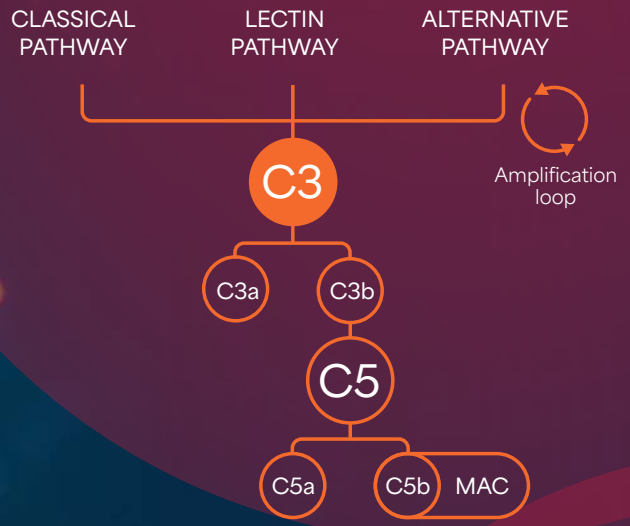
Rare, Chronic, Complement-Driven Glomerular Diseases

C3G and IC-MPGN

C3G, C3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis.

Apellis

Complement System[1-3]

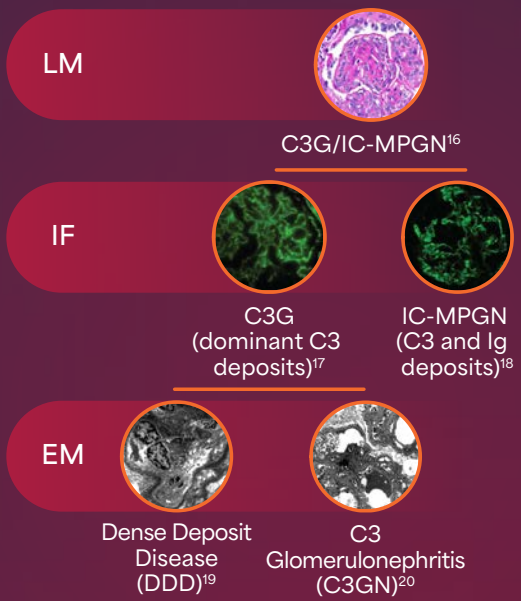


- Central component of the innate immune system comprising a network of proteins across 3 distinct pathways
- Activation initiates an interconnected downstream signaling cascade to eliminate foreign or damaged cells
- C3 represents the convergence point of the complement cascade

Schematic does not depict all proteins in the complement system.
MAC, membrane attack complex.

C3G and IC-MPGN

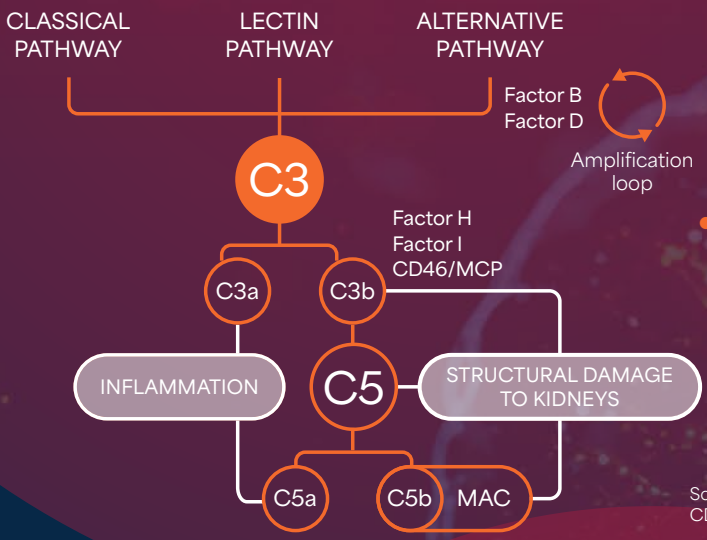
- Group of rare, progressive, complement-driven diseases estimated to affect ≈5000 individuals in the United States[4-6]
  - Incidence of C3G in the United States is 1-3 cases/1,000,000/year[5]
  - Up to 50% of patients progress to end-stage kidney disease (ESKD) in 5-10 years and may require transplantation(s)[5,7-9]
  - Disease recurrence post transplant occurs in up to 89% of patients; allograft loss due to disease recurrence occurs in up to 60% of posttransplant patients[7,8,10-15]



EM, electron microscopy; IF, immunofluorescence; Ig, immunoglobulin; LM, light microscopy.

