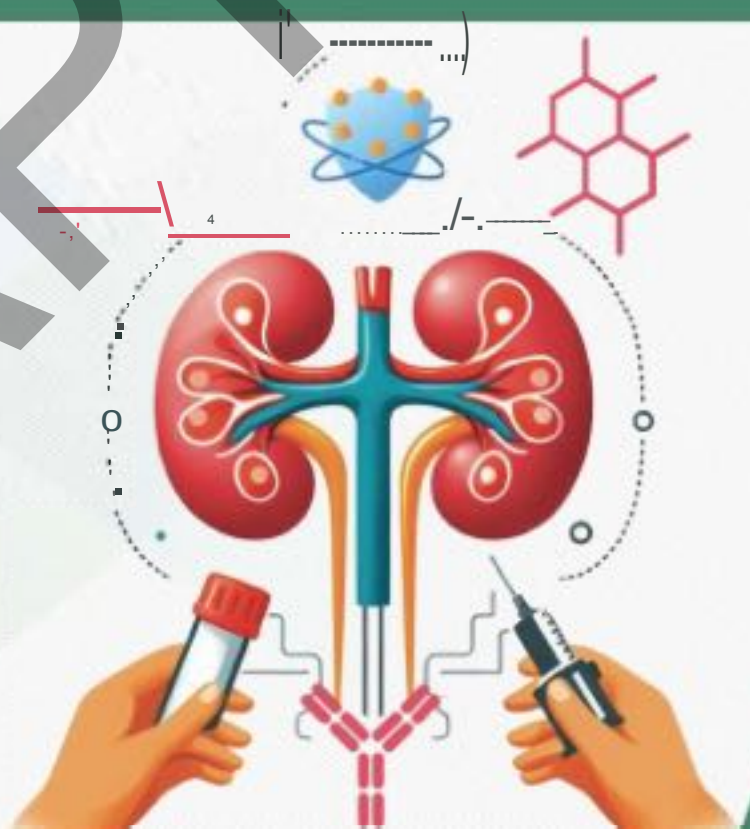
Overlap Between Complement-Mediated Kidney Diseases (CMKDs)



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Cairo University

AGENDA

- Overview of CMKD
- Shared genetics (pathophysiology)
- Clinical & histologic overlap
- Serological convergence
- Practical implications

Complement system is a “double-edged sword”

- Removal of apoptotic/necrotic cells
- Clearance of immune complexes

Deficiency of C1q, C1r, C1s, C2 or C4 strongly predisposes to the development of SLE

J Autoimmun. 2022;137:102979

- Bridge between innate/adaptive immunity >>> inflammatory reaction
- Activates coagulation to secure bleeding & tissue damage

Uncontrolled activation of complement system:

TMA , PNH, APLA, AAV, SIRS

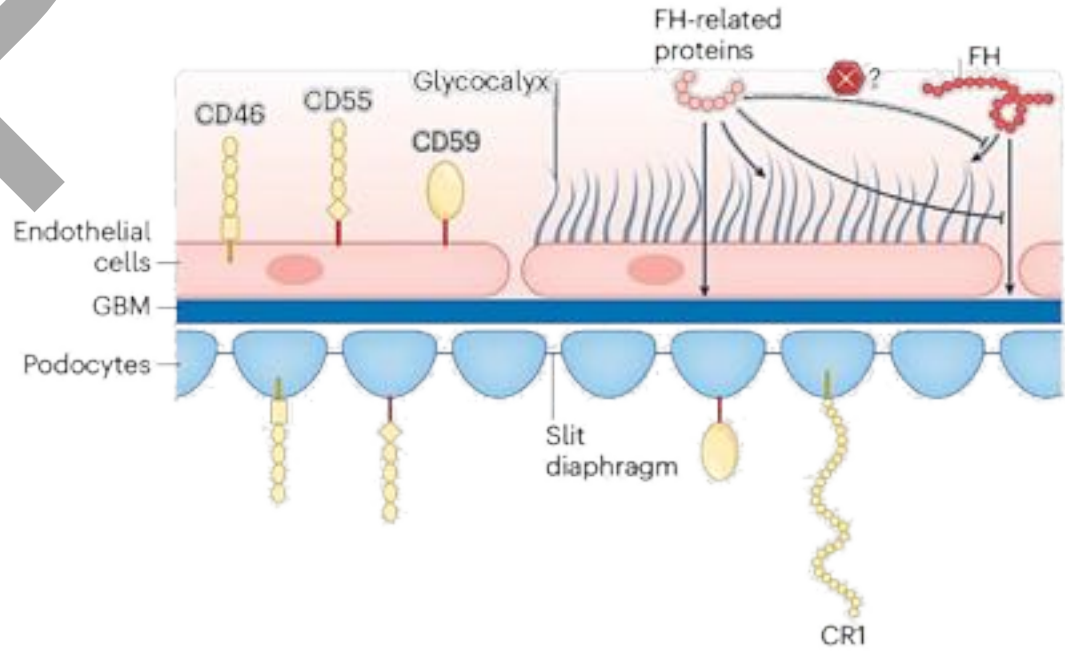
Trends Immunol 2007;28(4):184-192.

The Kidney is a primary target for complement disorders

High glomerular blood hydrostatic pressure and filtration of plasma in glomerular capillaries

