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Original Article

The Duffy blood group system and benign ethnic neutropenia: mechanisms, clinical implications, and global health perspectives

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ABSTRACT

The Duffy blood group system (FY) is one of the most therapeutically significant blood group systems due to its multiple roles in transfusion medicine, infectious disease susceptibility, and inflammatory control. The Duffy antigen receptor for chemokines (DARC) works as both a blood group antigen and a chemokine binding protein. DARC has been renamed by HUGO's Gene Nomenclature Committee. ACKR1 is now the accepted term and is used extensively by NCBI and LRG. This comprehensive analysis investigates the molecular genetics, population biology, and clinical importance of the Duffy blood type system, with a focus on its well-established link to benign ethnic neutropenia (BEN). We explain the pathophysiological processes that link the Duffy null phenotype Fy(a-b-) to neutropenia and its clinical significance, including the "chemokine sink" concept and abnormal neutrophil homeostasis. The clinical implications for hematology, oncology, psychiatry, and general medicine are thoroughly reviewed, emphasizing the necessity of identifying BEN to avoid misdiagnosis and provide equal therapy. New research on the Duffy system's significance in cancer biology, transplant immunology, and inflammatory illnesses is also discussed. Understanding these complicated relationships is critical for clinicians and researchers dealing with ethnically diverse groups.

Keywords: Duffy blood group, DAR, ACKR1, Benign ethnic neutropenia, *Plasmodium vivax*, Chemokine receptor

Introduction

The Duffy blood group system was discovered in 1950, and an antibody was described in a hemophiliac patient's serum that interacted with around 65% of Caucasian blood samples [1]. The Duffy blood group system, named after Mr. Duffy, was characterized by the discovery of the Fy^a and Fy^b antigens. Duffy-negative red blood cells exhibit resistance to Plasmodium vivax merozoites, highlighting the therapeutic importance of this system. This resistance accounts for the racial distribution of Duffy antigens and supports evidence of natural selection in human populations [2, 3]. The acknowledgment of lower neutrophil counts in individuals of African descent dates back to the early 20th century, identified later as a benign physiological variant termed "Benign Ethnic Neutropenia" (BEN). This condition, defined by low absolute neutrophil counts (1.0-1.8 × 10^9/L), affects healthy individuals primarily of African, Middle Eastern, and Jewish descent [4-7]. Recent genome-wide

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association studies (GWAS) have linked the Duffy null genotype to variations in neutrophil counts. This review delves into the Duffy blood group system, its connection to BEN, and discusses molecular causes, clinical implications, and directions for future research [8, 9].

Molecular biology and genetics of the Duffy system

Gene structure and protein characteristics

The Duffy blood group system, encoded by the ACKR1 gene on chromosome 1, consists of a single exon that produces a 336-amino acid protein typical of G-protein-coupled receptors (GPCRs). However, ACKR1 is classified as a unique chemokine receptor as it does not signal via G proteins. The Duffy glycoprotein features the Fy^a and Fy^b antigens, differentiated by a single amino acid change at position 42: glycine in Fy^a and aspartic acid in Fy^b, resulting from a single nucleotide mutation (rs12075, G125A) in the gene's coding region [10].

The Duffy-null phenotype and population genetics

The Duffy-negative phenotype (Fy(a-b-)) results from a single nucleotide polymorphism (rs2814778, T-33C) in the ACKR1 gene's promoter, disrupting the GATA1 transcription factor binding. This mutation prevents Duffy expression on erythrocytes but not on other cells. The Duffy-negative phenotype has a global distribution shaped by evolutionary pressures from Plasmodium vivax malaria, being highly prevalent in sub-Saharan Africa (>95%), observed in African-descended populations in the Americas and Caribbean, with intermediate frequencies in the Middle East and parts of Asia, but rare in European and East Asian populations [11] **(Figure 1)**.

