C3 glomerulopathy

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Objectives

- Definition
- Incidence
- Clinical presentation
- Complement system
- Role of the complement system
- Evaluation
- Treatment
- C3 GN and transplantation
- Predictors of renal outcome

Received: 4 February 2022 | Revised: 27 April 2022 | Accepted: 10 June 2022

DOI: 10.1002/ajmg.c.31986

AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics

WILEY

REVIEW ARTICLE

C3 glomerulopathy: Understanding an ultra-rare complement-mediated renal disease

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HEIDERSCHEIT ET AL, Am J Med Genet. 2022;190C:344–357

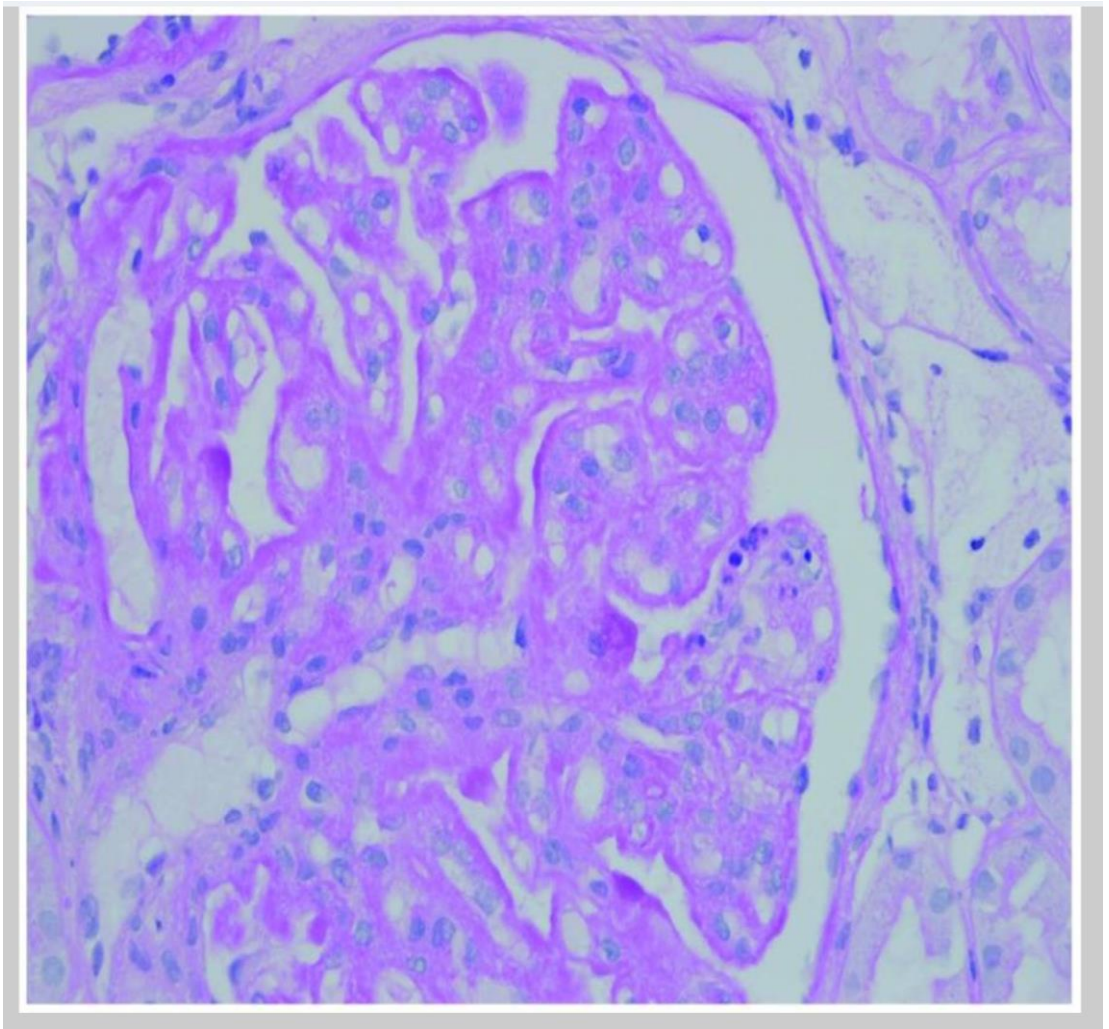
Definition

- C3 glomerulopathy (C3G) describes a pathologic pattern of injury.
- dominant deposition of (C3) in the renal glomerulus.

- The underlying pathophysiology is driven by dysregulation of the alternative pathway of complement in the **fluid phase** and in the **glomerular microenvironment.**

- Absence or near-absence of other immune reactants.

- Am J Med Genet. 2022;190C:344–357



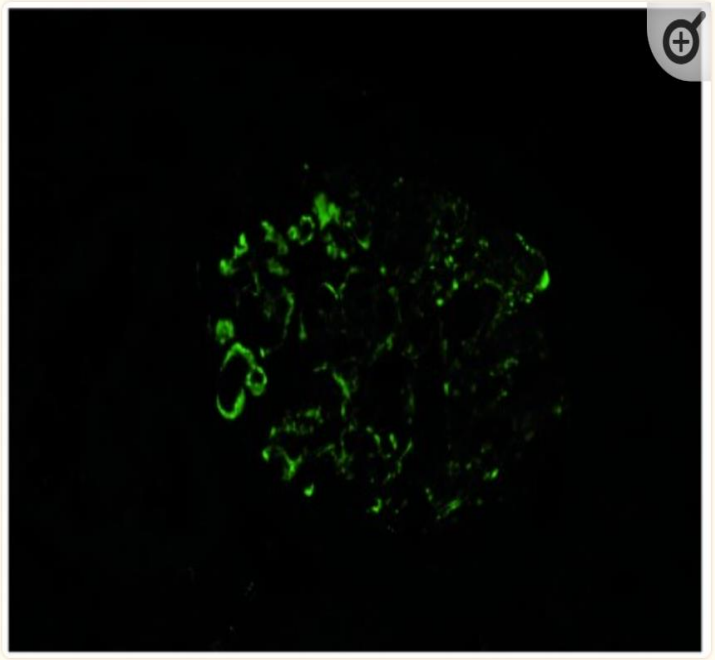


Figure 1.

C3 staining in C3 glomerulopathy.

Glomerulus showing staining for C3 in a case of C3 glomerulopathy. The kidney is stained with a fluorescently labelled antibody to C3.

- Adding an **electron microscopic evaluation** to IF facilitates the recognition of two subgroups of C3Glomerulopathy:
- Dense deposit disease (DDD)
- C3 glomerulonephritis (C3GN)

- Each subgroup is defined by the specific **localization pattern** and **characteristics of deposits** within renal tissue.

Am J Med Genet. 2022;190C:344–357

Electron Micrograph

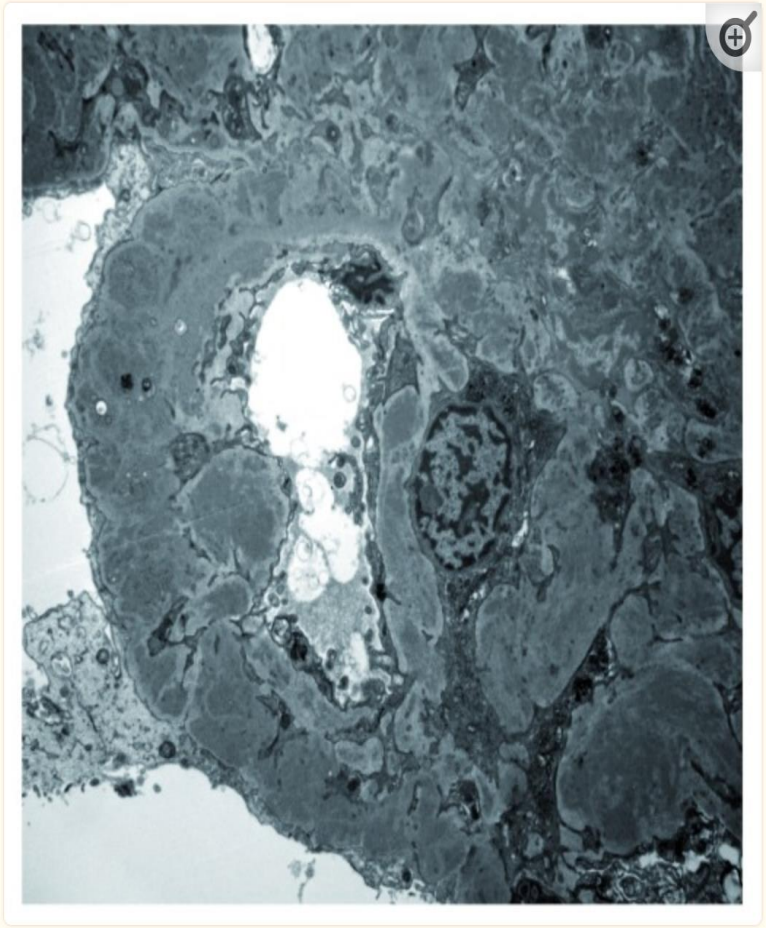


Figure 3.

Electron micrograph showing multiple electron-dense deposits in the mesangium and capillary wall of a glomerulus in a case of C3 glomerulonephritis.

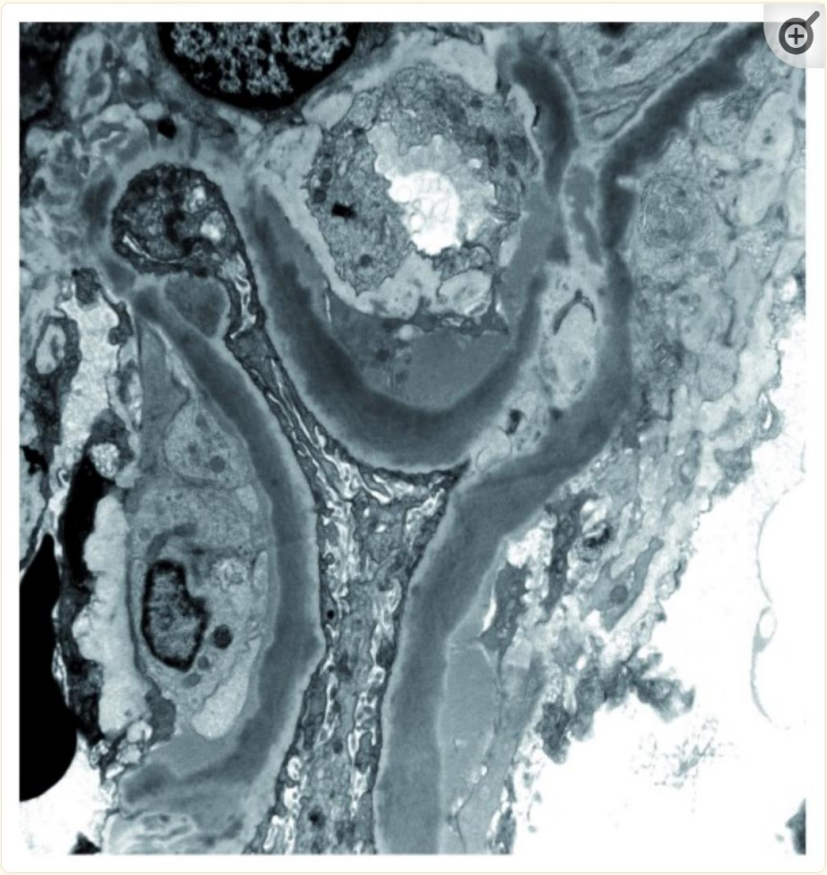


Figure 2.

Electron micrograph showing dense transformation of the glomerular basement membrane in a case of dense deposit disease.