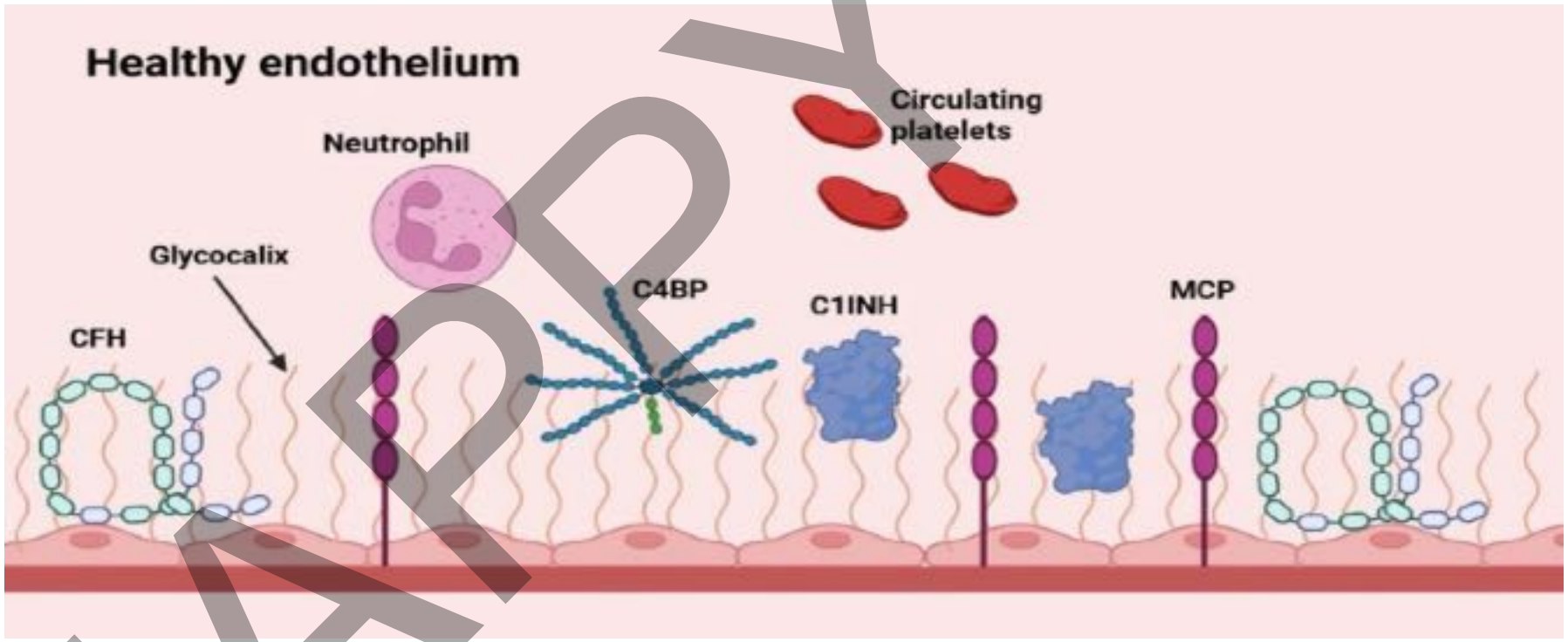
Presence of fenestrae in glomerular endothelial cells may increase access of large plasma proteins to the glomerular BM.

Lack of complement receptors in GBM & endothelial glycocalyx renders them more susceptible to injury by FH dysregulation



Kidney International (2024) 106, 369–391

Protective Mechanisms In Healthy endothelium



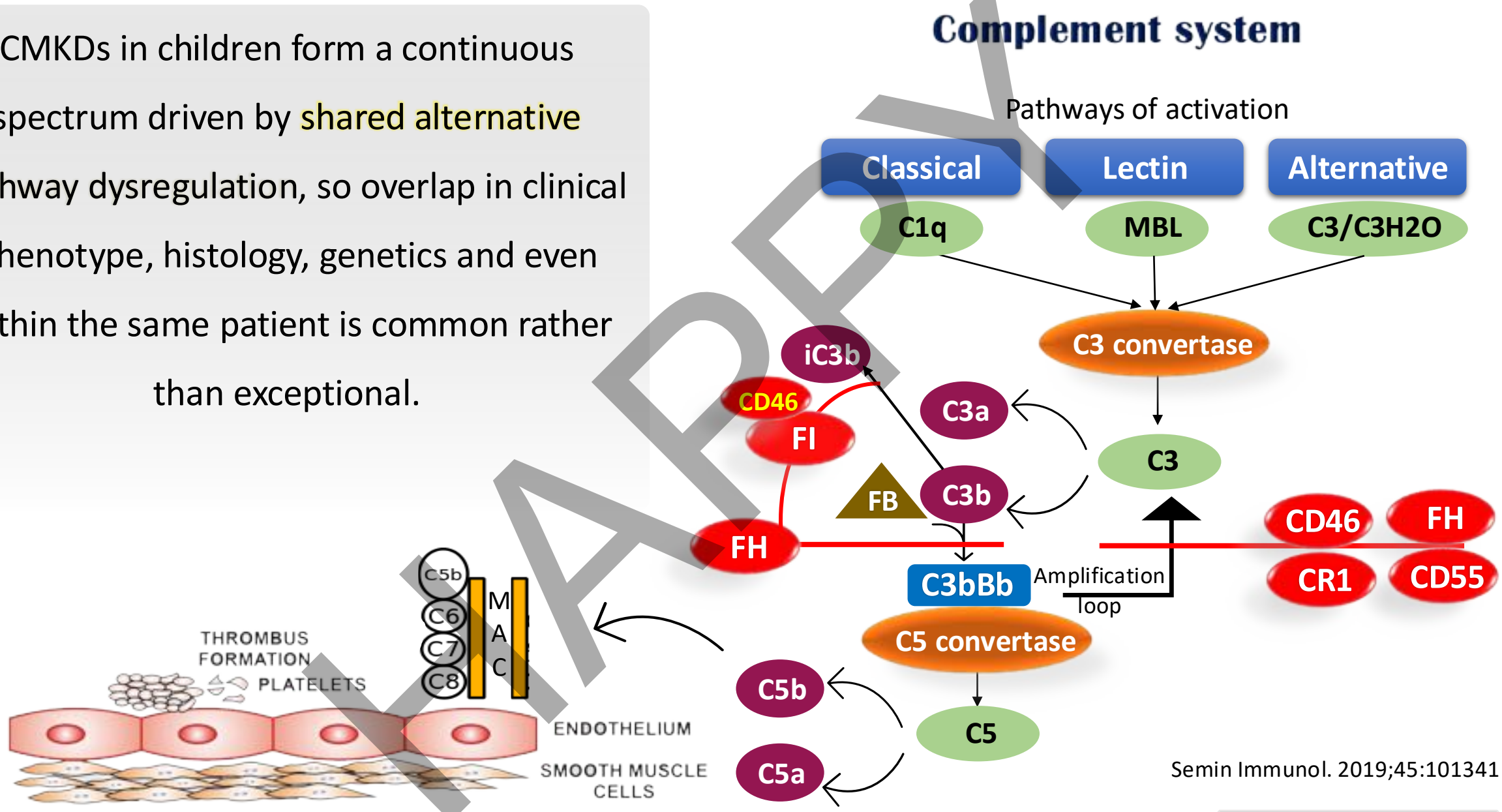
Healthy endothelium is protected by the glycocalyx, which binds several regulators of the complement system such as C1INH (C1 inhibitor), CFH, and C4BP (C4-binding protein), together with MCP that inhibits C3 and C5 convertases.

J Clin Invest. 2025;135(12):e188350

Role of complement in various kidney diseases

Kidney International (2024) 106, 369–391

CMKDs in children form a continuous spectrum driven by shared alternative pathway dysregulation, so overlap in clinical phenotype, histology, genetics and even within the same patient is common rather than exceptional.