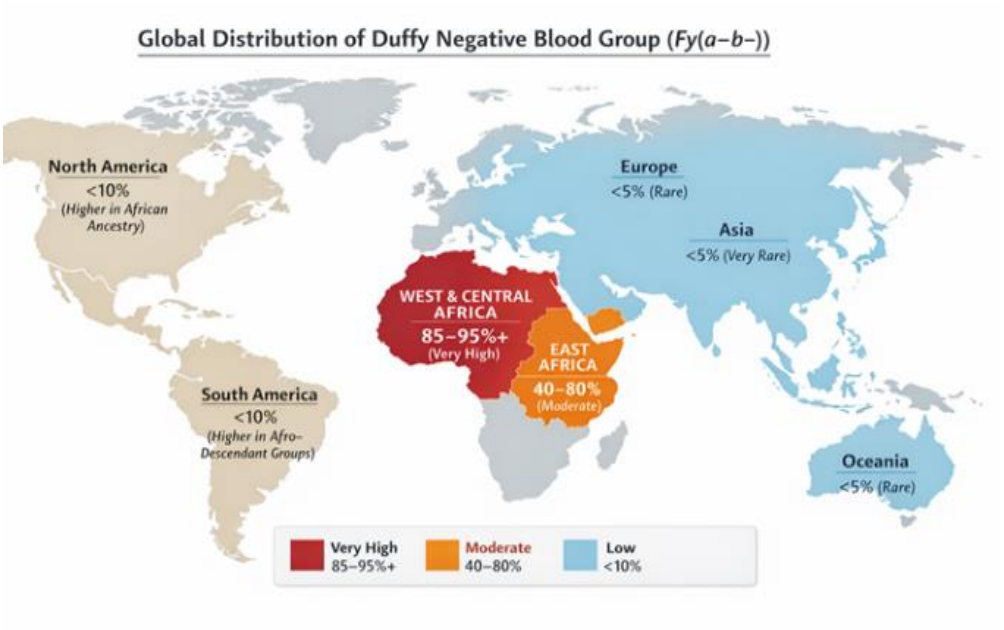

Figure 1. illustrates the Duffy null distribution in worldwide

Dual functions of ACKR1: malaria receptor and chemokine regulator

Role in plasmodium vivax invasion

ACKR1 is the primary receptor for Plasmodium vivax, the most prevalent human malaria parasite. The Duffy Binding Protein (PvDBP) binds specifically to ACKR1's N-terminal extracellular domain, facilitating the invasion of erythrocytes **(Figure 2)**. The Duffy-negative phenotype in West and Central Africa has historically posed a barrier to P. vivax transmission; however, recent cases of infection in Duffy-negative individuals suggest the emergence of Duffy-independent invasion mechanisms. These findings highlight significant implications for malaria control and elimination in Africa, showing that the DARC genotype, rather than ethnicity, is responsible for lower neutrophil counts associated with Duffy-null status. This pattern is less common in heterozygous or wild-type alleles found more in Asians and Europeans [12].