Incidence

- . In the United States, the incidence of C3 glomerulopathy is estimated to be between ~1 case per 1,000,000 and ~2–3 cases per 1,000,000 based on an analysis of C3 glomerulopathy registry data (49 cases per year over the past 3 years).

- Data derived from four European studies provide estimates of ~0.2–1.0 cases per 1,000,000 of the population.

- **Smith et al.**Nat Rev Nephrol. 2019 March ; 15(3): 129–143.

Disease presentation

- C3G presents as glomerulonephritis (**GN**).
- The classical constellation of signs and symptoms, includes hematuria, proteinuria, edema, and often hypertension.
- In most patients, serum C3 levels are also low.
- The differential diagnosis for GN is broad and if symptoms persist and C3 levels remain low for more than 3 months, a renal biopsy is warranted. [1]
- Patients often have a **history of haematuria and hypertension**, which can be severe and might be an associated **history** of (AKI) and/or (CKD). [2]

- 1.HEIDERSCHEIT ET AL, Am J Med Genet. 2022;190C:344–357
- **2. Smith et al.**Nat Rev Nephrol. 2019 March ; 15(3): 129–143

- The average age at diagnosis of C3G is 21 years, however stratifying by subgroups, **age at diagnosis is higher in C3GN** than in **DDD** (about 30 and 19 years old, respectively).[1]

- C3G is also associated with the development of **drusen,** making an **ophthalmologic evaluation** an essential part of a C3G patient's regular care.[2]
- It is the so-called **partial lipodystrophy**, which is characterized by a loss of **adipose tissue, predominantly affecting the upper half of the body (upper extremities and trunk).**

1.(Servais et al., 2012)
.2. Nasr et al., 2009)

- . **Autoantibodies** to the **C3 and C5 convertases** of complement are the **most commonly** detected **drivers of complement dysregulation**.

- **Genetic variation in complement-related genes** is a less frequent cause

- Approximately 30- 50% of the patients progress to end-stage renal disease within 10 years of diagnosis.

- High risk for disease **recurrence(90%)** and **allograft failure.**

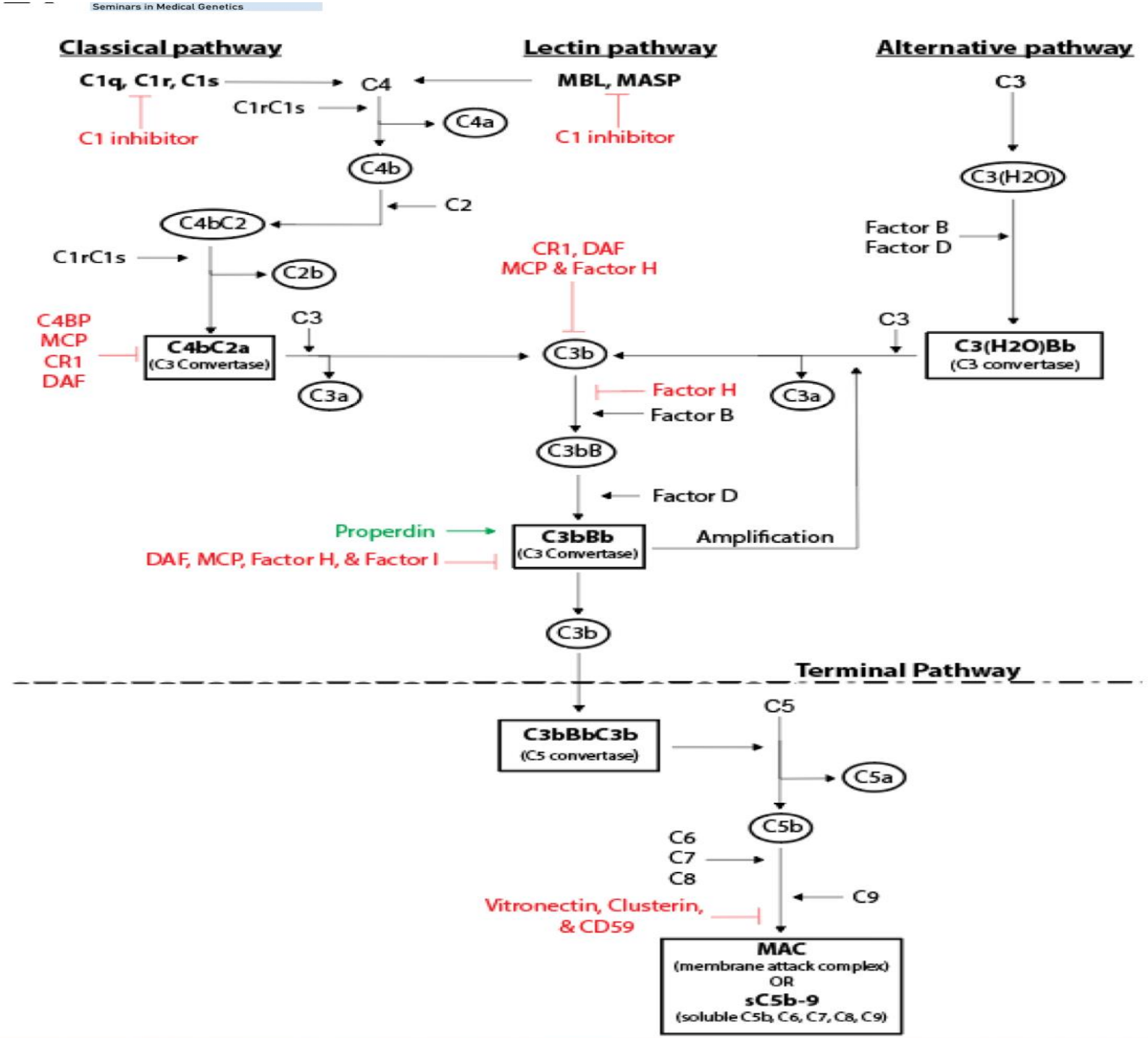
Am J Med Genet. 2022;190C:344–357

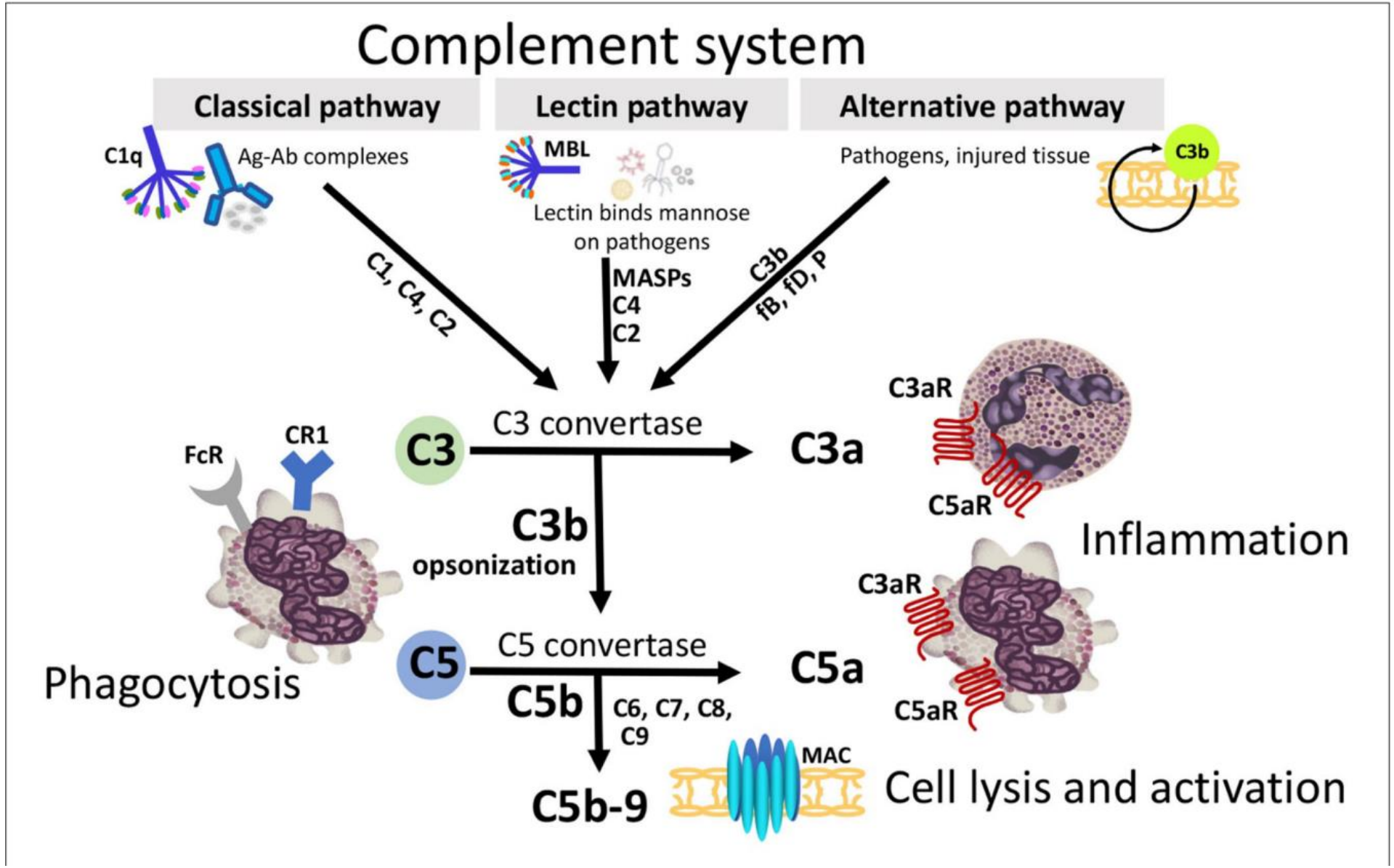
THE COMPLEMENT CASCADE

- The complement system is the cornerstone of innate immunity.
- It is the first line of defense against foreign and altered host cells, leading to the activation of adaptive immunity.

- Activation is facilitated by three different initiating pathways:
- classical pathway (**CP**), lectin pathway (**LP**), and **AP**.

Figure


Seminars in Medical Genetics
Classical pathway
Lectin pathway
Alternative pathway
C1q, C1r, C1s
C4
MBL, MASP
C3
C1rC1s
C4a
C1 inhibitor
C1 inhibitor
C3(H2O)
C4b
C2
C4bC2
Factor B
Factor D
C1rC1s
C2b
CR1, DAF
MCP & Factor H
C4BP
MCP
CR1
DAF
C3
C3
C4bC2a
(C3 Convertase)
C3b
C3(H2O)Bb
(C3 convertase)
C3a
C3a
Factor H
Factor B
C3bB
Factor D
Properdin
C3bBb
(C3 Convertase)
Amplification
DAF, MCP, Factor H, & Factor I
C3b
Terminal Pathway
C5
C3bBbC3b
(C5 convertase)
C5a
C5b
C6
C7
C8
C9
Vitronectin, Clusterin,
& CD59
MAC
(membrane attack complex)
OR
sC5b-9
(soluble C5b, C6, C7, C8, C9)


Complement system
Classical pathway
Lectin pathway
Alternative pathway
C1q
Ag-Ab complexes
MBL
Lectin binds mannose on pathogens
Pathogens, injured tissue
C3b
C1, C4, C2
MASPs
C4
C2
C3b
fB, fD, P
C3
C3 convertase
C3a
C3aR
C5aR
Inflammation
FcR
CR1
C3b
opsonization
C5
C5 convertase
C5a
C5b
C6, C7, C8, C9
C5b-9
MAC
Phagocytosis
Cell lysis and activation