Semin Immunol. 2019;45:101341

Renal pathologies caused by complement dysregulation

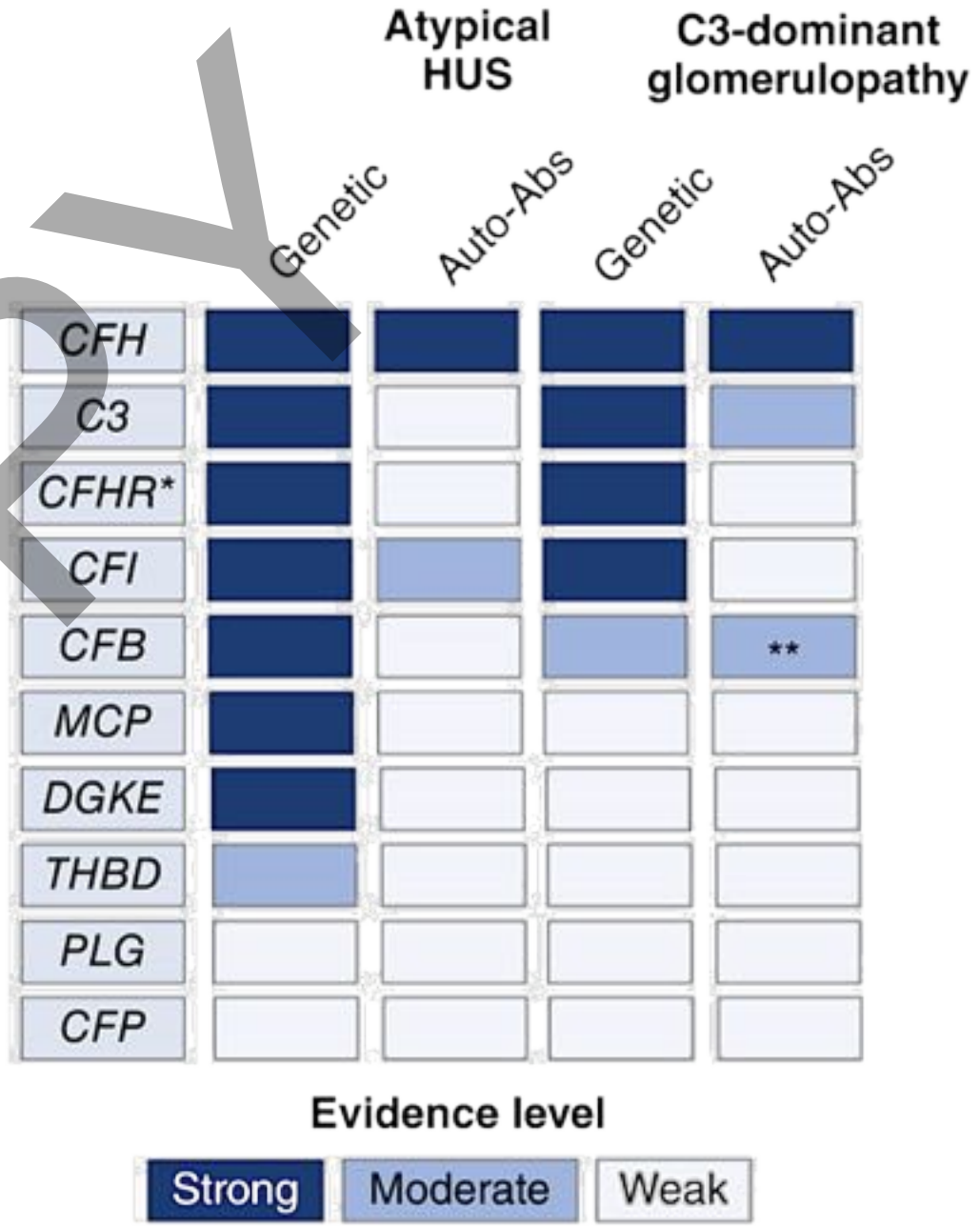
Kidney International (2024) 106, 369–391

Did you observe any Similarities or Differences between the TWO diseases?

aHUS	C3G
• **Rare disease**: acute that may turn chronic	• **Rare disease**: chronic that may turn acute
• **Genetic defects:** the majority	• **Genetic defects:** the minority
• **Acquired defects:** ~ 10% (anti factor H)	• **Acquired defects:** ~50-80% (C3Neph/C5Neph or anti factor H)
• **Triggers:** infections, Tx, drugs, autoimmune diseases	• **Triggers:** infections
• **C3 levels**: low in ~30% of cases	• **C3 levels**: low in ~ 75% of cases

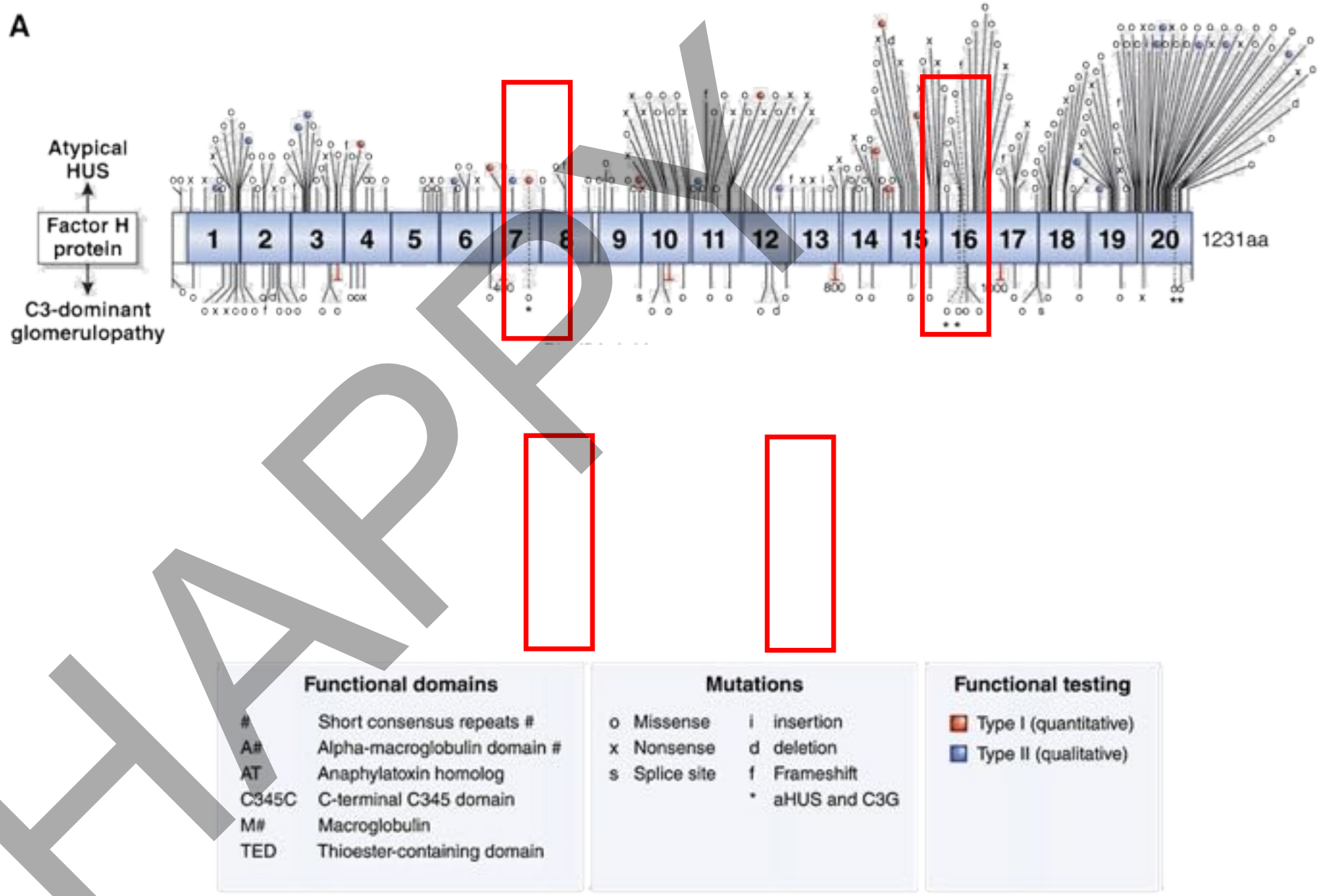
Many genes encoding complement factors are implicated in aHUS and C3G.

