathway on the platelet surface. This may accelerate platelet destruction, enhance inflammatory signaling, and reduce the post-transfusion platelet increment. Experimental work has shown that some anti-HLA antibodies can induce complement activation on platelets, supporting a biologically plausible pathway for refractory transfusion response in GT patients with alloantibodies [57].

The classical complement pathway is typically initiated when C1q binds to clustered IgG or IgM antibodies attached to cell-surface antigens. On transfused platelets, complement-fixing anti-HLA antibodies may trigger deposition of complement fragments such as C3b, which can promote opsonization and phagocytic clearance. Importantly, studies suggest that the geometry, density, and combination of anti-HLA antibodies influence whether complement activation occurs, meaning that antibody specificity may be as important as antibody titer. This may help explain why some alloantibody-positive patients remain clinically responsive while others develop severe refractoriness [58].

Complement biology also intersects with Fcγ receptor–mediated clearance. Antibody-coated platelets may be removed through parallel or synergistic pathways involving Fcγ receptors, complement receptors, macrophages, and splenic phagocytes. Anti-HLA class I antibodies have been shown to contribute to platelet clearance through several mechanisms, including FcγRIIa-dependent platelet activation and complement-mediated effects. This integrated model is particularly relevant in GT because transfused platelets are often given repeatedly across childhood and adolescence, increasing opportunities for immune priming, antibody maturation, and more efficient effector responses [59].

Innate immune activation may further amplify therapeutic resistance by increasing antigen presentation and inflammatory cytokine release. Infections, mucosal inflammation, surgery, and tissue injury can activate innate immune sensors and create a pro-inflammatory environment at the time of transfusion. Under these conditions, donor platelet antigens may be presented more efficiently to T cells, and existing alloantibodies may mediate stronger effector responses. Therefore, in GT patients, episodes of poor transfusion response should not be interpreted solely through antibody screening; clinical context, inflammation, fever, infection, and active bleeding severity must also be considered [60].

Complement-fixing capacity may eventually become a useful biomarker, but its clinical value in platelet refractoriness is not fully established. Diagnostic approaches such as C1q-binding antibody assays have been evaluated in other immune settings, yet platelet transfusion literature remains cautious regarding routine use. Some reviews note that complement-fixing antibodies are biologically important, but further studies are needed to define how well these assays predict clinically meaningful refractoriness. For GT, this means complement testing should currently be viewed as a research tool or specialized investigation rather than a standard requirement [61].

From a therapeutic viewpoint, complement involvement raises interest in targeted complement inhibition, but this remains experimental for platelet refractoriness and is not standard GT management. Current practical strategies still focus on preventing alloimmunization, using leukoreduced and preferably HLA-compatible or crossmatch-compatible platelets when needed, limiting unnecessary platelet exposure, and using recombinant activated factor VII in patients with platelet antibodies or refractoriness. The Glanzmann Thrombasthenia Registry supports the importance of rFVIIa as a major option in patients with antibodies or platelet ineffectiveness [62].

Genetic variation in complement regulatory proteins may also be relevant, although this area is almost unexplored in GT. Polymorphisms affecting complement activation, regulation, or receptor binding could theoretically influence the intensity of platelet opsonization and clearance after alloantibody formation. Candidate genes may include complement components and regulators such as C1q-related genes, C3, C4, CFH, CFI, and complement receptors. However, at present, these should be proposed as future research targets rather than established predictors of GT treatment response [63].

Overall, complement and innate immune pathways provide an important additional layer in the immunogenetic model of therapeutic resistance in GT. The strongest current evidence comes from broader platelet transfusion refractoriness studies, especially anti-HLA antibody research, while GT-specific evidence remains indirect. Future GT studies should combine anti-HLA and anti-αIIbβ3 antibody profiling with complement-fixing capacity, Fcγ receptor genotype, cytokine SNPs, infection status, and corrected

platelet count increments. This integrated approach may better identify which alloimmunized patients are at highest risk of true clinical treatment failure [64].

