Impact of FCGR3A V158F Polymorphism on Rituximab Efficacy: A Targeted Literature Review

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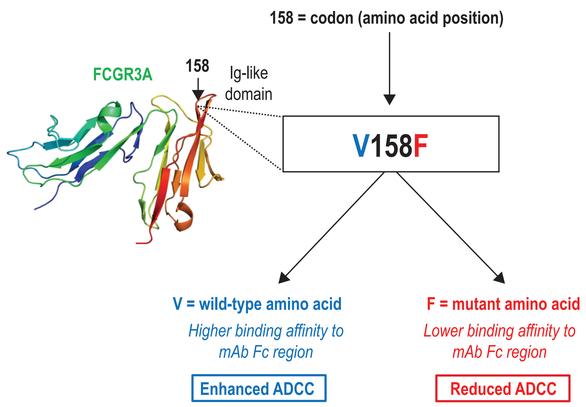
INTRODUCTION

- Rituximab is a chimeric monoclonal antibody that depletes CD20-expressing B-cells and is widely used in the treatment of B-cell-mediated autoimmune diseases and lymphomas, primarily through antibody-dependent cellular cytotoxicity (ADCC).[1]
- Rituximab is often used as an off-label therapy in the treatment of neuromyelitis optica spectrum disorder (NMOSD).
- Low-affinity immunoglobulin gamma Fc receptor IIIA (FCGR3A), a receptor expressed on immune cells such as natural killer (NK) cells, binds the Fc region of immunoglobulin G (IgG), leading to effector cell activation and ADCC.[2]
- The FCGR3A V158F genetic polymorphism affects IgG binding affinity[3] (**Figure 1**).
  - F/F genotype (low affinity): NK cells bind antibodies less effectively, resulting in reduced ADCC and weaker B-cell depletion.
  - V/F genotype (intermediate affinity): associated with a moderate ADCC response.
  - V/V genotype (high affinity): NK cells bind antibodies strongly, resulting in a robust ADCC response.
- To date, there is a lack of comprehensive evidence synthesis on the prevalence of FCGR3A polymorphisms and their impact on rituximab effectiveness.

Figure 1. FCGR3A V158F Genotypes and Their Impact on IgG Fc Binding and ADCC



Adapted from Kremer and Barb 2022.[3]
ADCC, antibody-dependent cell cytotoxicity; F, phenylalanine; FCGR3A, low affinity immunoglobulin gamma Fc receptor IIIA; IgG, immunoglobulin G; mAb, monoclonal antibody; V, valine.

OBJECTIVES

- To summarize and assess the evidence on the epidemiology of the FCGR3A V158F polymorphism and its relationship to rituximab effectiveness.

METHODS

- A targeted literature review was conducted through to August 2025 via PubMed, Google Scholar, and internet searches, with broad search terms including "FCGR3A V158F polymorphism" and related alternative terms (e.g., V158F FCGR3A gene polymorphism, V158F CD16 gene polymorphism, FCGR3A-V158F genotype, FCGR3A gene sequencing) to identify a comprehensive evidence base.
- Supplementary searches included structured large language model-assisted searches and hand searches of clinical trial registries, clinical guidelines, and health technology assessment submissions.
- Evidence across populations, diseases, and study designs was included to characterize the prevalence of FCGR3A V158F polymorphism (F/F, V/F, or V/V) and genotype-specific rituximab outcomes (**Table 1**).

Table 1. PICOS Eligibility Criteria for Study Selection

Description	Inclusion criteria
Population	Any
Intervention	• FCGR3A V158F prevalence: any • Association between FCGR3A V158F polymorphism and rituximab effectiveness: rituximab
Comparison	Any
Outcome	Any
Study design	• Randomized controlled trials, single-arm trials • Observational and real-world studies • Case series, case reports

FCGR3A, low affinity immunoglobulin gamma Fc receptor IIIA; PICOS, population, intervention, comparison, outcome, study design.

RESULTS

- A total of 60 publications met the study selection criteria (see Supplement for full reference list), including 8 intervention studies,[4-11] 35 observational studies,[12-46] 4 preclinical studies,[47-50] 1 case study,[51] and 12 reviews and meta-analyses.[52-63]
- Among the 8 intervention trials, 5 were from European countries and 3 were multinational, with sample sizes ranging from 49 to 1418.
- Observational studies were conducted in Africa (4), Asia (8), Europe (13), North America (6), and South America (2), and 2 were multinational. They included between 15 and 32,758 patients.
- Evidence was identified across therapy areas: 19 studies in patients with cancer, 15 studies in autoimmune diseases not including NMOSD, 6 in NMOSD, and 20 in other populations including transplant recipients, those with COVID-19, and healthy volunteers.
- Twenty-six studies investigated the FCGR3A V158F genotype and its association with rituximab efficacy: 11 studies in patients with cancer, 7 in autoimmune diseases, 4 in NMOSD, and 4 in other populations including transplant recipients and healthy volunteers.