Grading of the evidence level regarding the association of aHUS or C3G with genetic mutations



J Immunol. Author manuscript. 2018;200(7):2464-2478

Landscape of mutations in CFH and C3 associated with aHUS or C3G.



Clin J Am Soc Nephrol. 2021;16(6):942-956

Fluid phase vs. surface regulation

Front Immunol. 2017:8:1800

Qualitative nature of the mutation

Kidney Int Rep. 2025;11(2):103705.

Triggers and disease context

Intern Med. 2024;63(12):1777-1782

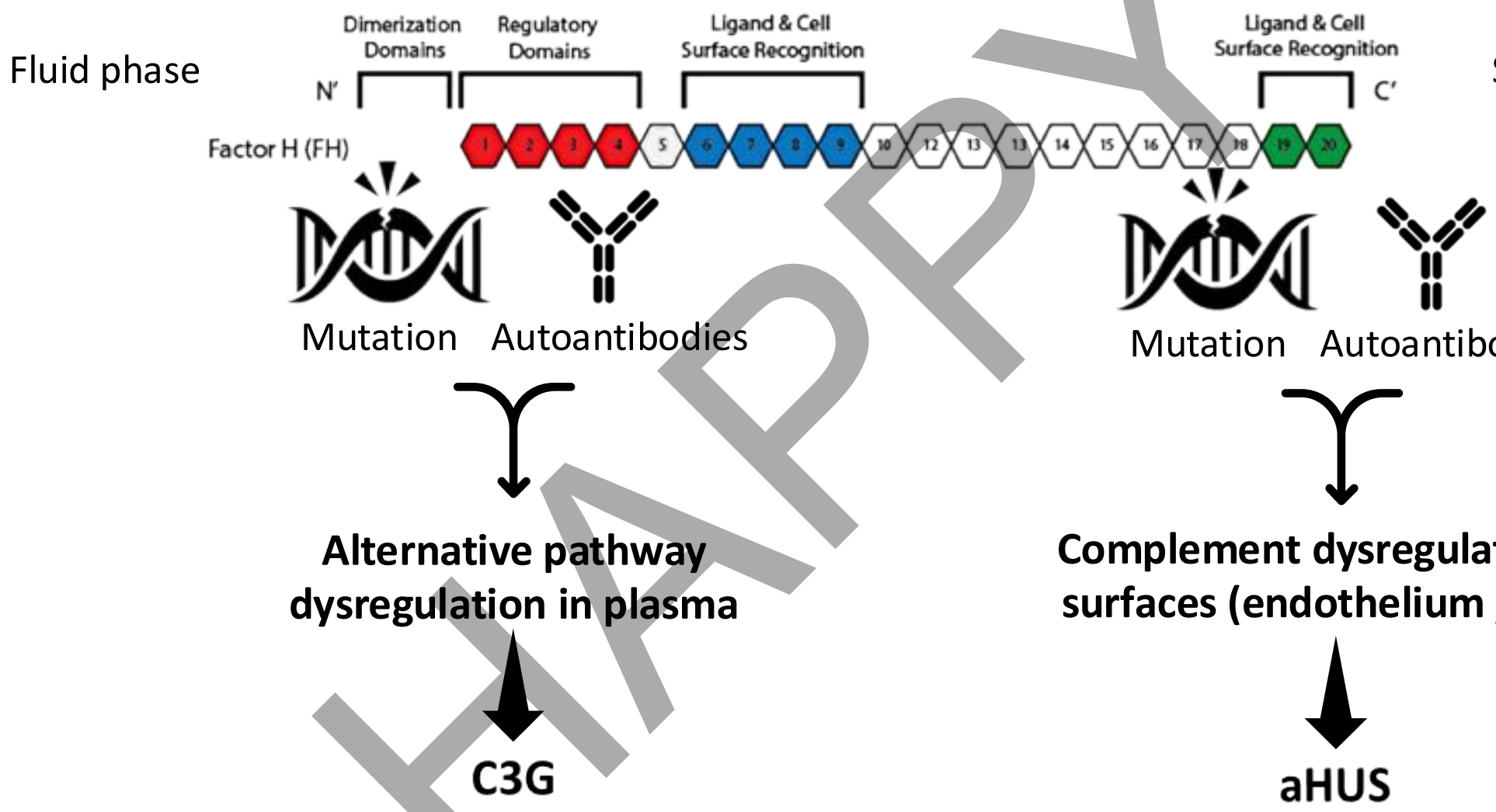
Sequential or overlapping phenotype

J Am Soc Nephrol. 2016;27(5):1334-42

Why?