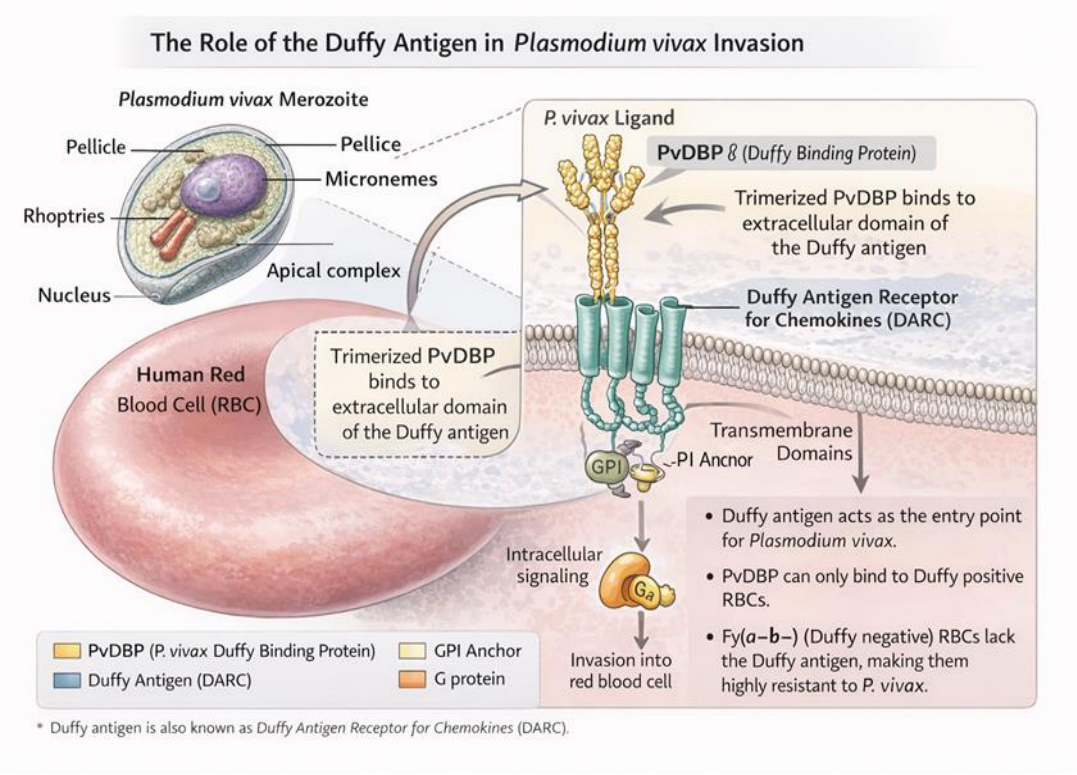

Figure 2. shows the role of Duffy group in *P. vivax* invasion

Chemokine binding properties

ACKR1 is a unique chemokine receptor that binds various inflammatory chemokines from both the C-C and C-X-C families with high affinity. Its broad specificity allows it to function as a chemokine scavenger and regulator. On endothelial cells, ACKR1 facilitates the transcytosis of chemokines across the vascular endothelium, enhancing leukocyte adhesion and extravasation, thereby playing a crucial role in regulating leukocyte trafficking during inflammation [13].

Chemokine transcytosis involves the transfer of chemokines from tissue to circulation across endothelial cells, significantly influenced by the ACKR1 receptor on postcapillary venular endothelial cells. When inflammatory chemokines bind to ACKR1, they are internalized and transported through vesicles to the luminal surface, where they are presented to leukocytes, promoting their recruitment to inflammation sites. This process does not involve standard G-protein signaling; instead, it relies on receptor-mediated internalization and trafficking, facilitating leukocyte adhesion and extravasation. In vitro studies confirm that ACKR1 acts as a chemokine transporter, showcasing its functionality beyond merely degrading receptors [14].

ACKR1 modulates inflammatory responses by influencing chemokine availability and leukocyte trafficking in tissue inflammation. Unlike traditional G-protein signaling, ACKR1, found in endothelial and red blood cells, acts as a chemokine buffer, binding various proinflammatory chemokines to stabilize their levels and prevent excessive leukocyte activation. During inflammation, ACKR1 enhances chemokine presentation on endothelial surfaces, aiding in the establishment of gradients that facilitate the extravasation of neutrophils and monocytes into inflamed tissues, thus promoting leukocyte recruitment. Animal studies indicate that the absence of ACKR1 results in decreased neutrophil recruitment and lower proinflammatory cytokine levels, such as IL-1β, IL-6, and CCL2, affecting both acute and chronic inflammation. In chronic disease models like atherosclerosis, ACKR1 expression is linked to higher inflammatory chemokines and greater lesion development, while ACKR1 deficiency leads to reduced chemokine levels and less inflammatory mononuclear cell content, emphasizing its role in managing inflammatory responses [15].

Recent research has challenged the notion that the Duffy-null promoter mutation entirely removes DARC (Duffy antigen) expression on erythroid cells. This T→C mutation affects GATA-1 binding, historically linked to resistance against Plasmodium vivax. However, studies show that erythrocytes from individuals homozygous for the Duffy-negative allele still produce functional Duffy protein, albeit at reduced levels. This suggests that the GATA-1 SNP results in a leaky promoter, allowing low-level expression during red cell development, potentially facilitating P. vivax infection in phenotypically Duffy-negative individuals by providing some receptor availability for the parasite [16].

Benign ethnic neutropenia: definition and epidemiology

Diagnostic criteria and prevalence

Benign ethnic neutropenia is described by the following characteristics:

a) Healthy persons have an absolute neutrophil count (ANC) of 1.0-1.8 × 10^9/L.
b) They are not more susceptible to infections.
c) Normal distribution of other blood cell lines.
d) Neutrophil count stability throughout time.
e) Associated with specific ethnicities.

The incidence of BEN varies greatly across populations, reflecting the distribution of the Duffy-null allele. Approximately 25-50% of African ancestors and 10-15% of Middle Eastern populations had neutropenia compatible with BEN, compared to only 2-5% of Europeans [17].

Genetic basis and GWAS findings

Genome-wide association studies (GWAS) have robustly identified ACKR1 as one of the most significant loci associated with quantitative variation in white blood cell (WBC) and neutrophil counts, particularly in populations of African ancestry:

Major GWAS associations

(a) In multiple GWAS of hematologic traits, the rs2814778 variant shows a very strong association with lower neutrophil and total WBC counts. For example, a GWAS of 552 African-ancestry individuals treated with clozapine found rs2814778 to be the most significant locus influencing neutrophil levels (genome-wide $p \approx 4.2 \times 10^{-21}$) and linked to neutropenia risk during clozapine therapy [18].
(b) Large multi-cohort GWAS like the COGENT study in ~16,000 African Americans confirmed the *DARC/*ACKR1 locus on 1q23 as a major determinant of WBC variation, replicating earlier findings that total and neutrophil counts are strongly influenced by local genetic variation, including rs2814778 [19]. Recent multi-cell type GWAS continue to replicate the ACKR1 association (e.g., in deconvoluted blood cell types), confirming its impact on neutrophils at genome-wide significance across independent datasets [20].