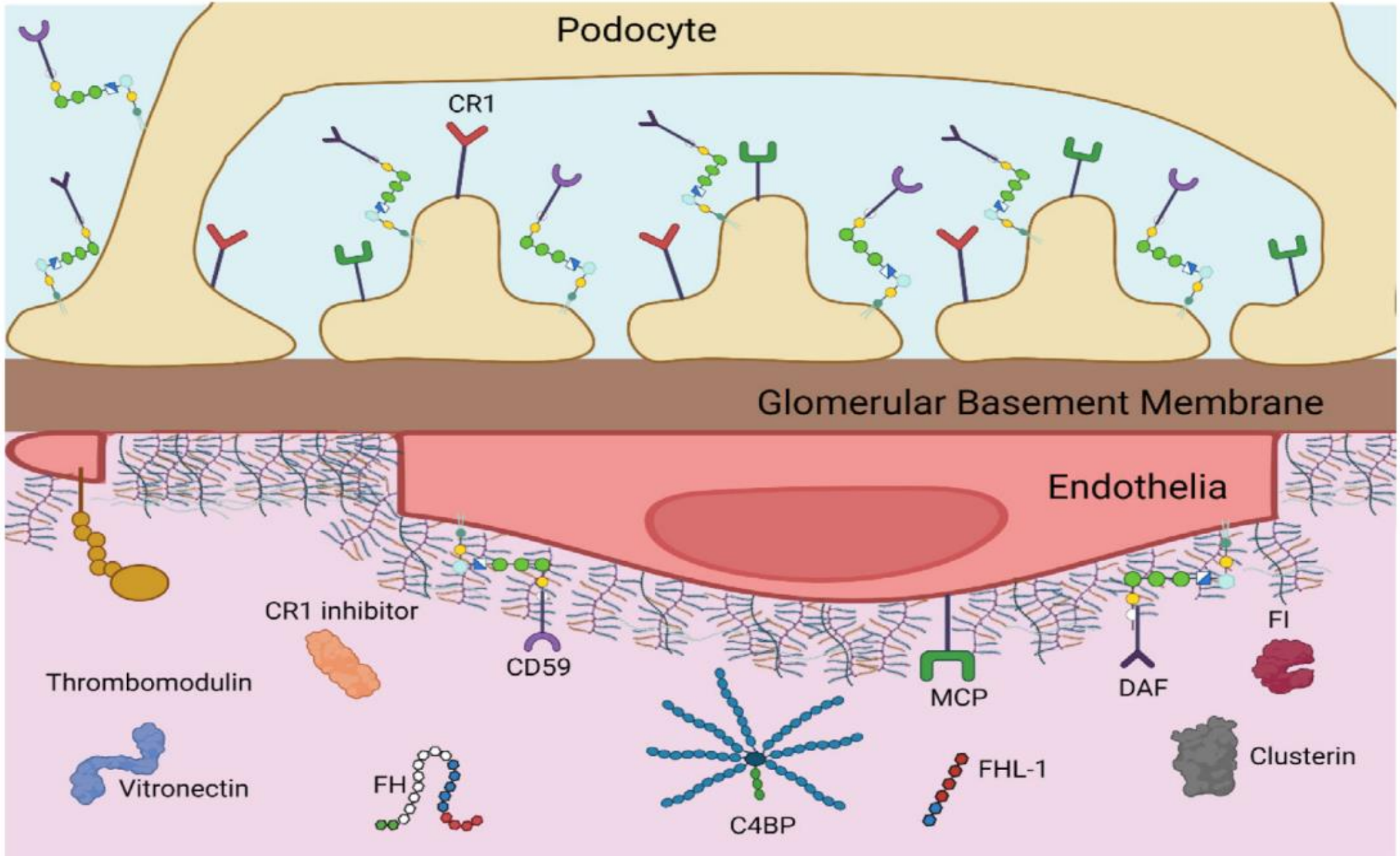
- Complement activity is tightly controlled by numerous proteins known collectively as regulators of complement activity **(RCAs)**, which are present in the:

- **fluid phase**
- **membrane-bound**.

- . ***Fluid phase regulators*** include :
- C4BP, vitronectin (S protein), clusterin, factor I (FI), factor H(FH), and factor H-like 1 (FHL-1).[1]

- **Membrane-bound RCAs**:
- decay accelerating factor **(DAF or CD55**),
- membrane cofactor protein **(MCP or CD46**)
- complement receptor 1 (**CR1 or CD35**)
- Protectin **(CD59)** .[2]

1.Norris & Remuzzi, 2015; Turkmen, Baloglu, & Ozer, 2021),
2.Carroll, 2008; Ricklin et al., 2016; Turkmen et al., 2021)


Podocyte
CR1
Glomerular Basement Membrane
Endothelia
CR1 inhibitor
CD59
Thrombomodulin
MCP
DAF
FI
Vitronectin
FH
C4BP
FHL-1
Clusterin

- **The RCA** that is **most relevant to C3G** is **FH**, *a linear protein* comprised of 20 short consensus repeat (SCR) units each about 60 amino acids in length connected one to another by short linker regions.

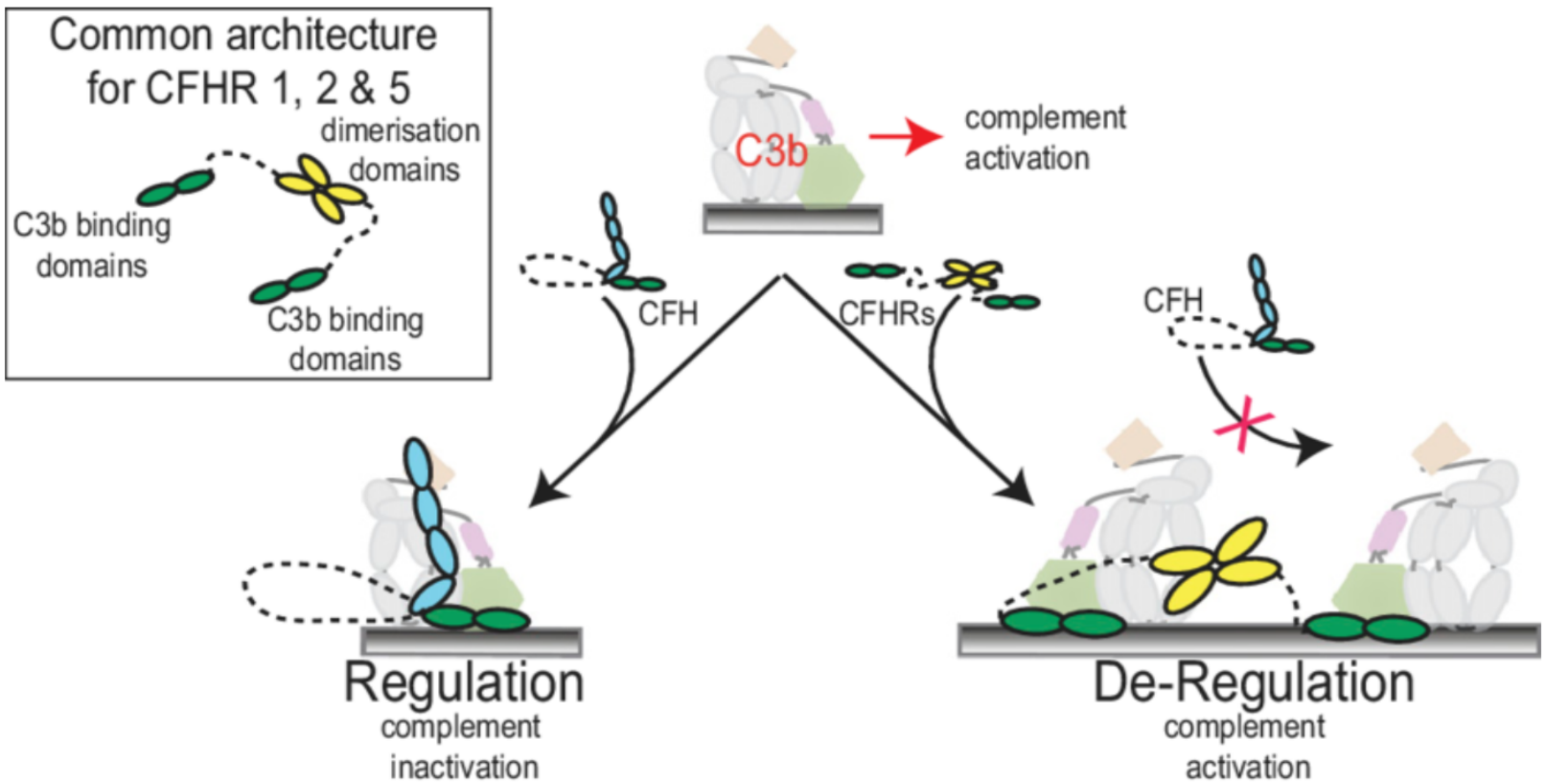
- **The four amino-terminal SCRs of FH can bind to C3b**, enabling FH to regulate complement activity at the level of C3 convertase by three mechanisms:
- (a) cleavage of C3b to inactive C3b (iC3b) through cofactor activity with FI,
- (b) decay accelerating activity (DAA) by sterically displacing Bb from the C3 convertase (C3bBb)
- (c) inhibition of C3 convertase formation by competing with FB for binding with C3b.[1]
-

1.(Reid et al., 1986).

- Type 1 FHRs, in particular FHR1 and FHR5, are prominently found in renal biopsies of C3G patients. [1]

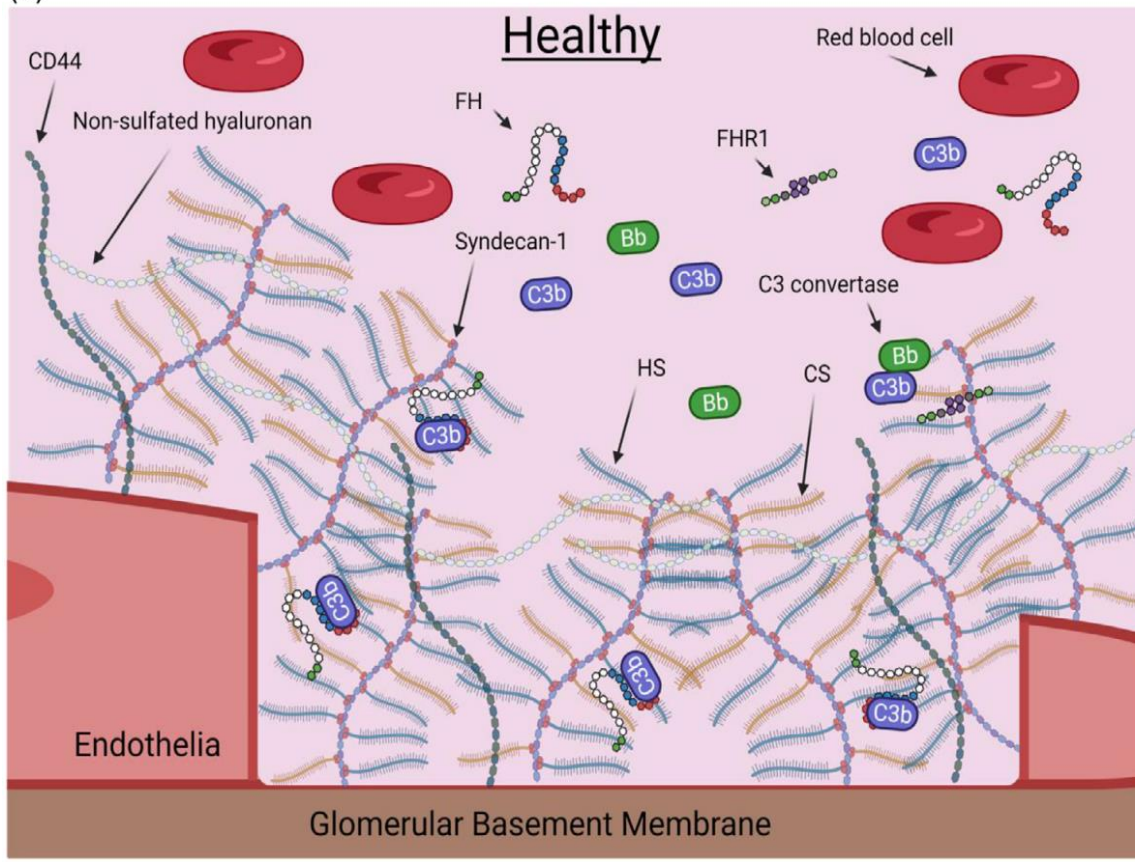
- In addition, pathologic type 1 FHR gene rearrangements that generate novel FHRs proteins are implicated in genetically driven types of C3G.[2]

1.Sethi et al., 2009).
2.(Xiao, Pickering, & Smith, 2014).