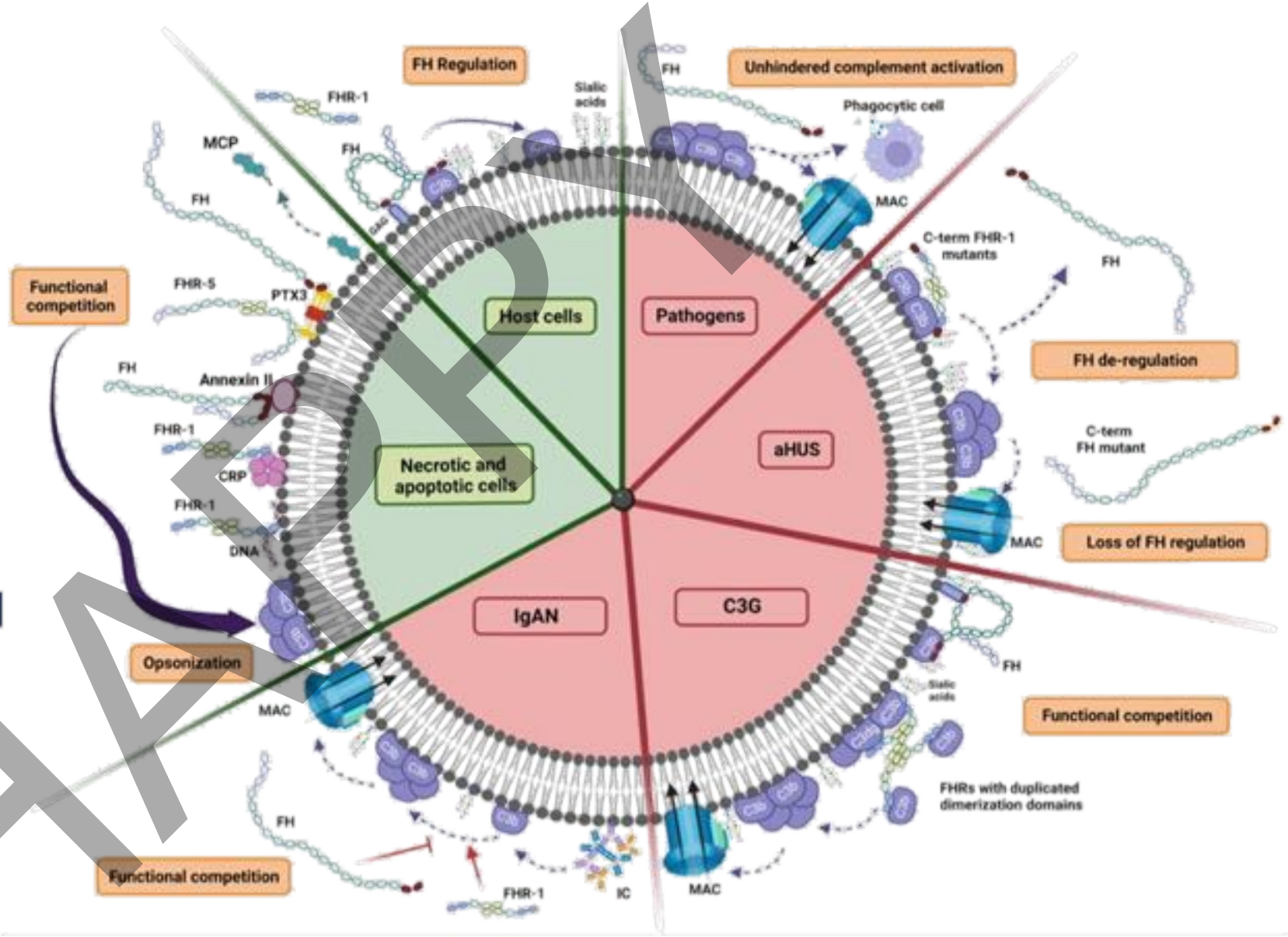
The same CFH or C3 defect can give either C3G or aHUS because it does not rigidly “encode a disease”; it shifts complement regulation, and the final phenotype depends on where and how AP activation becomes dominant

Factor H in C3G and aHUS



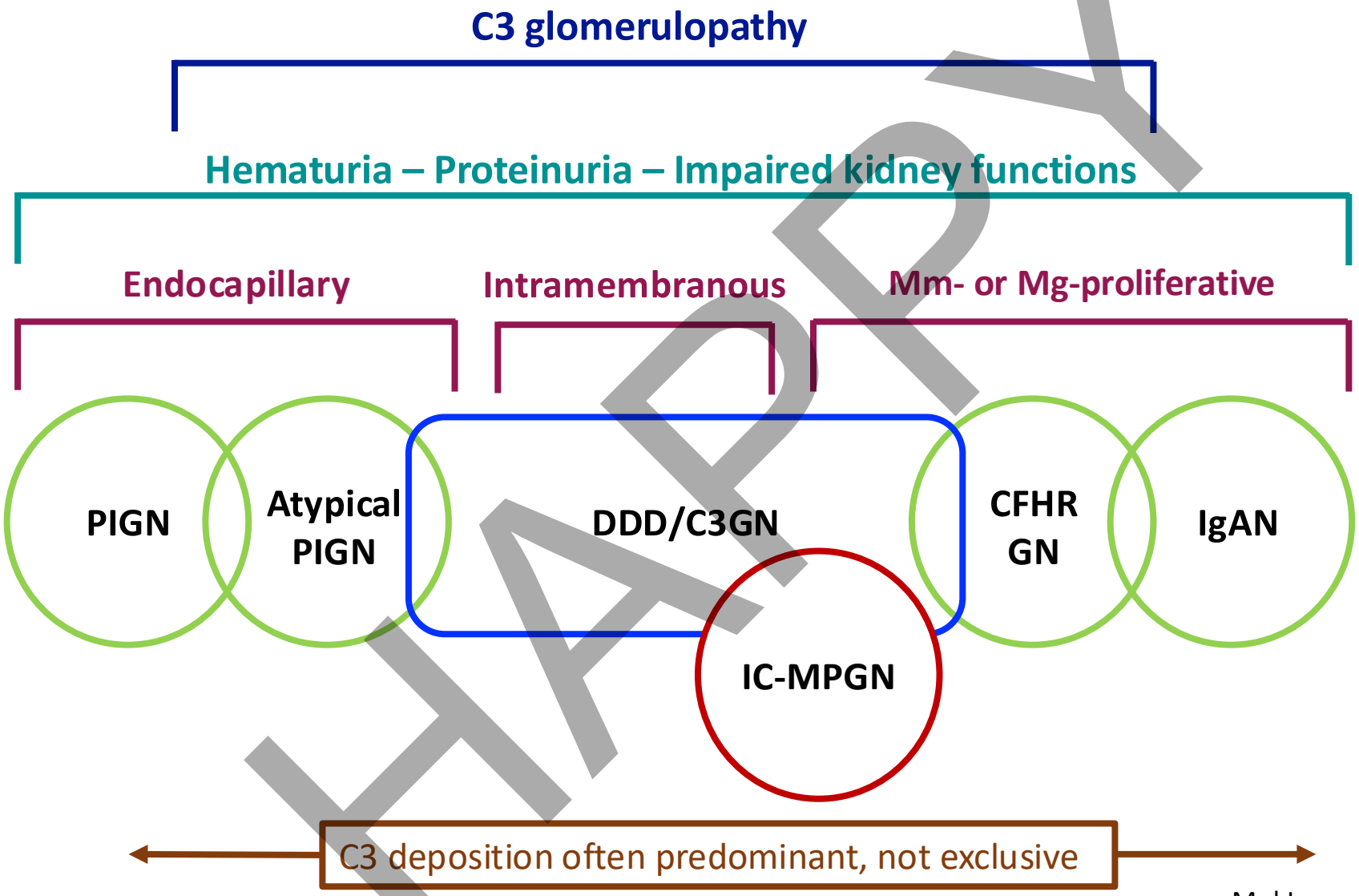
Front Immunol. 2017:8:1800

Regulation of AP activation on cell surfaces by the FH protein family under physiological & pathological conditions