These GWAS solidify rs2814778 as a genetic variant with one of the largest effect sizes for neutrophil variation in humans, particularly among individuals of African descent.

Methodological limitations in cited GWAS studies

While GWAS have been instrumental in identifying ACKR1's influence on hematologic traits, several methodological limitations must be considered when interpreting these results:

(a) Population Stratification and Ancestry Bias
(b) Many early Genome-Wide Association Studies (GWAS) largely focused on European-ancestry groups, leading to potential misestimation of effects or overlooking ancestry-specific associations due to inadequate population structure controls. ACKR1 null alleles are rare in Europeans but prevalent in Africans. While some studies attempt adjustments with principal components, residual stratification may still affect findings, particularly regarding P. vivax infections in Duffy-negative individuals where receptor availability for the parasite could intermittently exist [21].
(c) Imputation Limitations
GWAS often rely on genotype imputation rather than direct sequencing. Imputation accuracy depends heavily on the reference panel used and declines for rare or population-specific variants like rs2814778 or other ethnic-specific haplotypes, potentially leading to misclassification or reduced statistical power for detecting true associations in diverse populations.
(d) Phenotype Complexity and Measurement
Phenotypes such as neutrophil count are influenced by environmental factors, clinical context (e.g., drug use, infection), and measurement variability. GWAS typically test associations with single SNPs and may not accurately capture correlated effects of multiple genetic and non-genetic factors.
(e) Limited Representation of Diverse Populations
Many GWAS include a majority of European samples with smaller minority cohorts. As a result, signals that are population-specific (like ACKR1's effect on neutrophils in Africans) may be underpowered or overlooked in aggregated analyses, and findings may not generalize across global ancestries. This also limits downstream functions like fine-mapping and polygenic risk score construction in understudied populations.
(f) Single-Variant Focus
GWAS typically identify statistical associations rather than mechanistic causation. Even when rs2814778 shows a strong association with neutrophil count, the functional mechanisms (e.g., effects on chemokine binding and immune cell trafficking) cannot be fully elucidated by association alone and require separate functional studies [22].

Pathophysiological mechanisms linking duffy-null phenotype to neutropenia

The chemokine sink hypothesis

The primary mechanistic reason for BEN involves ACKR1's function as a chemokine scavenger on erythrocytes. In Duffy-positive individuals, erythrocytes bind proinflammatory chemokines, notably CXCL8 (IL-8), creating a "chemokine sink" that regulates plasma chemokine levels. Conversely, Duffy-

negative individuals lack erythroid ACKR1, resulting in higher free chemokine levels in the bloodstream. This chronic exposure may lead to desensitization or downregulation of chemokine receptors on neutrophils, increasing the threshold for their mobilization and lowering baseline neutrophil counts while still allowing effective responses to illness or stress [13].

(a) Molecular Mechanisms Proposed for ACKR1 Absence and Chemokine Signaling

The Duffy antigen receptor for chemokines (ACKR1) is an atypical chemokine receptor that operates without classical G-protein signaling, primarily found on endothelial cells and nucleated erythroid progenitors. It facilitates the migration and recruitment of neutrophils by presenting bound chemokines like CXCL1/CXCL2 to other receptors such as CXCR1/CXCR2. In ACKR1-null individuals, this process is disrupted, impacting hematopoietic homeostasis and leading to a unique neutrophil profile that exits circulation more readily, resulting in lower peripheral neutrophil counts. Furthermore, the lack of ACKR1 affects local chemokine gradients, which may impair effective GPCR activation and reduce chemokine receptor engagement, suggesting a diminished landscape for chemokine interaction rather than direct GPCR signaling desensitization in response to stress or illness [16].

(b) Evidence Definitively Proven or Still Theoretical?

Current research indicates that the absence of ACKR1 alters chemokine signaling and affects neutrophil counts, as evidenced by mouse models and human Duffy-negative individuals showing similar neutrophil characteristics. Though these changes suggest a link to altered hematopoiesis and neutrophil dynamics, the precise molecular mechanisms—such as GPCR desensitization and altered chemokine gradients—are not fully established. Existing studies highlight the impact on chemokine bioavailability but also note that aspects of receptor regulation related to ACKR1 deficiency require further exploration [23].