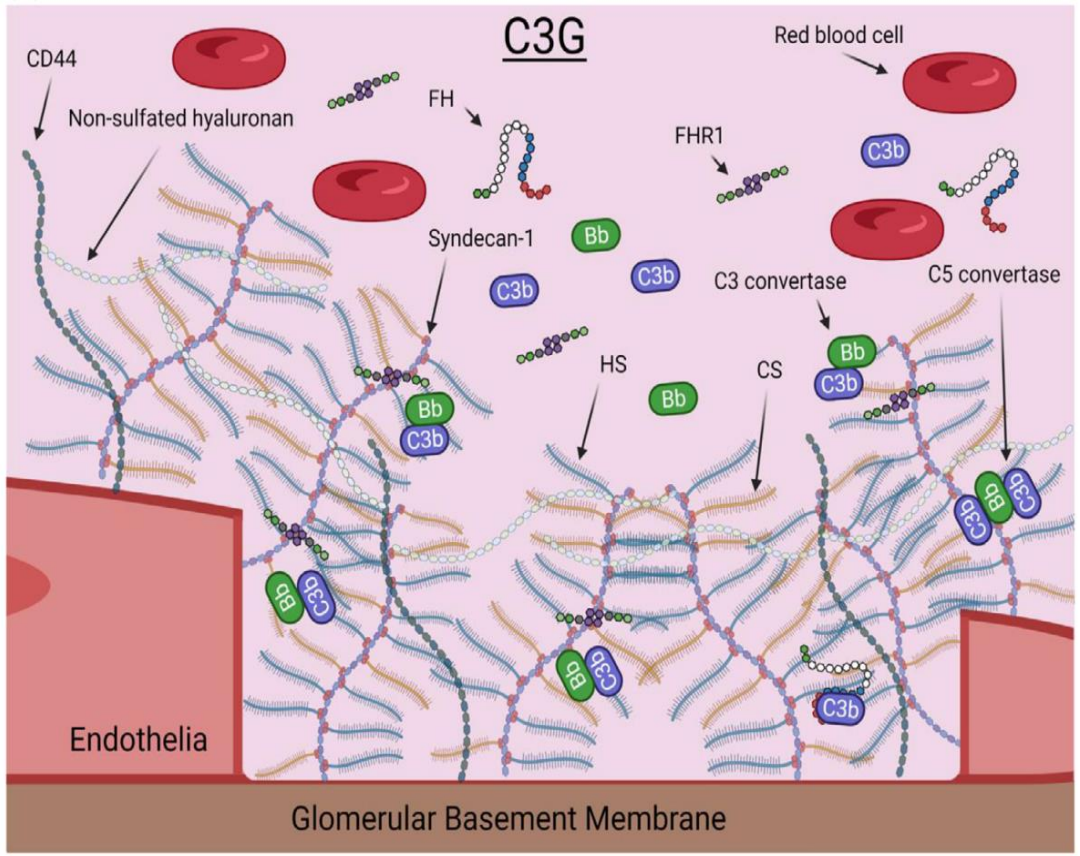


Modulation of complement in vivo by CFHR1, CFHR2, and CFHR5. These proteins compete with CFH for interaction with C3b (18–20). Unlike CFH, these proteins are devoid of intrinsic complement regulatory activity under physiological conditions. However, their interaction with C3b prevents the binding of C3b to CFH and thereby prevents inactivation of C3b by CFH. This process we term deregulation. Whether or not C3b interacts with CFH or components of the CFHR family will be influenced by factors such as C3b density, surface polyanions, and the local concentrations of CFH and CFHR proteins (see text). In this way, CFHR proteins provide a sophisticated means through which complement activation can be modulated in vivo. (Inset) A general schematic for the functionally important portions of CFHR1, CFHR2, and CFHR5.

(a)

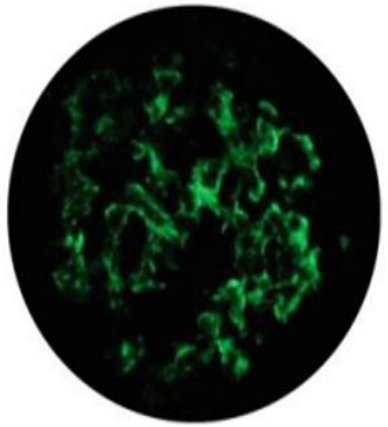

Healthy
CD44
Non-sulfated hyaluronan
FH
FHR1
Red blood cell
C3b
Syndecan-1
Bb
C3b
C3b
C3 convertase
Bb
C3b
HS
Bb
CS
C3b
C3b
C3b
C3b
Endothelia
Glomerular Basement Membrane

(b)


C3G
CD44
Non-sulfated hyaluronan
FH
FHR1
Red blood cell
C3b
Syndecan-1
Bb
C3b
C3b
C3 convertase
C5 convertase
Bb
C3b
HS
Bb
CS
Bb
C3b
Bb
C3b
Bb
C3b
C3b
C3b
Endothelia
Glomerular Basement Membrane

Evaluation

C3 dominant staining

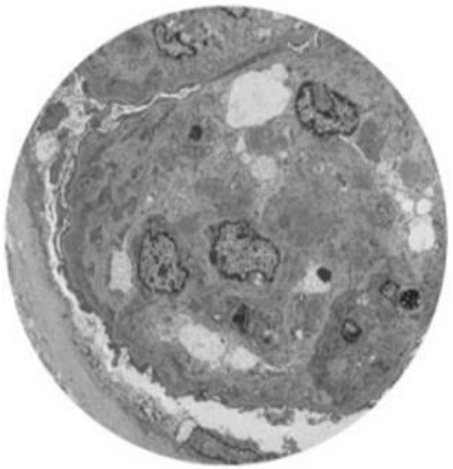


PIGN

- C3 dominant staining is found in ~30% of cases
- Complement abnormalities are typically part of infection recovery
- C3 should normalize after 8-12 weeks

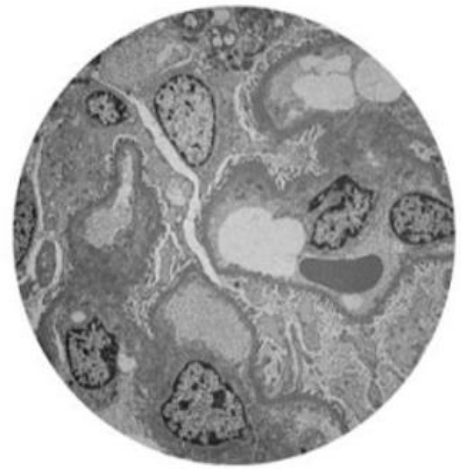
MGRS

- C3 dominant glomerulonephritis is frequently seen in adults age >50 years
- Paraproteins may act as a FH autoantibody or nephritic factor leading to complement dysregulation
- Targeted therapy at paraproteins can improve disease projection



C3G

- C3G is classified by C3 deposition of at least 2 orders of magnitude or more than any other immunoreactant in renal tissue



C3GN

- ~66% of C3G cases are diagnosed as C3GN
- Electron microscopy shows less dense discontinuous, ill-defined intramembranous deposits
- Mass spectrometry shows terminal complement components in deposits

DDD

- ~33% of C3G cases are diagnosed as DDD
- Electron microscopy shows intramembranous electron-dense, sausage shaped deposits in the lamina densa causing thickening of capillary walls
- Mass spectrometry shows complement components in deposits

kidney INTERNATIONAL

VOL 100 | ISSUE 4S | OCTOBER 2021

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group

Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, and CFHR1-5 MLPA
Plasma cell disorders[‡]	Serum free light chains, serum and urine electrophoresis, and immunofixation[†]
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3, negative or minimal Ig, negative C4d)

- Drivers of disease |
  Acquired drivers

- **C3 nephritic factors (C3Nefs) against C3bBb are most common**, and are reported in **50–80% of DDD** patients and **44–50% of C3GN** patients.[1]

- This **convertase in the fluid phase**, typically leading to an associated **reduction in serum levels of C3** with a concomitant **increase in levels** of its **cleavage product, C3c** .[2]

1.Iatropoulos et al., 2016; Servais et al., 2012; Yuzhou Zhang et al., 2012

2.Servais et al., 2012; Xiao et al., 2014.

- **C5 nephritic factors (C5Nefs) are also common**.

- The likelihood of **co-positivity for both C3Nefs and C5Nefs is high**.

- As a general rule, **C5Nefs are more frequently associated with C3GN** than

DDD.[1]

1. Marinozzi et al., 2017

- **Less frequently, C4 nephritic factors (C4Nefs)**, which bind to and stabilize **C4b2a**, are identified.[1]

- In addition to nephritic factors, **autoantibodies against FH and FB** are occasionally detected.[2]

- These autoantibodies **impair FH regulation** and s**tabilize the C3 convertase against FH-mediated decay**, respectively.[3]

1 . Halbwachs, Leveilla, Lesavre, Wattel, & Leibowitch, 1980; McLean & Nilson, 1979).

2.Chiara Marinozzi et al., 2017

3.Blanc et al., 2015; Chen, Muller, Rudolph, et al., 2011; Goodship et al., 2012; Strobel, Zimmering, Papp, Prechl, & Jozsi, 2010).

Genetic drivers

- Approximately **25% of C3G** patients carry **rare variants** or **genomic rearrangements** in complement genes.[1]
- Testing should focus on genes implicated in C3G, which include
- **C3**
- **CFB**
- **CFH**
- **CFI**
- **DGKE**
- **CFHR5**

1.(Servais et al., 2012).

Genetic drivers

- . In addition, the **CFHR genomic region** should be screened for complex rearrangements typically by **multiplex-ligation-dependent probe amplification (MLPA), a multiplex PCR-based method** that can detect the copy number of each CFHR gene.