Immunol Rev. 2023;313(1):25-45

Classification of C3G/IC-MPGN



Mol Immunol. 2015;67(1):21-30 (modified)

Coexistence of aHUS & C3G

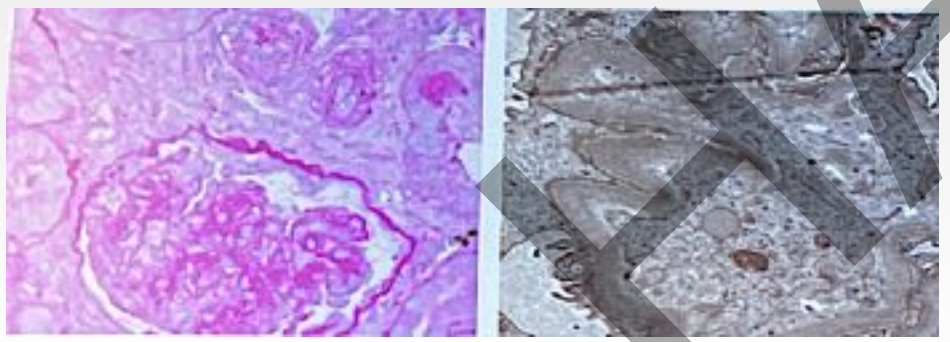
4 y/o boy with aHUS:

Nephrotic syndrome following recovery from aHUS (Dx by biopsy: C3GN)

Partial remission of proteinuria with steroids

Genetics: No identified mutation

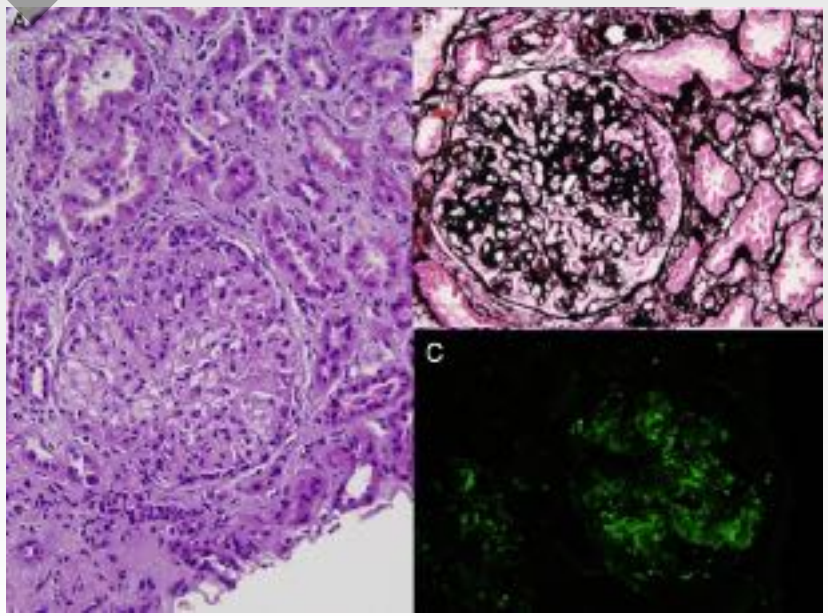
? Ravulizumab



15 y/o girl with C3G (proteinuria & impaired KFT) with normal C3 level. Biopsy >>> C3G

2 mo. later developed aHUS

Dx: CFI pathogenic variant



Nefrologia (Engl Ed). 2018;38(4):450-452

History:

A 12-y-old boy presented w non-nephrotic proteinuria (0.6 g/d) w normal KFT and low C3 level (9 mg/dl) and normal C4.

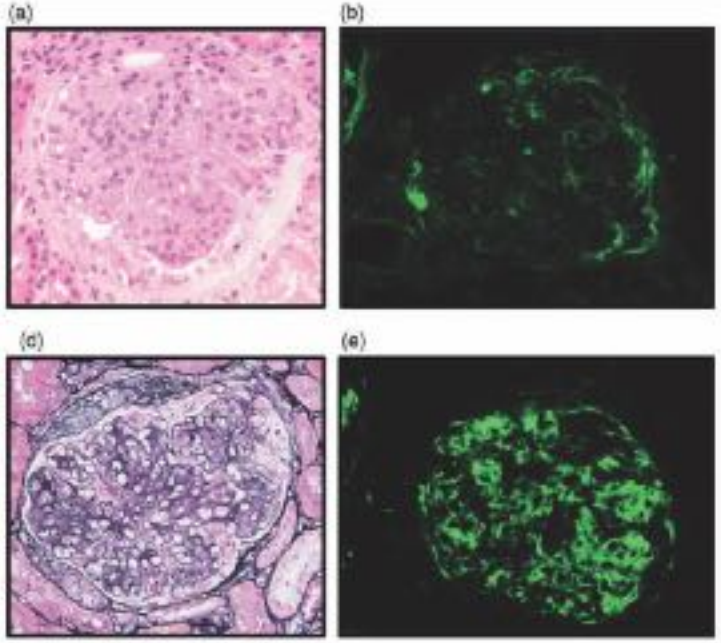
-ve family H of nephropathy.