(c) Alternative or Competing Hypotheses for BEN and Dynamics of Neutrophil Pools

Changes in hematopoietic stem/progenitor cell (HSPC) biology may contribute to BEN, as indicated by the role of ACKR1 on nucleated erythroid cells that influences stem cell contact and lineage differentiation. The absence of ACKR1 leads HSPCs to favor neutrophil/myeloid pathways, resulting in neutrophils with altered surface markers and trafficking. Consequently, these neutrophils may preferentially move into tissues like the spleen, leading to reduced peripheral neutrophil counts without compromising host defense [16].

(d) The dynamics of neutrophil "margination" vs. circulating pools

Neutrophil distribution in benign ethnic neutropenia (BEN) indicates that rather than being less produced, neutrophils are redistributed from circulation into organs like the spleen due to changes in chemokine presentation. This reallocation maintains normal total body neutrophil counts, which explains the lack of increased infection susceptibility in individuals with BEN, despite their low peripheral neutrophil counts [24].

Altered neutrophil kinetics and homeostasis

ACKR1 deletion mouse models illustrate the role of ACKR1 in neutrophil homeostasis, revealing altered neutrophil trafficking with reduced baseline circulating numbers, yet normal inflammatory responsiveness. Neutropenia in these models results from the redistribution of the neutrophil pool rather than production or functional deficiencies. Additionally, radiolabeled neutrophil studies in humans with BEN indicate normal neutrophil production and survival, suggesting that this syndrome reflects physiological variability in neutrophil regulation rather than impaired granulopoiesis [25].

Inflammatory modulation and clinical consequences

The altered chemokine environment in Duffy-negative individuals impacts more than neutrophil count; it influences inflammatory responses and heightens vulnerability to inflammatory diseases. Studies indicate that Duffy-negative individuals exhibit lower neutrophil recruitment and cytokine production in endotoxemia, potentially affecting the progression of sepsis and related inflammatory conditions [26].

Clinical implications and management considerations

Recognition and diagnosis to prevent misdiagnosis

Failure to recognize BEN is a leading source of needless medical procedures. Patients with BEN are frequently misdiagnosed as having immunological neutropenia, drug-induced neutropenia, or bone marrow failure syndromes, resulting in unnecessary testing, specialist referrals, and therapy adjustments. Key strategies for differentiating BEN from pathological neutropenia include:

(a) Determine ethnicity
(b) Review previous complete blood counts
(c) Check for infection history
(d) Document stability over time
(e) Rule out other hematological abnormalities [27].

Implications for pharmacotherapy: the clozapine example

The use of clozapine for treatment-resistant schizophrenia illustrates the therapeutic challenges posed by BEN, particularly the standard ANC threshold requirements for treatment. Updated monitoring standards in some countries, like the U.S. Clozapine REMS program, permit lower ANC thresholds (≥1000/109L) for patients with BEN, ensuring safety and increasing access to effective therapy for diverse ethnic groups [28].

Cancer chemotherapy and neutropenia risk assessment

Neutropenia caused by chemotherapy should be carefully managed in patients with BEN, as existing risk prediction models may inaccurately assess its severity, potentially resulting in overly cautious dose reductions that could compromise treatment effectiveness. Future clinical research should focus on creating ethnicity-specific guidelines for chemotherapy management [29, 30].

Transfusion medicine and alloimmunization

Alloimmunization to donor red blood cell (RBC) antigens, particularly in patients with hemoglobinopathies like β-thalassemia major or sickle cell disease, poses significant clinical challenges. The risk of developing alloantibodies increases with repeated transfusions, with rates varying between 10% and over 30%, influenced by donor matching practices. Specific antibodies, such as anti-Fy^a and anti-Fy^b, complicate finding compatible blood, prolong pre-transfusion processes, and raise the risk of delayed hemolytic transfusion reactions. This immune response can reduce the lifespan of transfused RBCs, exacerbate anemia, and increase transfusion needs, emphasizing the necessity for comprehensive antigen matching beyond standard ABO and Rh typing to improve patient outcomes [31].

(a) Diagnostic algorithm / flowchart for identifying BEN

BEN diagnosis starts with identifying chronic isolated neutropenia in healthy individuals, indicated by an ANC persistently below 1.5×10^9/L without severe infections. Secondary causes such as infections, autoimmune conditions, nutritional deficiencies, and bone marrow pathology must be systematically excluded. Stability in neutrophil counts, normal hemoglobin and platelet levels, and certain ancestry backgrounds support BEN diagnosis, which is a diagnosis of exclusion characterized by stable laboratory patterns rather than invasive testing [17, 32].