Prevalence

- The prevalence of the FCGR3A 158 F/F genotype varied across interventional studies from 19% to 48%,[4-10] with a median estimate of 39% (**Table 2**).
- Observational studies reported a wider range in F/F genotype prevalence varying from 1% to 90%, with a median estimate of 39%.
- Across 11 studies reporting genotype distribution in the general population or control groups, the median prevalence was highest for V/F (48%, range 20%–93%), followed by F/F (39%, range 5%–75%), and V/V (15%, range 3%–25%).
- Six studies in patients with cancer found the prevalence of F allele carriers (F/F and V/F) ranged from 53% to 85%,[12,14-16,28,45] and 8 studies in autoimmune diseases found a prevalence of between 30% and 97%.[17,26-27,35-36,39,41,43]
- In patients with NMOSD, the prevalence of F allele carriers ranged from 65% to 92% across 4 studies (**Figure 2**).[18,29,34,48] The prevalence of F allele carriers was found to be higher in Asian populations compared with other groups.

Association with outcomes in cancer

- Eight studies in patients with cancer reported inferior outcomes with rituximab among those who had the FCGR3A 158 F/F or V/F genotypes compared with those who had the V/V genotype.[4,6-7,9,14,28,45-46] Three studies reported no association.[5,10,15]
  - In patients with non-Hodgkin lymphoma, the objective response rate with rituximab was lower in F carriers (51%) than in patients who had the V/V genotype (90%).[6] Similar findings were reported in follicular lymphoma (FL) (F/F 30% vs V/V 75%).[46]
  - Overall survival (OS) was lower in patients who had the F/F genotype compared with those who had the V/V genotype (OS at 2 years in diffuse large B-cell lymphoma [DLBCL]: 63% vs 100%, OS at 5 years in FL: 75% vs 100%).[9,14]
  - Event-free survival (EFS) and progression-free survival (PFS) at 3 years were also lower in patients with DLBCL who had the F/F genotype versus those who had the V/V genotype (EFS: 65% vs 77%; PFS: 68% vs 81%).[4]

Association with outcomes in autoimmune diseases

- In patients with autoimmune diseases, meta-analyses[54-55] demonstrated statistically significantly higher odds of response to rituximab among patients with FCGR3A 158 V/V and V/F genotypes compared with F/F.

Association with outcomes in NMOSD

- In patients with NMOSD, 3 observational studies[18,29,34] reported that FCGR3A 158 F carriers (V/F or F/F) were associated with higher relapse risk, more frequent rituximab dosing, and greater treatment discontinuation compared with V carriers (**Table 3**).

Table 2. Prevalence of the V158F FCGR3A F/F Genotype in Interventional Studies

Reference, year	Disease	Country	Study name (design)	N	F/F genotype (%)
Strefford, 2021[10]	FL, DLBCL	Multinational	GALLIUM (RCT) GOYA (RCT)	1202 1418	42 45
Ahlgrimm, 2011[4]	DLBCL	Germany	RICOVER-60 (RCT)	512	19
Ghielmini, 2005[7]	FL, mantle cell lymphoma	Switzerland	Not reported (RCT)	273	38
Kim, 2023[8]	NMOSD	Multinational	N-MOmentum (RCT)	142	48
Persky, 2012[9]	FL	Multinational	SWOG (RCT)	142	40
Burkhardt, 2016[5]	B-NHL (children)	Germany	Not reported (SAT)	105	35
Cartron, 2002[6]	FL	France	Not reported (SAT)	49	35

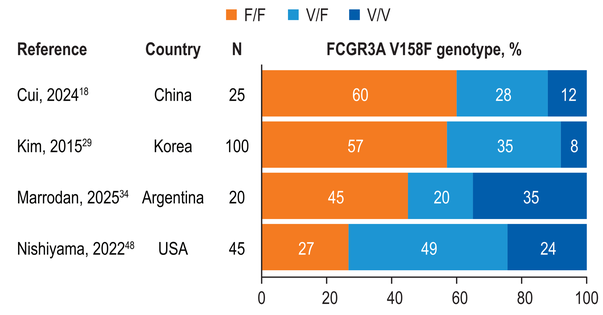
B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FCGR3A, low affinity immunoglobulin gamma Fc receptor IIIA; F, phenylalanine; FL, follicular lymphoma; NMOSD, neuromyelitis optica spectrum disorder; RCT, randomized controlled trial; SAT, single-arm trial.