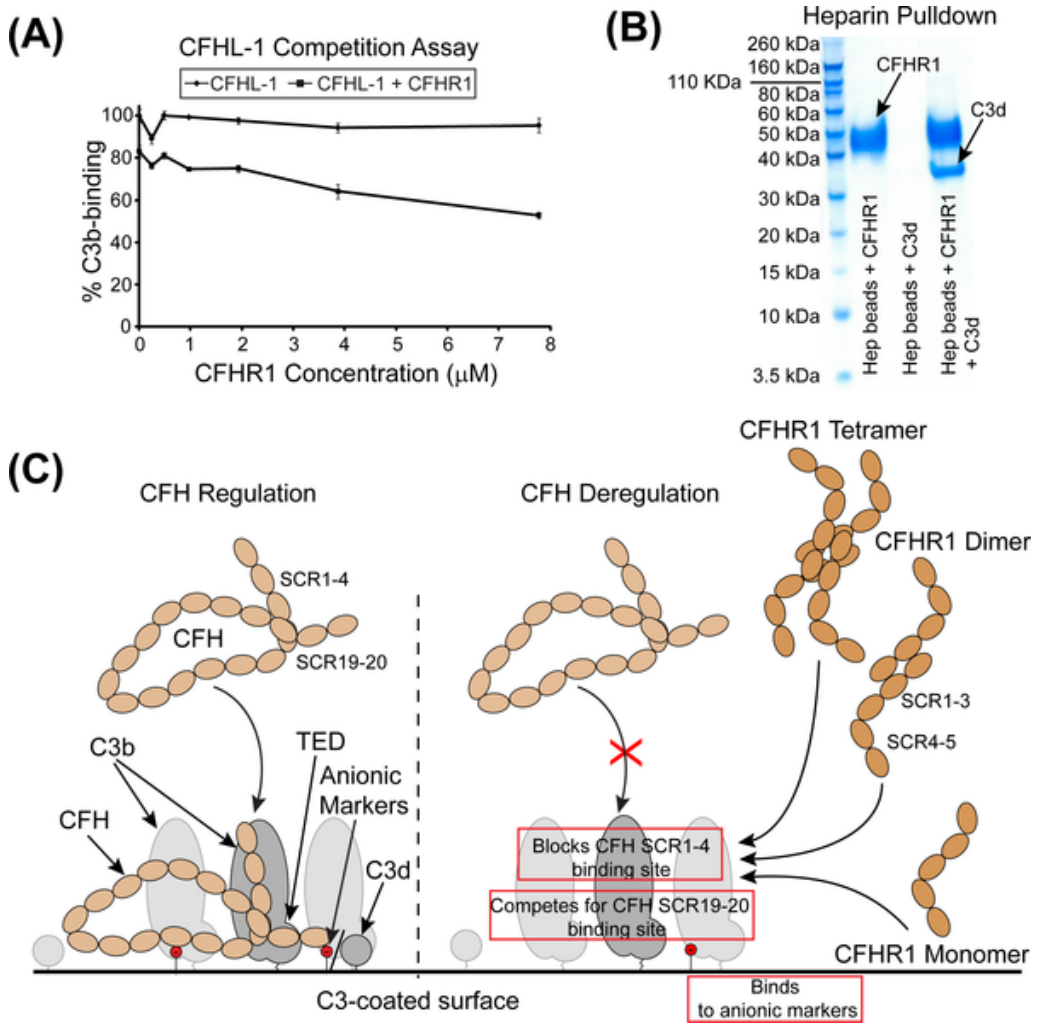
- When **exon-specific probes** are used, CFHR genomic rearrangements such as the CFHR5 fusion gene endemic to Cyprus can be easily identified

- (Gale et al., 2010; Garam et al., 2021; Schouten et al., 2002).

- The **prototypical example** of this process is **CFHR5 nephropathy**, a subtype of C3GN that is endemic to **Cyprus, where it affects 1 in 6,000** persons.

- The mutant protein shows **increased avidity for C3 ligands** and interacts with **surface C3 within glomeruli** more efficiently than FH, thereby promoting complement activation through a gain-of-function mechanism.

Fig 6. CFHR1 blocks other CFH-interaction sites on C3b.



Hannan JP, Laskowski J, Thurman JM, Hageman GS, Holers VM (2016) Mapping the Complement Factor H-Related Protein 1 (CFHR1):C3b/C3d Interactions. PLOS ONE 11(11): e0166200. https://doi.org/10.1371/journal.pone.0166200
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0166200

- The clinical hallmark of this process is **microscopic hematuria, almost always exacerbated by respiratory infections.**

- About **25–50%** **of affected persons report macroscopic hematuria** as well.
- Importantly, there is **generally no evidence of systemic complement dysregulation**; rather, **AP dysregulation** is confined to the **glomerular microenvironment**.

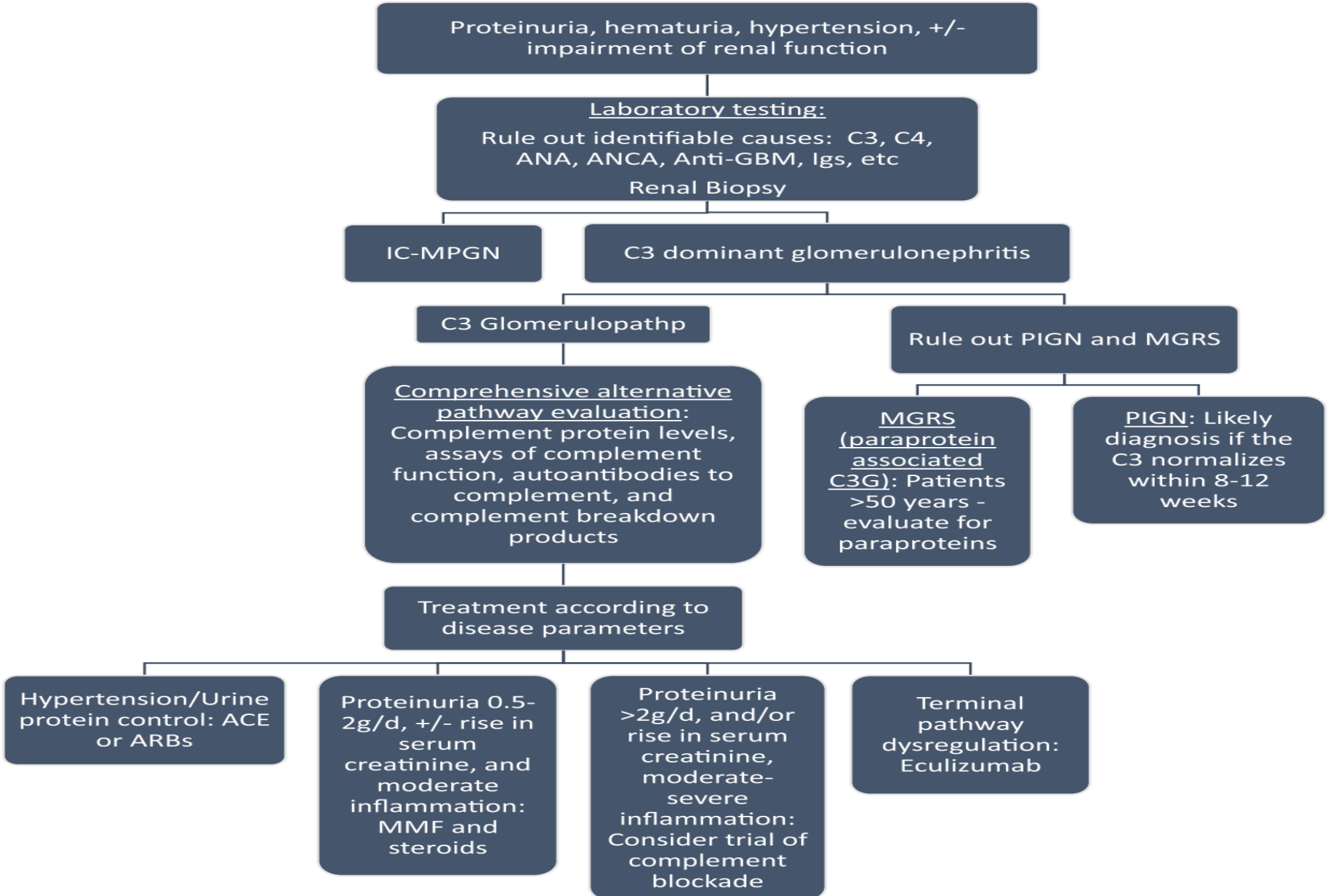
- The eventual outcome is that over **80% of males** **but only a small proportion of females suffer a stepwise deterioration in renal function that leads to ESRD usually between 30 and 70 years of age.**[1]

1.(Gale & Pickering, 2011

PATIENT EVALUATION AND TREATMENT

- There are guideline recommendations to support renal health, most recently those published by the KDIGO Glomerular Diseases Work Group, which reflect the expert opinion and the collective experience derived from a number of clinical case series.[1]

- 1. (Rovin et al., 2021).


Proteinuria, hematuria, hypertension, +/- impairment of renal function
Laboratory testing:
Rule out identifiable causes: C3, C4, ANA, ANCA, Anti-GBM, Igs, etc
Renal Biopsy
IC-MPGN
C3 dominant glomerulonephritis
C3 Glomerulopathp
Rule out PIGN and MGRS
Comprehensive alternative pathway evaluation: Complement protein levels, assays of complement function, autoantibodies to complement, and complement breakdown products
MGRS (paraprotein associated C3G): Patients >50 years - evaluate for paraproteins
PIGN: Likely diagnosis if the C3 normalizes within 8-12 weeks
Treatment according to disease parameters
Hypertension/Urine protein control: ACE or ARBs
Proteinuria 0.5-2g/d, +/- rise in serum creatinine, and moderate inflammation: MMF and steroids
Proteinuria >2g/d, and/or rise in serum creatinine, moderate-severe inflammation: Consider trial of complement blockade
Terminal pathway dysregulation: Eculizumab

Nonspecific treatments

- Angiotensin-converting enzyme (**ACE**) inhibitors and/or angiotensin receptor blockers (**ARBs**) are first line treatments for proteinuria and blood pressure control as their use has been shown to improve renal survival. [1]
- **Lipid-lowering agents** can also be considered.
- If **proteinuria increases, general immunosuppressive therapy** should be considered with **mycophenolate mofetil (MMF) plus steroids**.

1. (Servais et al., 2012; Turkmen et al., 2021).

Clin J Am Soc Nephrol. 2018 Mar 7; 13(3): 406–413.
Published online 2018 Jan 11. doi: 10.2215/CJN.09080817

PMCID: PMC5967675
PMID: 29326307

Mycophenolate Mofetil in Combination with Steroids for Treatment of C3 Glomerulopathy

A Case Series

Rupali S. Avasare,[1] Pietro A. Canetta,[2] Andrew S. Bomback,[2] Maddalena Marasa,[2] Yasar Caliskan,[3] Yasemin Ozluk,[4] Yifu Li,[2] Ali G. Gharavi,[2] and Gerald B. Appel[2]

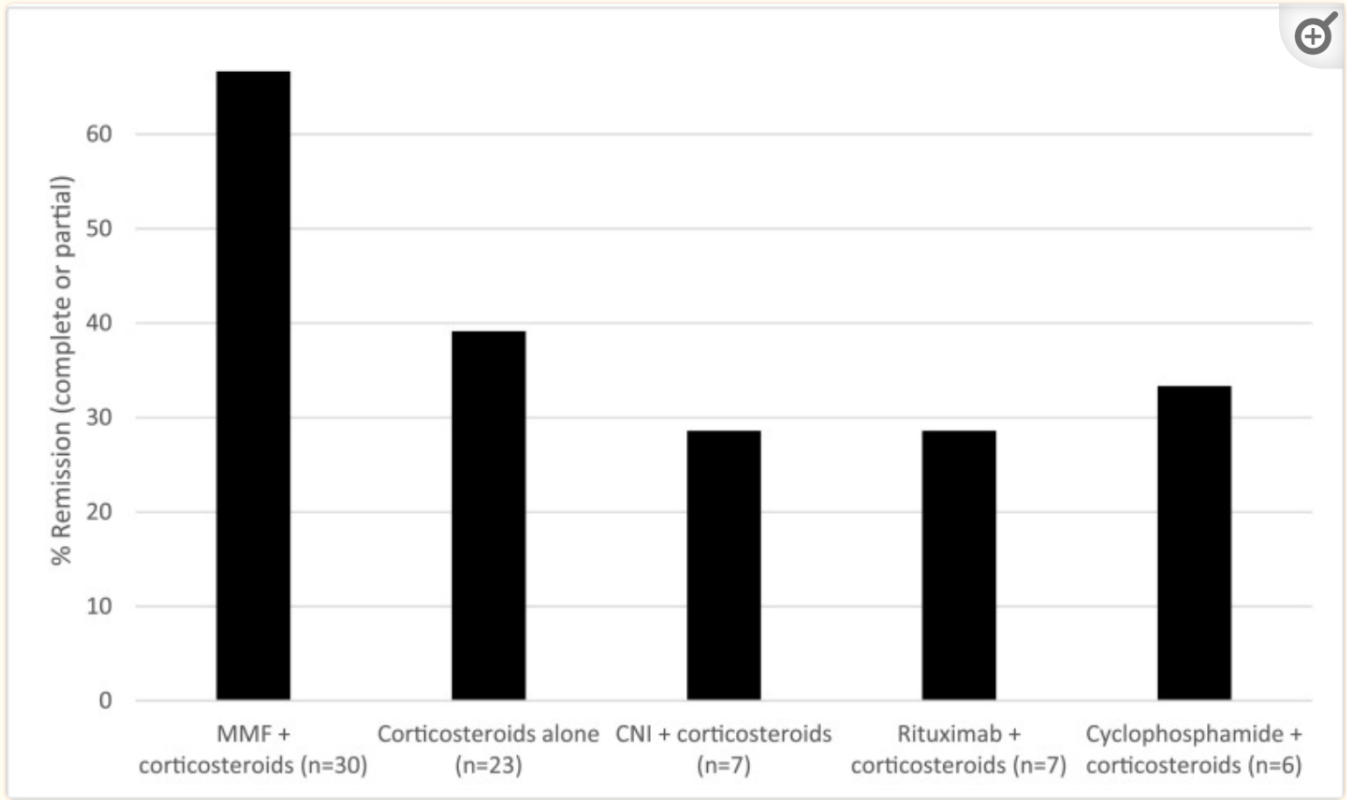


Figure 2.