(b) ANC thresholds for different clinical scenarios

Large observational studies indicate that individuals with Benign Ethnic Neutropenia (BEN) generally have absolute neutrophil counts (ANCs) between 0.8 and 1.5×10^9/L without a higher risk of infections. ANCs of $\geq 1.0 \times 10^9$/L are deemed safe for BEN patients, while the general population often uses a lower normal limit of 1.5×10^9/L, potentially leading to misclassification. Severe neutropenia ($<0.5 \times 10^9$/L) is rare in BEN and necessitates urgent reassessment. Hematology reviews highlight the importance of not applying uniform ANC thresholds without considering individual genetic backgrounds and baseline values [33, 34].

(c) Step-by-step management of BEN in clozapine and chemotherapy

Regulatory authorities now classify benign ethnic neutropenia (BEN) as a special category for clozapine treatment. The FDA's REMS program allows initiation and continuation of clozapine in BEN patients with a baseline ANC of $\geq 1.0 \times 10^9$/L, compared to $\geq 1.5 \times 10^9$/L for the general population. Management includes documenting BEN, applying specific ANC thresholds, and monitoring closely. Studies show that inappropriate clozapine discontinuation leads to psychiatric relapse. In chemotherapy, BEN patients face unnecessary treatment delays without using individualized ANC assessments, which are preferred over absolute cutoffs. Granulocyte colony stimulating factor should be used selectively. When managed correctly, BEN does not increase infectious risk during cancer therapy [35].

(d) When Duffy (ACKR1) genotyping is indicated and cost-effective

Duffy (ACKR1) genotyping reveals the rs2814778 promoter variant linked to the Duffy-null phenotype, which is common in BEN cases. While not essential for routine diagnosis, genotyping is beneficial in uncertain cases, for clozapine candidates, or during chemotherapy delays due to low ANC. Economic evaluations indicate that one-time genotyping is cost effective, reducing unnecessary drug discontinuations, lab tests, bone-marrow biopsies, or hospitalizations, especially in health systems with high clozapine or chemotherapy usage **(Table 1)** [35].

Table 1. Practical clinical pearls [33, 35]

Clinical pearl	Rationale
BEN is a diagnosis of exclusion	Secondary causes must be ruled out
Stable ANC over time is key	Single low values are misleading
BEN does not increase infection risk	Total neutrophil function is preserved
Use BEN-specific ANC cutoffs for clozapine	Prevents unnecessary discontinuation
Compare ANC to personal baseline in chemotherapy	Avoids inappropriate dose delays
Duffy genotyping is selective, not routine	Most cost-effective in high-impact scenarios

Global health perspectives and health equity

Laboratory reference ranges and population-specific values

The reliance on laboratory reference ranges derived from European populations has led to systemic biases in interpreting total blood counts among ethnically diverse patients. Recommendations include adopting ethnicity-specific reference ranges or using independent interpretation criteria for patients with BEN, which would enhance diagnostic accuracy and help reduce health disparities in multiethnic healthcare systems [36].

Pharmacogenomics and personalized medicine

The Duffy system is a powerful demonstration of how genetic diversity affects drug responsiveness and safety. Incorporating Duffy genotyping into therapy algorithms for drugs with neutrophil-related toxicity may result in more customized and equitable care [37-46]. As pharmacogenomic techniques become more widely used in clinical practice, the Duffy system could serve as a model for integrating ancestry-informed prescribing [47].

Future directions

Duffy system in cancer biology and metastasis

ACKR1's ability to bind angiogenic chemokines has led to a relationship with tumor biology in addition to its role in neutrophil control. Loss of ACKR1 expression has been linked to increased tumor angiogenesis and metastasis in a variety of cancers, including prostate, breast, and colorectal carcinoma. The potential therapeutic benefits of modifying ACKR1 function in malignancy are an interesting area for further investigation [48-50].

Proposed mechanisms linking ACKR1 to metastasis

ACKR1 (formerly DARC) plays a crucial role in cancer biology by influencing tumor metastasis through chemokine sequestration and modulation of the tumor microenvironment. It acts as a decoy chemokine receptor, binding proinflammatory chemokines like CCL2 and CXCL8, thus reducing their availability. Higher ACKR1 expression in tumors has been linked to decreased angiogenesis and metastatic potential, as it lowers chemokine levels, microvessel density, and matrix metalloproteinase expression. Notably, low ACKR1 levels in breast cancer correlate with increased metastasis and poor survival, indicating that effective chemokine scavenging by ACKR1 may inhibit tumor migration and invasion [51].

Transplantation Immunology

Emerging research suggests that Duffy status may influence solid organ transplant outcomes. Some studies have found greater rates of acute rejection in Duffy-negative kidney transplant recipients, which could be attributed to altered inflammatory responses to ischemia-reperfusion injury. More research is required to explain these associations and determine their clinical relevance [52].