Kidney Int Rep. 2020;6(2):534-537

History:

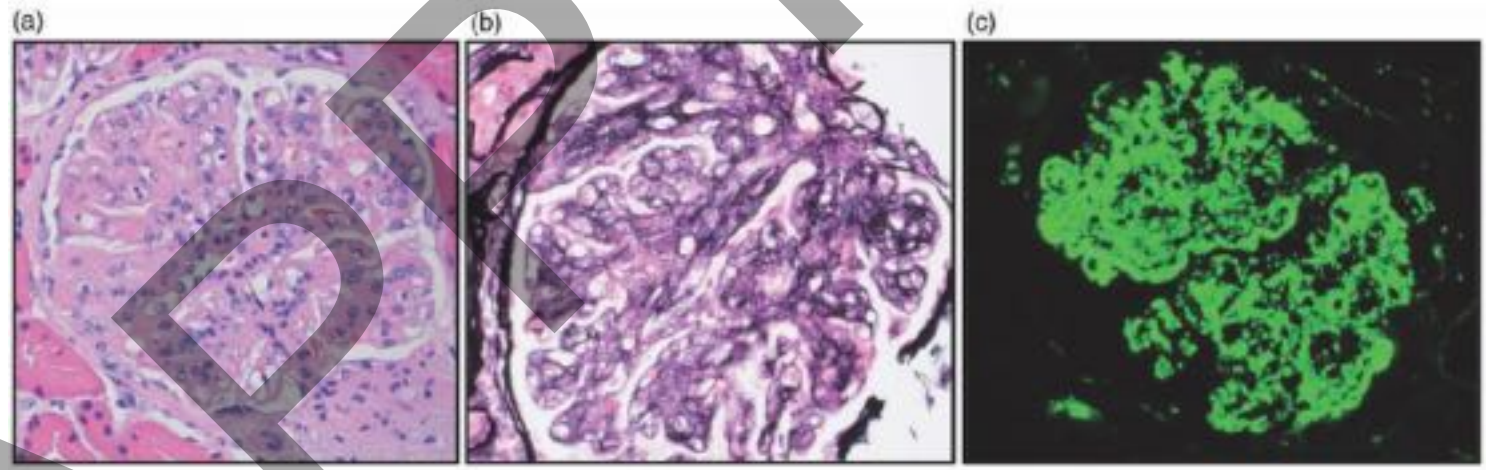
The patient was admitted again 2 weeks later in an anasarcatic state with HTN. During hospitalization, worsening of anemia, low platelet count, and elevated hemolysis indices.

C3G and previous diagnosis of SLE



Diffusive proliferative LN (class IV) with mesangial & irregular capillary loop IF staining IgG and C3

20 y old female
Malar rash, + ANA, + anti-dsDNA



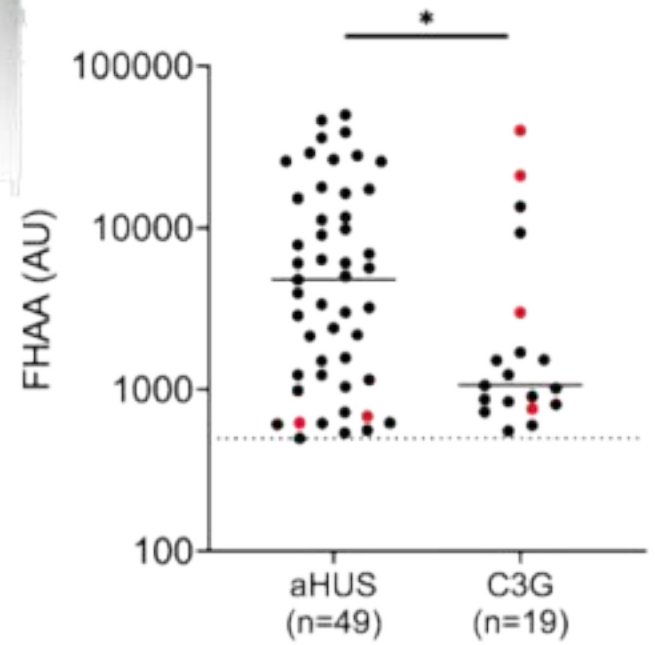
Repeat renal biopsy showing C3GN. a,b. MmPGN c. I/F staining of C3

C3GN could represent an additional mechanism of renal injury in SLE mediated by alternative complement pathway dysregulation in genetically susceptible individuals.

Lupus 2021; 30(10):1671-1678

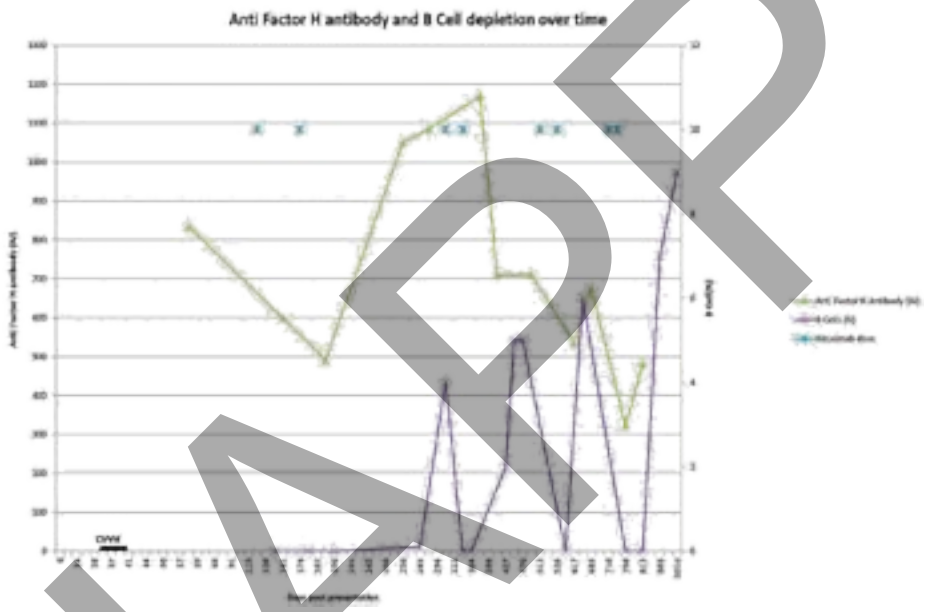
BMC Nephrol 2015; 16: 40.