Mycophenolate combined with steroids outperforms other common immunosuppressive regimens. Response to nonselective immunosuppression in C3 glomerulopathy. Mycophenolate mofetil (MMF) in combination with steroids outperforms therapy with other commonly used immunosuppressive agents with respect to complete or partial remission. Data on patients treated with other forms of immunosuppression are adapted from a Columbia University Medical Center–based observational cohort published elsewhere (33). CNI, calcineurin inhibitor.

Mayo Clin Proc. 2018 August ; 93(8): 991–1008. doi:10.1016/j.mayocp.2018.05.019.

C3 Glomerulopathy: 10-Years Experience at the Mayo Clinic

Aishwarya Ravindran, MBBS[1], **Fernando C. Fervenza, MD, PhD**[2], **Richard J.H. Smith, MD**[3], **An S. De Vriese, MD, PhD**[4], and **Sanjeev Sethi, MD, PhD**[1]

[1]Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN;

- —A total of **114 C3G** patients seen at Mayo Clinic from January 1, 2007 to December 31, 2016

- Results:The mean age at diagnosis for the entire cohort was 40.4 (±22.3) years, with median serum creatinine and proteinuria of 1.6 mg/dl and 2605 mg/24h, respectively.

- C3/C4 levels were low in 44.6%/11.8% of patients

- A genetic variant in complement genes, C3 nephritic factor, and other autoantibodies were present in 37.1%, 43.5%, and 13.4 % of patients, respectively.

- In patients, at a median follow-up of 22.3 months, median serum creatinine and proteinuria were 1.4 mg/dL and 825.5 mg/24 hours, with 7 patients (10.3%) progressing to ESRD.

- Conclusion—C3 glomerulopathy is a heterogeneous disease entity with complex triggering events and abnormalities of the alternative pathway of complement.
- The disease tends to be progressive and shows a variable response to immunosuppressive therapy.

- In aggregate, these results suggest that while **MMF plus steroids may be effective in some C3G patients**; however, there is a pressing need for **disease-specific treatments**.

Mycophenolate Mofetil in C3 Glomerulopathy and Pathogenic Drivers of the Disease

Caravaca-Fontán, Fernando[1,2]; Díaz-Encarnación, Montserrat M.[3]; Lucientes, Laura[4]; Cavero, Teresa[5]; Cabello, Virginia[6]; Ariceta, Gema[7]; Quintana, Luis F.[8]; Marco, Helena[9]; Barros, Xoana[10]; Ramos, Natalia[11]; Rodríguez-Mendiola, Nuria[12]; Cruz, Sonia[13]; Fernández-Juárez, Gema[14]; Rodríguez, Adela[15]; Pérez de José, Ana[16]; Rabasco, Cristina[17]; Rodado, Raquel[18]; Fernández, Loreto[19]; Pérez Gómez, Vanessa[20]; Ávila, Ana I.[21]; Bravo, Luis[22]; Lumbreras, Javier[23]; Allende, Natalia[24]; Sanchez de la Nieta, Maria Dolores[25]; Rodríguez, Eva[26]; Olea, Teresa[27]; Melgosa, Marta[28]; Huerta, Ana[29]; Miquel, Rosa[30]; Mon, Carmen[31]; Fraga, Gloria[32]; de Lorenzo, Alberto[33]; Draibe, Juliana[34]; Cano-Megías, Marta[35]; González, Fayna[36]; Shabaka, Amir[37]; López-Rubio, Maria Esperanza[38]; Fenollosa, María Ángeles[39]; Martín-Penagos, Luis[40]; Da Silva, Iara[3]; Alonso Titos, Juana[41]; Rodríguez de Córdoba, Santiago[42]; Goicoechea de Jorge, Elena[3,42]; Praga, Manuel[1,2]; on behalf of the Spanish Group for the Study of Glomerular Diseases GLOSEN

Author Information

CJASN 15(9):p 1287-1298, September 2020. | ***DOI:*** 10.2215/CJN.15241219

Abstract

- This study aims to analyze the main determinants of disease progression and response to corticosteroids and MMF
- A **retrospective, multicenter, observational cohor**t study in 35 nephrology departments from the Spanish group.
  Patients with C3 glomerulonephritis (N= 81) or DDD(N=16)between 1995 and 2018 were enrolled.
- Multivariate and propensity score matching analyses were used to evaluate the association of clinical and genetic factors with response to treatment with Gc and MMF as measured by the proportion of patients with disease remission and kidney survival.

Results

- 97 patients (**84%** C3 glomerulonephritis, **16%** DD).
- **42** patients were treated with **corticosteroids + MMF**, this treatment was associated with a higher rate **of remission 79%,** and a lower rate of **kidney failure 14%.**
- With **other immunosuppressives**, remission was **24%**, and **kidney failure was 59%**.
- **Eculizumab remission was 33%,** kidney failure was 67%,
- conservative management remission was 18%, and kidney failure was 65%.
- **GC and MMF's** therapeutic effect was observed in patients with **complement abnormality and with autoantibodies.**
- Patients with **pathogenic variants in complement genes** only achieved **partial remission** and complete emission was common in antibody-mediated forms.
- **Relapses** occurred after treatment **discontinuation in33%,** longer treatment length of MMF was associated with a lower risk of relapse.

Plasma therapy and exchange.

- plasma therapy was effective in a **pair of siblings with C3 glomerulopathy** caused by **homozygosity for an in-frame amino-acid deletion in factor H** that altered its ability to control complement activity .
- Plasma therapy has also been useful in patients with **C3 glomerulopathy who have AKI, but has been unsuccessful in patients with C3 nephritic factors**, presumably because production of these autoantibodies continues after they are removed.
- One **15-year-old girl with recurrence of DDD** after renal transplantation received **thrice-weekly plasma exchanges**, which were successful in **removing circulating C3 nephritic factors;** however, when this treatment was discontinued (after more than 100 exchanges) the allograft failed .
- These data suggest that the **precise role of plasma therapy in C3 glomerulopathy patients remains to be defined.**

Anti complement therapy

- When these drugs are compared to **Eculizumab and Ravulizumab, both of which target C5** to prevent the propagation of the terminal pathway**.**

- **Eculizumab** is currently available to treat C3G on an **off-label** basis and is often considered when **proteinuria and disease progression** are **refractory to immunosuppressive treatment with MMF**.

- **Eculizumab is most effective in patients with rapidly progressive C3G,**
- **10–20%** will have **a global response,**
- **20–25%** will have a **partial response,**
- **55– 70% will have no response to treatment.**[1]

1.Le Quintrec et al., 2018; Ruggenenti et al., 2019

Anti-complement therapy with Eculizumab.

- The authors concluded that some but not all patients respond to **eculizumab and that an elevated soluble C5b-9 level** is a **potentially useful marker of response** to this agent.

- This finding mirrors data generated in **animal models of C3 glomerulopathy**, which show that C5 blockade alleviates glomerular inflammation and reduces proteinuria but does not affect complement deposition in the kidney.

- Among treated C3G patients, data on soluble membrane attack complex of complement (sMAC) were limited to patients treated with eculizumab (N = 7).
- **80% of patients with elevated sMAC before eculizumab responded to treatment**.
- In addition, **all patients** who **responded to eculizumab** had **normal sMAC levels after post-eculizumab**.
- .

- Preventing C3 convertase formation **should prevent C5 convertase** formation and preventing the formation **of both convertases should provide disease-specific treatment for C3G**.

- Each of these targets is predicted to **halt the amplification phase of complement activity**.

1.Le Quintrec et al., 2018; Ruggenenti et al., 2019

medical sciences

MDPI

Article

Treatment of C3 Glomerulopathy in Adult Kidney Transplant Recipients: A Systematic Review

Maria L Gonzalez Suarez [1,2,*], Charat Thongprayoon [2,*], Panupong Hansrivijit [3], Karthik Kovvuru [4], Swetha R Kanduri [4], Narothama R Aeddula [5], Aleksandra I Pivovarova [1], Api Chewcharat [6], Tarun Bathini [7], Michael A Mao [8], Arpita Basu [9] and Wisit Cheungpasitporn [1,2,*]

- Results:
- Twelve studies (7 cohort studies and 5 case series) consisting of 122 KTx patients with C3G (73 C3 glomerulonephritis (C3GN) and 49 (DDD) were included.
- The pooled estimated rates of allograft loss among KTx patients with **C3G was**
- **33%** (95% CI: 12–57%) after eculizumab,
- **42%** (95% CI: 2–89%) after (**TPE)**,
- **81%** (95% CI: 50–100%) after **rituximab**.