Magnitude of rejection risk increase in transplantation

ACKR1's role in transplant outcomes is nuanced, primarily involving leukocyte recruitment during acute renal transplant rejection. Increased ACKR1 expression in endothelial cells correlates with the presence of CCR5-positive leukocytes, indicating a potential role in inflammation post-graft damage. Though clinical assessments of DARC's impact on rejection risk are scarce, registry data suggest that variations in DARC/ACKR1 could affect delayed graft function and antibody-mediated responses [53-62]. Duffy phenotypes are linked to delayed graft function and allograft failure, with differing opinions on the detrimental effects of ACKR1-positive versus negative status [52].

Inflammatory and immune disorders

ACKR1's immunomodulatory action may contribute to autoimmune and chronic inflammatory diseases. Documented associations between Duffy status and conditions like asthma, rheumatoid arthritis, and HIV progression show inconsistent results in research. Further understanding these interactions could illuminate disease mechanisms and reveal new treatment targets [63-65].

Global health perspectives implementation challenges

(a) Cost and Accessibility of Duffy Genotyping in Resource-Limited Settings

Duffy (ACKR1) genotyping identifies the rs2814778 promoter variant linked to the Duffy-null phenotype and is not widely available in lower-resource health systems, often limited to specialized labs. Commercial testing for the Duffy antigen or genotype is significantly cheaper than invasive procedures like bone marrow biopsy, potentially lowering health expenditures by eliminating unnecessary biopsies when benign ethnic neutropenia (BEN) is suspected [66]. Accessibility to molecular genotyping in Africa, the Middle East, and other low- and middle-income regions is limited due to the need for trained personnel and necessary equipment, which are often unavailable. In these regions, serologic Duffy antigen phenotyping may be utilized as a simpler alternative, as the lack of the Duffy antigen

is strongly associated with the null genotype, aiding in the diagnosis of BEN without extensive molecular testing [67]. Resource constraints therefore mean that Duffy testing is available but not uniformly accessible, and its implementation depends on laboratory capacity. In settings where genotyping is unavailable, establishing context-specific reference ranges and clinical judgment may remain the primary diagnostic tools [17].

(b) Strategies for Updating Laboratory Reference Ranges Internationally

A major factor in misdiagnosis and inappropriate intervention for neutropenia is the reliance on ANC reference ranges primarily from White populations, which do not accurately reflect neutrophil counts in those with the Duffy-null phenotype or in areas with prevalent BEN. Research indicates that the lower limit of ANC in healthy Arab adults often falls below the standard cutoff of 1.5 $\times 10^9$/L without adverse clinical effects, suggesting the need for local or genotype-specific reference ranges instead of universal thresholds [68].

To update laboratory reference ranges internationally, several strategies have been proposed:

1- Genotype-specific reference intervals: Recent work has focused on stratifying ANC by Duffy genotype to establish normal ANC distributions for Duffy-null individuals rather than relying on ethnic or racial labels.
2- Population-specific data collection: Large laboratory datasets from diverse global populations can be analyzed to define normal ANC percentiles that reflect true biological variation rather than imported thresholds.
3- Clinical consensus and guideline revision: Hematology societies and laboratory standard-setting bodies should integrate genetic variation into guidelines, replacing the inappropriate application of a single normal range for all individuals.

Updating reference ranges internationally will require collaboration between laboratories, clinicians, and public-health authorities to ensure reference intervals reflect population diversity and reduce misclassification of healthy individuals as neutropenic [68, 69].

(c) Educational Initiatives for Health-Care Providers in Diverse Settings

Misinterpretation of neutrophil counts can cause unnecessary investigations, anxiety, and inappropriate treatment changes in individuals with normal counts for their genotype but below conventional thresholds. For instance, Black patients may face unnecessary bone marrow biopsies due to low absolute neutrophil counts caused by the Duffy-null genotype, which prompts standard neutropenia evaluations.

To address this, and improve Sustainable Development Goal (SDG 4 Good Education) educational initiatives should emphasize:

1- Understanding genetic determinants of hematologic variation: Providers should be taught about the molecular basis of BEN, the Duffy-null phenotype, and the implications for neutrophil counts.
2- Interpreting laboratory results in context: Clinicians and laboratorians need training on when conventional ANC reference ranges may be inappropriate and how to use genotype-aware or population-specific values.
3- Avoiding racial assumptions: Education must stress that race is a social construct and should not substitute for genetic or clinical evidence when interpreting lab tests.

Educational outreach can be accomplished through:

1- Continuing medical education (CME) modules on ANC interpretation
2- Integration of hematology genetics into medical curricula
3- Targeted workshops in regions with high BEN prevalence
4- Decision aids embedded in electronic health records that flag Duffy status when available [66, 70].