Table 3. Outcomes with Rituximab by FCGR3A V158F Genotype in Patients with NMOSD

Reference	Country	N	Population	Rituximab dosing	Genotype	Key outcomes
Kim, 2015[29]	Korea	100	Relapsing NMOSD	For at least 6 months (dose not reported)	F/F vs V/V	F/F associated with higher risk of relapse (Cochran-Armitage trend test with additive model, $P < 0.05$; shorter time to retreatment [NS])
Marrodan, 2025[34]	Argentina	20	NMOSD (AQP4+)	Dose and duration not reported	V/V	Treatment failure: 4/9 (44.4%)
					F/F	Treatment failure: 3/9 (33.3%)
					V/F	Treatment failure: 2/9 (22.2%)
Cui, 2024[18]	China	16	NMOSD (AQP4±)	Induction: 375 mg/m^2 Q4W or 1000 mg bi-weekly	V/V or V/F	Relapse: 2/10 (20%) Time to first relapse: 16.5 months Dose adjustments: 4/20 (20%)
				Low-dosage induction: varied dosing	F/F	Relapse rate post RTX: 9/15 (60%); log-rank test F/F vs V/V or V/F, $P < 0.05$ Time to first relapse: 6.1 months; log-rank test, $P < 0.05$ Dose adjustments: 11/15 (73%); $P < 0.05$

Statistical significance was evaluated using a log-rank test stratified by different FCGR3A V158F genotypes (F/F vs V/V or V/F).
AQP4, Aquaporin-4; F, phenylalanine; FCGR3A, low affinity immunoglobulin gamma Fc receptor IIIA; NMOSD, neuromyelitis optica spectrum disorder; NS, not significant; Q4W, every 4 weeks; RTX, rituximab; V, valine.

Figure 2. Distribution of FCGR3A V158F Genotypes in Observational Studies of NMOSD



F, phenylalanine; FCGR3A, low affinity immunoglobulin gamma Fc receptor IIIA; NMOSD, neuromyelitis optica spectrum disorder; V, valine.

- Data from these studies suggest 2- to 5-fold higher odds of relapse for F/F versus V/V carriers.
- An additional case study described a patient with the F/F genotype who experienced 6 relapses within 2 years.[51] The patient received rituximab, oral steroids, mycophenolate mofetil, and tacrolimus, and was diagnosed as a rituximab non-responder.

LIMITATIONS

- The evidence base is heterogeneous, with included studies varying widely in disease types, study designs, rituximab regimens, and outcome definitions, which limits the ability to draw firm conclusions across indications.
- Findings specific to NMOSD are derived from a small number of observational studies, and should be considered hypothesis-generating rather than definitive.

CONCLUSIONS

- Across cancers and autoimmune diseases, the FCGR3A 158 F/F genotype is generally associated with reduced rituximab effectiveness, consistent with variability in Fc receptor-mediated mechanisms of B-cell depletion.
- In NMOSD, observational studies suggest that rituximab effectiveness may be reduced in patients who carry the FCGR3A 158 F/F genotype compared with those who are V allele carriers.
- In NMOSD, where relapses can result in severe and irreversible neurological disability, reduced treatment effectiveness may have important clinical consequences.
  - Based on the literature, it can be inferred that B-cell-depleting therapies whose efficacy is not influenced by FCGR3A genotype may offer more consistent pharmacodynamic effects.
  - These findings raise the possibility that strategies to enhance or bypass FCGR3A-mediated ADCC, including Fc glycoengineering approaches, may be relevant, but require direct evaluation in NMOSD.
- Improved understanding of FCGR3A polymorphisms may support more personalized treatment approaches and improved outcomes in patients treated with rituximab.

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3. Kremer PG and Barb AW. *J Biol Chem* 2022;298:102329.
4–63. The full reference list is provided in the Supplement via the QR code.

DISCLOSURES

SHu and HJK declare that this research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.
MD and SHo are employees of Oxford PharmaGenesis.
JS, DC, TAdM, MS, and IMM are employees of Amgen.

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