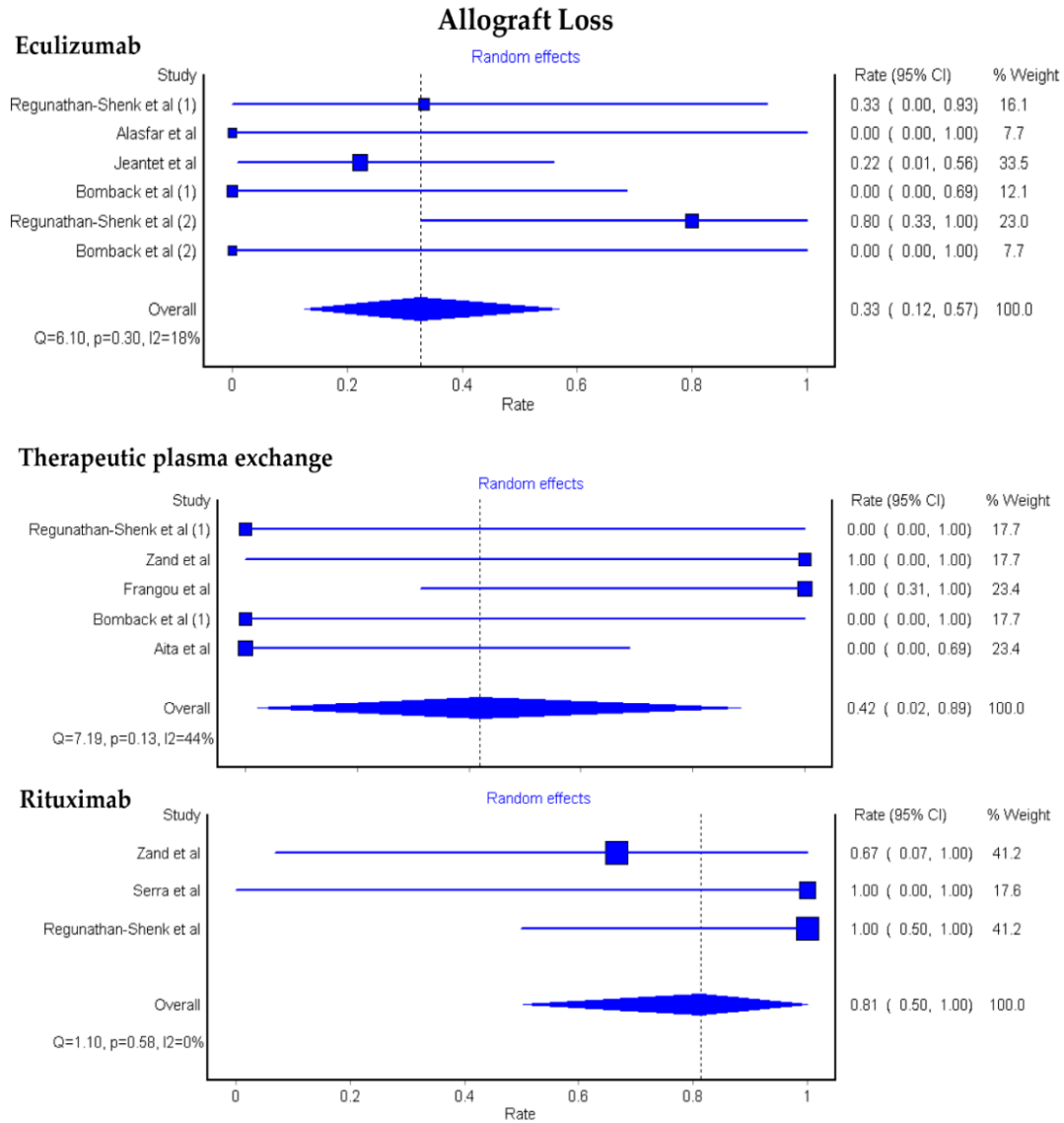


Figure 2. Pooled estimated rates of allograft loss among KTx patients with C3G.

3.2. Allograft Loss among KTx Patients with C3GN and DDD

AJN
American Journal
of Nephrology

**Patient-Oriented, Translational Research:
Research Article**

Am J Nephrol 2022;53:675–686
DOI: 10.1159/000527166

Received: June 16, 2022
Accepted: September 1, 2022
Published online: November 18, 2022

Baseline Clinical Characteristics and Complement Biomarkers of Patients with C3 Glomerulopathy Enrolled in Two Phase 2 Studies Investigating the Factor D Inhibitor Danicopan

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ORIGINAL ARTICLE: GLOMERULAR AND TUBULOINTERSTITIAL DISEASES

Association of Histologic Parameters with Outcome in C3 Glomerulopathy and Idiopathic Immunoglobulin-Associated Membranoproliferative Glomerulonephritis

Lomax-Browne, Hannah J.[1]; Medjeral-Thomas, Nicholas R.[1]; Barbour, Sean J.[2]; Gisby, Jack[1]; Han, Heedeok[3]; Bomback, Andrew S.[3]; Fervenza, Fernando C.[4]; Cairns, Thomas H.[5]; Szydlo, Richard[6]; Tan, Sven-Jean[7]; Marks, Stephen D.[8,9]; Waters, Aoife M.[8]; Appel, Gerald B.[3]; D'Agati, Vivette D.[10]; Sethi, Sanjeev[11]; Nast, Cynthia C.[12]; Bajema, Ingeborg[13]; Alpers, Charles E.[14]; Fogo, Agnes B.[15]; Licht, Christoph[16]; Fakhouri, Fadi[17]; Cattran, Daniel C.[18]; Peters, James E.[1]; Cook, H. Terence[1]; Pickering, Matthew C.[1]

Author Information

CJASN 17(7):p 994-1007, July 2022. | *DOI:* 10.2215/CJN.16801221

- To improve the **identification of patients with poor prognoses**, we performed a detailed analysis of kidney biopsies in a large cohort of patients.
- Using a validated histologic scoring system, we analyzed **156 native** diagnostic kidney biopsies from a retrospective cohort of **123 patients with C3 glomerulopathy** and **33 patients with Ig-associated MPGN**
- We used linear regression, survival analysis, and Cox proportional hazard models to assess the relationship between histologic and clinical parameters and outcomes.

Results

- Multivariate analysis showed **negative associations** between eGFR and crescents, interstitial inflammation, and interstitial fibrosis/tubular atrophy.

- **Proteinuria** was positively associated with **endocapillary hypercellularity and GBM double contours**.

- Analysis of **second native biopsies** did **not demonstrate** associations between **immunosuppression treatment and improvement in histology**.

BASIC RESEARCH: GLOMERULONEPHRITIS AND INTERSTITIAL NEPHRITIS

Factor H–Related Protein 1 Drives Disease Susceptibility and Prognosis in C3 Glomerulopathy

Márquez-Tirado, Bárbara[1]; Gutiérrez-Tenorio, Josué[1]; Tortajada, Agustín[1]; Lucientes Continente, Laura[1]; Caravaca-Fontán, Fernando[2]; Malik, Talat H.[3]; Roldán Montero, Raquel[4]; Elías, Sandra[5]; Saiz Gonzalez, Ana[6]; Fernández-Juarez, Gema[7]; Sánchez-Corral, Pilar[8]; Pickering, Matthew C.[3]; Praga, Manuel[2,9]; Rodríguez de Córdoba, Santiago[10]; Goicoechea de Jorge, Elena[1]

Author Information

JASN 33(6):p 1137-1153, June 2022. | ***DOI:*** 10.1681/ASN.2021101318

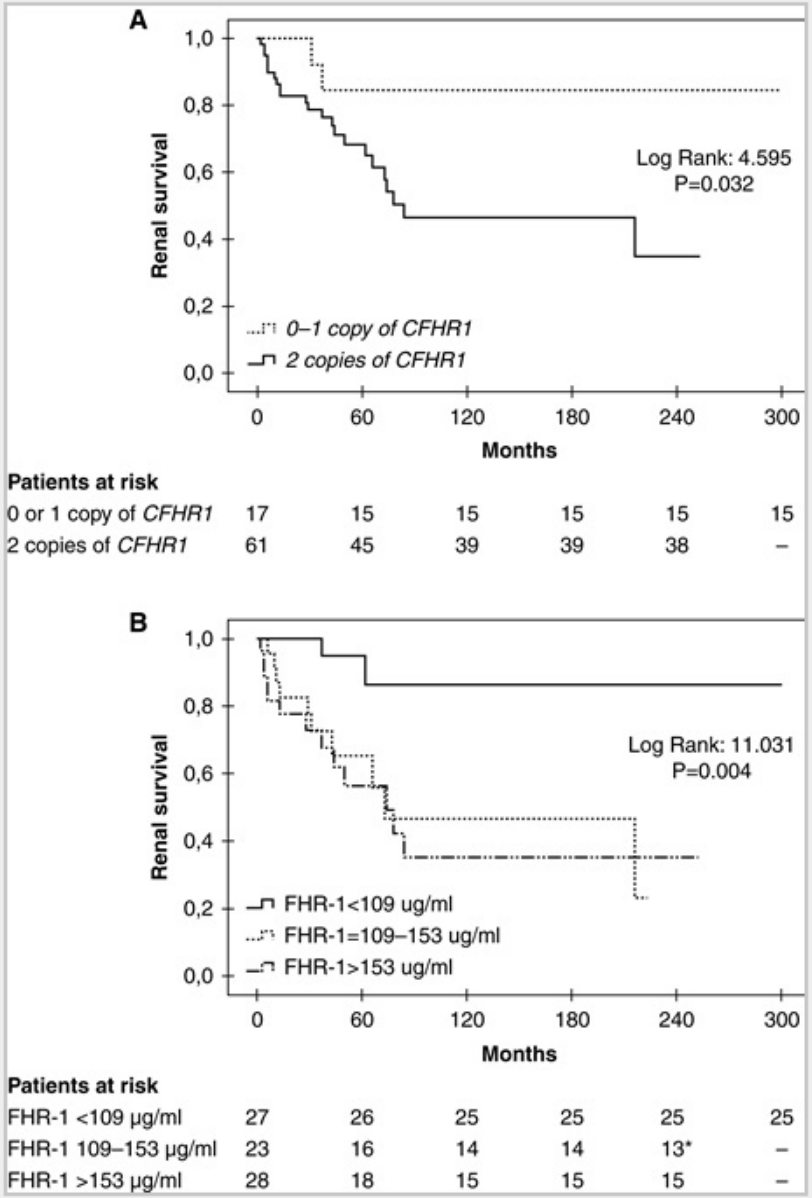


Figure 7.: Kaplan–Meier curves illustrate that lower number of *CFHR1* copies or lower levels of plasma FHR-1 at diagnosis are associated with better renal survival. ESKD was considered as the event and a follow-up of 300 months is depicted. (A) The number of *CFHR1* copies was established considering the presence of $\Delta_{CFHR3\text{-}CFHR1}$ and the deletion of *CFHR1–CFHR4*. (B) Plasma FHR-1 levels were determined in patient samples at diagnosis. Patients with a significant deterioration of renal function at diagnosis and who developed ESKD within the first month were excluded from the analysis. *A patient reached ESKD by month 216 and the maximum follow-up time for this group of patients was 223 months.

- Patients with C3G from cohort 1 (*n*=89) were obtained from a well-defined and previously reported cohort of patients belonging to the Spanish Group for the Study of Glomerular Diseases.

- They also showed that elevated levels of FHR-1 are associated with poor renal prognosis for patients with C3 G,
- whereas a genetic deficiency of FHR-1 offers protection against C3 development.
  These findings advance our understanding of C3G pathogenesis and suggest that **inhibition of FHR-1 may have therapeutic potential** in C3G.

Kidney International
Volume 102, Issue 4, October 2022, Pages 904-916

Clinical Investigation

Results from a nationwide retrospective cohort measure the impact of C3 and soluble C5b-9 levels on kidney outcomes in C3 glomerulopathy

Sophie Chauvet [1 2 3], Jill J. Hauer [4], Florent Petitprez [5], Marion Rabant [6], Paula Vieira Martins [7], Véronique Baudouin [8], Yahsou Delmas [9], Noémie Jourde-Chiche [10], Alexandre Cez [11], David Ribes [12], Sylvie Cloarec [13], Aude Servais [14], Mohamad Zaidan [15], Eric Daugas [16], Michel Delahousse [17], Alain Wynckel [18], Amélie Ryckewaert [19], Anne Laure Sellier-Leclerc [20], Olivia Boyer [21], Eric Thervet [1]...Véronique Frémeaux-Bacchi [2 7]

- In a large cohort of **165 patients** from the **French National registry**, we retrospectively assess the prognostic value of C3, soluble C5b-9, C3 nephritic factor, and rare disease–predicting variants in complement genes in predicting the clinical outcome of patients.

- By, multivariate analysis, **normal C3/high sC5b-9** levels or **low C3/normal sC5c-9 levels** remained independently associated with a worse kidney prognosis, with a **relative risk of 3.7 - 8 times higher**, respectively.
- In children only the presence of rare –disease predicting variants correlated with kidney survival.