C3G and IC-MPGN Are Driven by Complement Overactivation

Overactive Complement System Leads to Glomerulopathy[5,6,21,22]



- Excessive deposition of C3 fragments (with or without immunoglobulins) in the glomeruli leads to kidney damage[5,6,21]

Schematic does not depict all proteins in the complement system.
CD46, cluster of differentiation 46; MCP, membrane cofactor protein.

Primary and Secondary Causes

PRIMARY CAUSES

- C3/C5 nephritic factors (autoantibodies) in 50%-80% of patients[5]
- Genetic variance in complement-related genes in up to 25% of patients[5,6]

COMMON SECONDARY CAUSES

- Chronic infections (eg, hepatitis B/C)[23]
- Autoimmune disease (eg, systemic lupus, Sjögren's syndrome, rheumatoid arthritis)[23]
- Monoclonal gammopathy[23]
- Chronic antibody-mediated rejection (ie, transplant glomerulopathy)[24]
- Malignancy[23]

C3G and IC-MPGN Are Histopathological Diagnoses

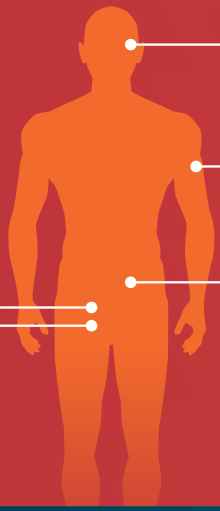
Signs and Symptoms

LOW SERUM C3
Due to excessive deposition of C3 fragments in the glomeruli, patients may have low serum C3[11,25,26]

FATIGUE & EDEMA[27]

HEMATURIA
Due to damaged glomeruli that allow red blood cells to pass through[5,17]

PROTEINURIA
Due to damaged glomeruli that allow protein to pass through[5,17]



DRUSEN
Yellow-colored deposits under the retina, made up of lipids and proteins, presumably due to complement hyperactivity[28]

HYPERTENSION
Can be severe[5]

DECREASED GLOMERULAR FILTRATION RATE
Severely damaged glomeruli no longer filter blood[5,17]

Diagnostic Pathway: Essential Role of Kidney Biopsy

CLINICAL PRESENTATION → SEROLOGY → KIDNEY BIOPSY → IMMUNOLOGICAL TESTS → GENETIC TESTS

Light Microscopy
- MPGN pattern of injury[6]
- Not sufficient for diagnosis[5]

Immunofluorescence
- Diagnosis of and differentiation between C3G and IC-MPGN[6]
  - **C3G:** C3 staining ≥2 OOM more intense than any other immune reactant[5]
  - **IC-MPGN:** immunoglobulin deposits dominant or co-dominant with C3[29]

Electron Microscopy
- Further distinguishes between DDD and C3GN[5,6]
  - **DDD:** dense, ribbon-like deposits in the glomerular basement membrane[5,21,30]
  - **C3GN:** clusters of deposits in the subendothelial and subepithelial space and mesangium[21,30]

Renal pathology expertise is needed for confirmatory diagnosis

MPGN, membranoproliferative glomerulonephritis; OOM, order of magnitude.

Treatment Landscape

Supportive Treatments Do Not Target the Underlying Pathophysiology[5,31]

Diet Changes[5,31]	• Lower sodium and protein in the diet to reduce the waste load on the kidneys • Measures that support good health are encouraged
ACE Inhibitors and ARBs[5]	• Typically used first line • Aim to reduce proteinuria and control blood pressure • Substantially improved renal survival in 1 retrospective study
Immunosuppressive Agents[5]	• Aim to limit the inflammatory effects of complement overactivity • Data are inconsistent; some studies report an impact on renal survival, whereas others report no change in progression to ESKD
Plasma Therapy and Exchange[5,17]	• Removes autoantibodies and mutated proteins • Robust data are lacking

Complement Inhibitors[5,32]

- Aim to target complement overactivation, the underlying cause of C3G and primary IC-MPGN