Anti FH Ab



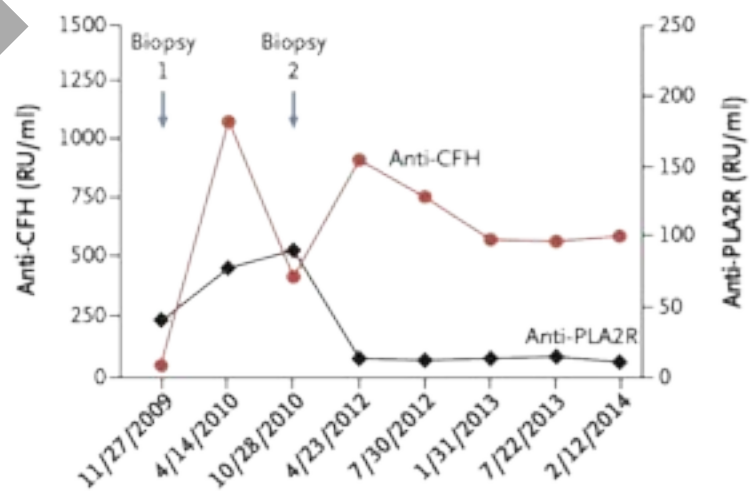
In aHUS and C3G

Front Immunol. 2020;11:607211



In IC-MPGN

BMJ Case Rep 2022;15:e246281

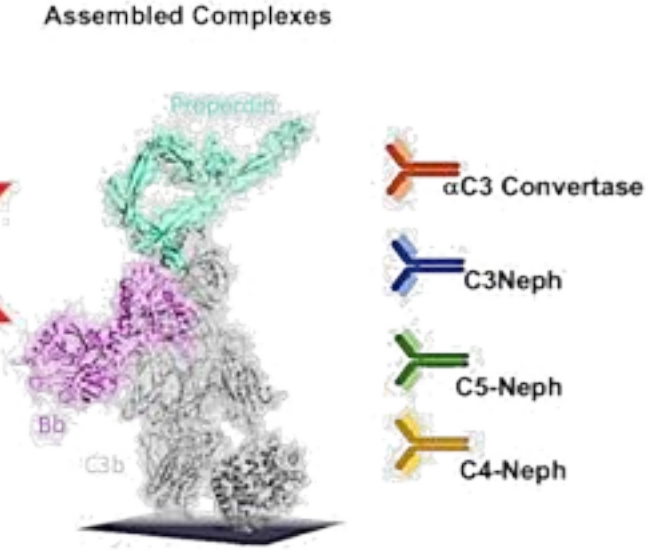


Creatinine (mg/dl)	1.18	2.26	2.83	5.57	4.87	4.87	4.32	4.17
Proteinuria (g/24 hr)	20.9	17.6	24.6	NA	4.8	4.0	2.3	1.6

In membranous nephropathy

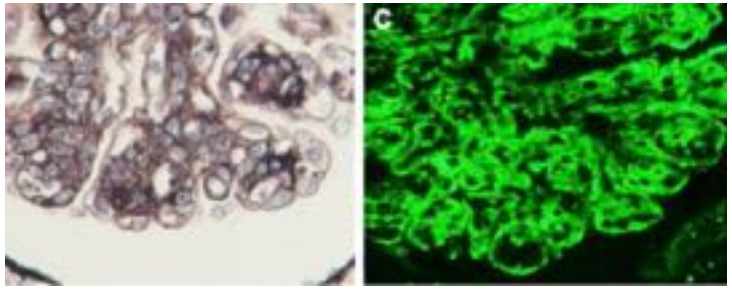
N Engl J Med. 2018;379(25):2479-2481

C3Neph



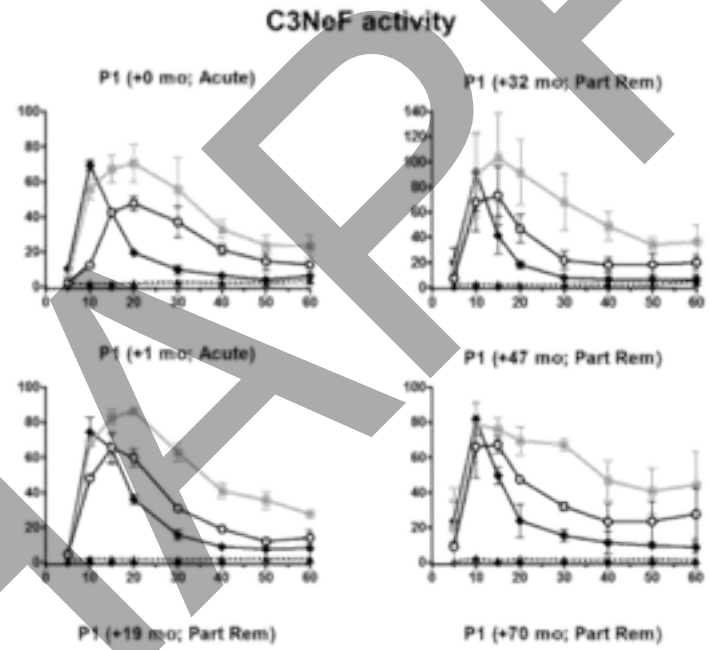
C3NeF factors bind to neoepitopes of the AP C3 convertase, stabilizing the enzyme and leading to increased activity and C3 consumption.

Front Nephrol. 2024;4:1460146.



C3G

Pediatr Nephrol 2014; 29:85–94



IC-MPGN

Front Immunol. 2021;12:715704

Atypical PIGN

Nephrol Dial Transplant. 1994;9(12):1747-50

SLE

QJM. 1994;87(10):609-15

C3 / C4

Disease	C3 level	C4 level	Notes
C3G J Clin Pathol 2024;77(7): 503-506	Usually low	Usually normal	Can be normal in some cases or later phases
IC-MPGN Front Immunol. 2021;12:715704	Normal to mild low	Often low	Immune-complex driven CP/LP activation
PIGN Glomerular Dis. 2021;1(2):82-91	Low and normalizes > 8 w	Usually normal	Persistent ↓C3 = atypical PIGN
aHUS Kidney Int. 2017;91(3):539-551	Low in ~30% of cases	Usually normal	Non-sensitive marker
IgA J Am Soc Nephrol. 2015;26(7):1503-12	Usually normal	Usually normal	↓C3 indicates poor prognosis
SLE Curr Rheumatol Rep. 2021;23(3):16	Usually low	Usually low	Immune-complex driven CP activation

CMKDs in children form a continuous spectrum driven by shared alternative pathway dysregulation, so overlap in clinical phenotype, histology, genetics and even within the same patient is common rather than exceptional.

You need a dynamic, clinicopathologic approach: don't anchor on the first biopsy or on genetics alone, and expect the pattern to evolve over time.

Kidney Biopsy

Repeat biopsy in C3G/MPGN

1. Unexpected clinical course
2. Poor response to therapy
3. Shift towards chronic sclerosing or TMA

KDIGO and recent C3G/MPGN reviews highlight repeated biopsy as important to assess activity vs chronicity, monitor response to complement-targeted drugs, and refine etiology over time

Kidney Int. 2024;106(3):369-391

DO NOT rely on genetics alone

1. Both aHUS and C3G show incomplete penetrance and broad pleiotropy

Kidney Int. 2017;91(3):539-551

2. About 40% of primary aHUS without identified genetic mutation

3. The same CFH, C3, CFI, or CFHR variant may be found in healthy carriers

4. For living-related donors, genetics are crucial but still probabilistic

Curr Transplant Rep. 2025;12(1):11.

- **CMKDs in children form a continuous spectrum driven by shared alternative pathway dysregulation.**
- **Different CMKDs can share genetics or clinical phenotypes.**
- **We need a dynamic, clinicopathologic approach: don’t anchor on the first biopsy or on genetics alone, and expect the pattern to evolve over time.**