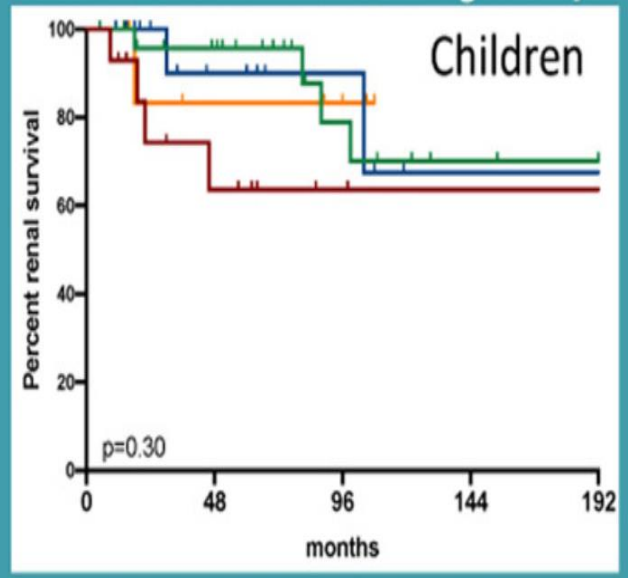
Cohort and Methods:

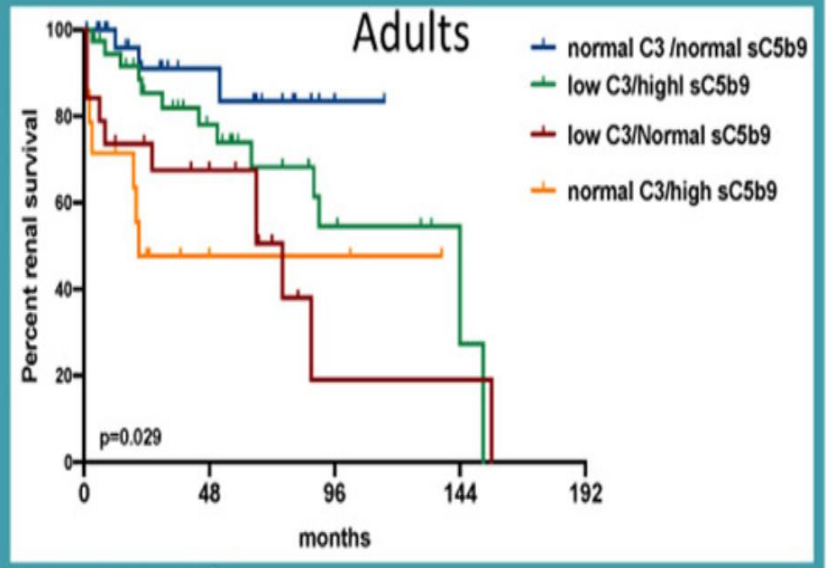
Clinical and immunological characteristics of 165 patients with C3 glomerulopathy

- Normal C3 / Normal sC5b-9 — N=47
- Normal C3 / High sC5b-9 — N=21
- Low C3 / Normal sC5b-9 — N=34
- Low C3 / High sC5b-9 — N=63

ESKD risk evaluation

Renal outcomes according to C3/sC5b-9 level profile





Factors predictive of renal outcomes (Multivariate analysis)

In children:

rare disease-predicting variants in complement genes (HR 3,22; p= 0.054)

(No association with complement biomarkers profile)

In adults

Renal failure at diagnosis (HR 9.5, p<0.0001), rare disease-predicting variants in complement genes (HR 2,54, P=0.017) and normal C3/high sC5b-9 levels (HR 4.79, p=0.013) or low C3/normal sC5b-9 levels (HR 3.48; p=0.037)

Chauvet S et al, 2022

CONCLUSION :

Profiles of biomarkers of C3 and C5 convertase are independent predictors of renal outcomes in adults with C3G

Pediatric Nephrology (2022) 37:521–535
https://doi.org/10.1007/s00467-021-05088-7

EDUCATIONAL REVIEW

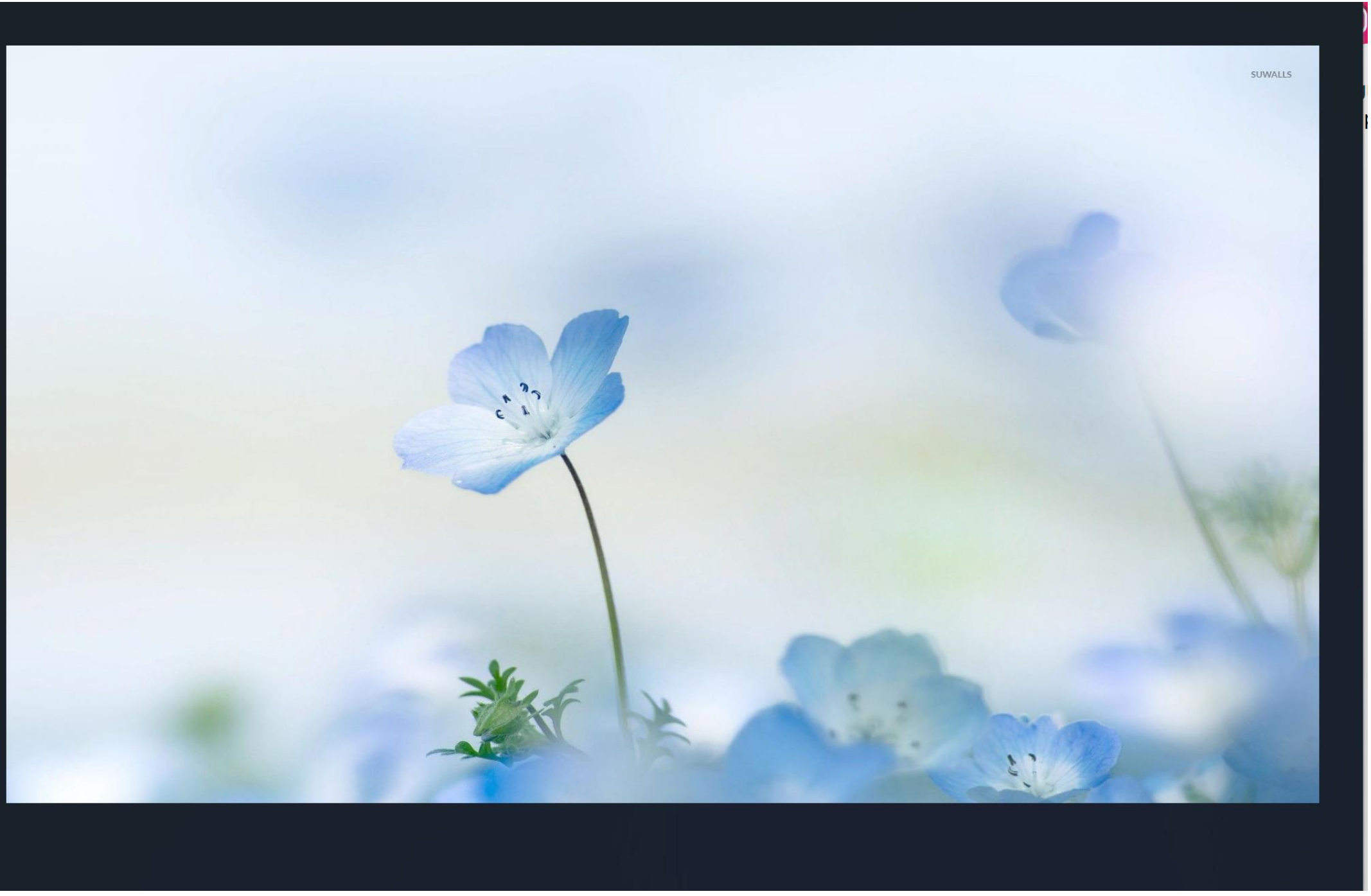
A clinical approach to children with C3 glomerulopathy

Marina Vivarelli[1] · Nicole van de Kar[2] · Raffaella Labbadia[1] · Francesca Diomedi-Camassei[3] · Joshua M. Thurman[4]

Table 2 Complement inhibitory drugs undergoing testing in glomerular disease

Drug	Target	Diseases
LPN023 (Novartis)	FB	C3G, IgAN
ACH4471 (Astra Zeneca)	FD	C3G, MPGN
OMS721 (Omeros)	MASP2	aHUS, C3G, IgAN, Lupus nephritis, MN
AMY-101 (Amyndas)	C3	C3G
APL-2 (Apellis)	C3	C3G, IgAN, Lupus nephritis, MN
Cemdisiran (Alnylam)	C5	IgAN, aHUS
CCX168 (Chemocentryx)	C5aR1	ANCA-associated vasculitis, C3G, IgAN

MASP, mannose associated serine protease; *aHUS*, atypical hemolytic uremic syndrome; *C3G*, C3 glomerulopathy; *IgAN*, IgA nephropathy; *ANCA*, anti-neutrophil cytoplasmic antibody; *C5aR1*, C5a-receptor 1; *MPGN*, membranoproliferative glomerulonephritis; *MN*, membranous nephropathy


SUWALLS

Clinicopathologic Implications of Complement Genetic Variants in Kidney Transplantation

Zhen Ren[1], Stephen J. Perkins[2], Latisha Love-Gregory[3], John P. Atkinson[4] and Anuja Java[5]*

Ren et al. Front. Med. November 2021 | Volume 8 | Article 775280

- **The risk of recurrent** disease after kidney transplantation is impacted by underlying **genetic abnormalities**.
- **Genetic variants in complement proteins** are identified **in 30–40% of C3G** patients.
- Recently, **Ren et al. evaluated the clinicopathologic significance of genetic variants** in a **TMA and C3G** kidney transplant cohort.
- The group reported **10 variants in CFH**, of which were **four pathogenic**, **one was likely benign**, and five were classified as variants of uncertain significance.[1]
- The **presence of pathogenic variants increased the risk for recurrent disease in the transplant**.

1.(Ren, Perkins, Love-Gregory, Atkinson, & Java, 2021).

TABLE 2 | Summary of the functional analyses for *CFH* variants.

Patient (s)	Variant	Location	Recombinant secretion (μg/ml)	C3b binding	Heparin binding	Cofactor activity	Cell-surface regulation using patient serum	ACMG interpretation	Modified interpretation (based on functional and structural analysis)
1	I372V	CCP 6	Comparable to WT	N	N	N	Defective (C3b deposition assay)	VUS	Deleterious
2	I453L	CCP 8	Comparable to WT	N	N	N	Defective (sheep red cell hemolytic assay)	VUS	Deleterious
3, 4	G918E	CCP 15	Decreased	ND	ND	__	Not done	VUS	Deleterious
3, 4	G918E/N1050Y	CCP 15/18	Decreased	ND	ND	__	Not done	VUS	Deleterious
6	T956M/E936D	CCP 16	Comparable to WT	N	N	__	Not done	VUS	Normal function
7	T956M	CCP 16	Comparable to WT	MD	N	__	Not done	VUS	Likely benign
8	L1207I	CCP20	Comparable to WT	N	N	__	Not done	VUS	Normal function

Secretion of I372V (5.9 μg/ml) and I453L (6.2 μg/ml) was comparable to WT CCP1–8 (4.0 μg/ml) ($P > 0.05$, SEM 1.15) as measured by ELISA. C3b binding and cofactor activity were normal but cell surface regulation was defective for both I372V and I453L. Variant G918E was not secreted. Secretion of SNP N1050Y (4.1 μg/ml) was comparable to WT CCP 15–20 (3.6 μg/ml) ($P < 0.05$, SEM 0.1). Secretion of G918E/N1050Y was markedly reduced compared to WT. Secretion of T956M (2.6 μg/ml) and T956M/E936D (3.5 μg/ml) were comparable with WT CCP 15–20 (3.6 μg/ml) ($P = 0.7855$, SEM 0.1). Secretion of L1207I was comparable to WT CCP 18–20 (2 μg/ml) ($P > 0.05$, SEM 0.16). ACMG, American College of Medical Genetics; VUS, variant of uncertain significance. Patient 5 did not undergo genetic testing due to financial/insurance issues. N, normal; ND, not done; MD, marginally decreased. I, isoleucine; V, valine; L, leucine; G, glycine; E, glutamic acid; T, threonine; M, methionine.