Clinical Risk Stratification and Prediction of Therapeutic Resistance

Clinical risk stratification in Glanzmann thrombasthenia (GT) should begin with recognition that therapeutic resistance is not a single event, but a progressive interaction between disease severity, transfusion exposure, alloantibody formation, and immune effector capacity. Platelet transfusion remains the standard therapy for severe bleeding and perioperative hemostasis, yet repeated exposure can lead to anti-HLA and anti-GPIIb/IIIa antibodies that reduce platelet effectiveness. The Glanzmann Thrombasthenia Registry confirms that platelet-based therapy is widely used but that antibody formation and platelet ineffectiveness remain major clinical concerns [65].

A practical risk model should include the molecular subtype of GT, baseline αIIbβ3 expression, age at first transfusion, cumulative number of platelet exposures, bleeding severity, and history of poor response to previous transfusions. Patients with type I GT and absent or near-absent αIIbβ3 expression may be particularly vulnerable to anti-GPIIb/IIIa alloimmunization because transfused normal platelets introduce an antigen that may be immunologically unfamiliar. However, transfusion burden and inflammatory context remain essential modifiers, meaning that genotype alone cannot predict resistance with certainty [66].

Objective assessment of platelet refractoriness requires more than clinical impression. In transfusion medicine, refractoriness is defined by repeated lower-than-expected platelet count increments after transfusion, commonly assessed using corrected count increment measurements. Expert reviews emphasize that non-immune causes such as fever, sepsis, bleeding, splenomegaly, disseminated intravascular coagulation, and medications must be excluded before attributing refractoriness to alloimmunization. This distinction is essential in GT because active bleeding itself may consume transfused platelets and mimic immune failure [67].

Immunologic evaluation should include anti-HLA antibody screening, platelet-specific antibody testing, and when available, assessment for anti-GPIIb/IIIa reactivity. HLA class I antibodies account for most immune-mediated platelet refractoriness in general transfusion practice, while platelet-specific antibodies are less common but highly relevant in GT because αIIbβ3 is the disease-defining receptor. Patients with persistent poor increments and compatible clinical history should be considered for HLA-matched, HLA-compatible, or crossmatch-compatible platelet products [68].

Prediction of therapeutic resistance should also incorporate treatment response to recombinant activated factor VII (rFVIIa). Registry studies show that rFVIIa is effective in many GT patients, including those with platelet antibodies and/or refractoriness, and it is frequently used for bleeding episodes and surgical procedures. Therefore, a child with prior platelet ineffectiveness should not simply be classified as “untreatable”; rather, the risk profile should guide early selection of alternative hemostatic strategies, including rFVIIa and adjunctive antifibrinolytics [69].

The immunogenetic component of risk stratification remains investigational but conceptually important. HLA-DR/DQ alleles may influence antigen presentation, cytokine polymorphisms may shape inflammatory amplification, Fcγ receptor variants may affect antibody-mediated clearance, and complement-related variation may modify platelet opsonization. At present, these markers should not replace clinical and laboratory monitoring, but they provide a strong framework for future predictive models. The most useful future approach will likely be a composite score combining immunogenetic data, antibody profile, transfusion history, and measured platelet increments [70].

From a pediatric standpoint, early risk stratification has special value because GT is lifelong and many patients begin treatment in infancy or childhood. Each unnecessary platelet exposure may increase future alloimmunization risk, especially in children likely to require surgeries, dental procedures, or management of severe mucosal bleeding. A preventive strategy should prioritize local hemostatic measures, tranexamic acid when appropriate, careful transfusion justification, and early hematology consultation before invasive procedures. This is particularly important for adolescent girls, in whom menorrhagia, pregnancy planning, and delivery may become major future hemostatic challenges [71].

Overall, clinical prediction of therapeutic resistance in GT should move from a reactive model toward a layered risk-assessment model. The most robust current predictors remain transfusion history, antibody status, platelet response measurements, and prior clinical response to therapy. Immunogenetic markers are promising but require validation in multicenter GT cohorts with standardized antibody testing and clinical endpoints. Until then, they should be used to guide research design and personalized thinking rather than routine decision-making [72].

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