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

REFERENCES

1. Baines AC, et al. *Blood Rev*. 2017;31(4):213-223.

2. Dobó J, et al. *Front Immunol*. 2018;9:1851.

3. Merle NS, et al. *Front Immunol*. 2015;6:257.

4. Data on file. Apellis Pharmaceuticals, Inc.

5. Smith RJH, et al. *Nat Rev Nephrol*. 2019;15(3):129-143.

6. Caravaca-Fontán F, et al. *Nephron*. 2020;144(6):272-280.

7. Servais A, et al. *Kidney Int*. 2012;82(4):454-464.

8. Zand L, et al. *J Am Soc Nephrol*. 2014;25(5):1110-1117.

9. Caravaca-Fontán F, et al. *Kidney Int Rep*. 2025;10(4):1223-1236.

10. Caravaca-Fontán F, et al. *Nephrol Dial Transplant*. 2023;38(1):222-235.

11. Medjeral-Thomas NR, et al. *Clin J Am Soc Nephrol*. 2014;9(1):46-53.

12. Regunathan-Shenk R, et al. *Am J Kidney Dis*. 2019;73(3):316-323.

13. Frangou E, et al. *Nephrol Dial Transplant*. 2019;34(10):1780-1788.

14. Tarragón B, et al. *Clin J Am Soc Nephrol*. 2024;19(8):1005-1015.

15. Patry C, et al. *Pediatr Nephrol*. 2024;39(12):3569-3580.

16. Arkana Laboratories. Mesangioendocapillary proliferation with lobular accentuation. Accessed Jul 1, 2025. https://www.dropbox.com/scl/fi/nsk7048c2yi94r6bxdte9/Arkana-Labs-Photo-Reference-Library.zip?e=2&file_subpath=%2FArkana+Labs+Photo+Rereference+Library%2FDense+Deposit+Disease%2FMesangioendocapillary+Proliferation+with+Lobular+Accentuation.jpg&rlkey=3j34a8afr2cy2ouseni1icx2d.

17. Schena FP, et al. *Int J Mol Sci*. 2020;21(2):525.

18. Sethi S, et al. *J Am Soc Nephrol*. 2015;26(11):2852-2859.

19. Arkana Laboratories. Dense GBM transformation on EM_2. Accessed Jul 1, 2025. https://www.dropbox.com/scl/fi/nsk7048c2yi94r6bxdte9/Arkana-Labs-Photo-Reference-Library.zip?e=3&file_subpath=%2FArkana+Labs+Photo+Reference+Library%2FDense+Deposit+Disease%2FDense+GBM+Transformation+on+EM_2.jpg&rlkey=3j34a8afr2cy2ouseni1icx2d.

20. Arkana Laboratories. Subendothelial deposits with cellular interposition on EM. Accessed Jul 1, 2025. https://www.dropbox.com/scl/fi/nsk7048c2yi94r6bxdte9/ Arkana-Labs-Photo-Reference-Library.zip?e=3&file_subpath=%2FArkana+Labs+Photo+Reference+Library%2FC3+Glomerulonephritis%2FSubendothelial+Deposits+with+Cellular+Interposition+on+EM.jpg&rlkey=3j34a8afr2cy2ouseni1icx2d.

21. Sethi S, et al. *N Engl J Med*. 2012;366(12):1119-1131.

22. Dixon BP, et al. *Kidney Int Rep*. 2023;8(11):2284-2293.

23. Masani N, et al. *Clin J Am Soc Nephrol*. 2014;9(3):600-608.

24. Sablik KA, et al. *Transpl Int*. 2018;31(8):900-908.

25. Pickering MC, et al. *Kidney Int*. 2013;84(6):1079-1089.

26. Zhang Y, et al. *Clin J Am Soc Nephrol*. 2014;9(11):1876-1882.

27. National Kidney Foundation. Accessed Jul 1, 2025. https://www.kidney.org/sites/default/files/C3G_EL-PFDD_VoP-Report_3-29-18.pdf.

28. Bradley DT, et al. *Eye (Lond)*. 2011;25(6):683-693.

29. Hou J, et al. *Kidney Int*. 2014;85(2):540-546.

30. Martín B, et al. C3 Glomerulopathy. In: *GeneReviews* [Internet]. University of Washington; 2018. Accessed Jul 1, 2025. https://www.ncbi.nlm.nih.gov/books/NBK1425/.

31. National Kidney Foundation. Accessed Jul 1, 2025. https://www.kidney.org/kidney-topics/complement-3-glomerulopathy-c3g.

32. Noris M, et al. *Nephrol Dial Transplant*. 2024;39(2):202-214.