(d) Policy Recommendations for Health Systems

To reduce inequities and improve care, health systems and promote the Sustainable Development Goal (SDG 3 Good Health and Well-being) should consider the following policy actions, grounded in evidence and expert consensus:

1- Adopt genotype-informed diagnostic frameworks: Policies should encourage the use of Duffy genotyping or phenotyping when evaluating neutropenia, especially in populations with high prevalence, to avoid unnecessary invasive diagnostics and inappropriate treatment exclusions.
2- Revise laboratory reference standards: National and international bodies (e.g., IFCC, WHO, national ministries of health) should work to define genotype-specific reference ranges for ANC and other hematologic parameters rather than one range for all.
3- Ensure equitable clinical trial eligibility: Clinical trial guidelines should be updated to incorporate genotype-adjusted neutrophil thresholds so that individuals with the Duffy-null phenotype are not excluded from potentially beneficial treatments. This need has been highlighted by recent research showing that strict ANC cutoffs lead to disproportionate exclusion of African and Middle Eastern individuals in cancer trials.
4- Support capacity building in genomics: Health systems should invest in genomic infrastructure, including laboratory personnel training and affordable access to genotyping technologies, to improve early and accurate diagnosis of benign genetic traits like BEN.
5- Monitor health inequities systematically: Health systems should collect data on diagnostic workups and outcomes stratified by genotype to identify disparities in care and inform continuous improvement [69].

Specific future research questions to be addressed

Current research points to several important open questions that should be priorities for future investigation:

1- Mechanistic Dissection of Chemokine Modulation: How exactly does ACKR1 binding of chemokines in specific tumor microenvironments affect downstream signaling through conventional GPCR chemokine receptors on tumor and immune cells? Can we define the structural and quantitative basis of chemokine sequestration versus presentation *in vivo*?
2- Population Bias and Disease Risk: Does Duffy-null status influence cancer incidence or progression across diverse populations independent of other risk factors, and how does that intersect with inflamm-aging and immunosenescence?
3- Transplant Immunobiology: What is the precise impact of donor and recipient DARC/ACKR1 status on graft survival, acute and chronic rejection rates, and long-term outcomes?
4- Therapeutic Targeting: Can ACKR1 be modulated pharmacologically (e.g., agonists enhancing chemokine clearance) to reduce metastasis, chronic inflammation, or adverse graft outcomes?
5- Biomarker Development: What role might ACKR1 expression patterns play in predicting patient responses to immunotherapy or chemo-/radiotherapy across cancer types?

These questions span molecular mechanisms, clinical associations, and interventional science and will clarify the multifaceted roles of ACKR1 beyond its classical blood-group function [71].

Ongoing clinical trials

Current research indicates that there are few or no clinical trials focusing on ACKR1/DARC as a primary target, unlike other chemokine receptors such as CXCR4 or CCR5. Nevertheless, literature suggests potential therapeutic applications of modulating ACKR1 interactions, such as using ACKR1 agonists to inhibit angiogenesis and metastasis in cancer. Additionally, there is a growing interest in developing ACKR1-based therapies for inflammatory diseases and hematopoiesis, which may lead to targeted clinical studies in the future [72].

Conclusion

The Duffy blood group system shows the intricate interplay of human genetics, infectious illness pressure, and physiological regulation. The relationship between the Duffy null phenotype and benign ethnic neutropenia exemplifies how neutral evolutionary adaptations can have important clinical implications in modern healthcare settings.

Key findings from this comprehensive analysis include:

1- The Duffy-negative phenotype is caused by a promoter polymorphism that suppresses erythroid production while maintaining ACKR1 activity in other tissues.
2- Recognizing BEN, a common physiological variation, can help prevent misdiagnosis and unneeded procedures.
3- BEN's pathophysiology presumably involves disrupting chemokine homeostasis and altering neutrophil dynamics.
4- To achieve equitable care, clinical management of neutrophil monitoring circumstances, such as clozapine medication and cancer chemotherapy, should take BEN into consideration.
5- A new study reveals ACKR1 has a larger role in cancer biology, transplantation, and inflammatory illnesses.

Future research should focus on the molecular mechanisms connecting ACKR1 deficiency to neutrophil homeostasis, develop clinical guidelines considering ethnic variability in hematological parameters, and explore the therapeutic possibilities of modulating ACKR1 function in different diseases. Understanding the impact of common genetic polymorphisms like the Duffy null polymorphism is vital for delivering equitable and effective healthcare to diverse patient groups as medicine advances toward greater individualization.

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