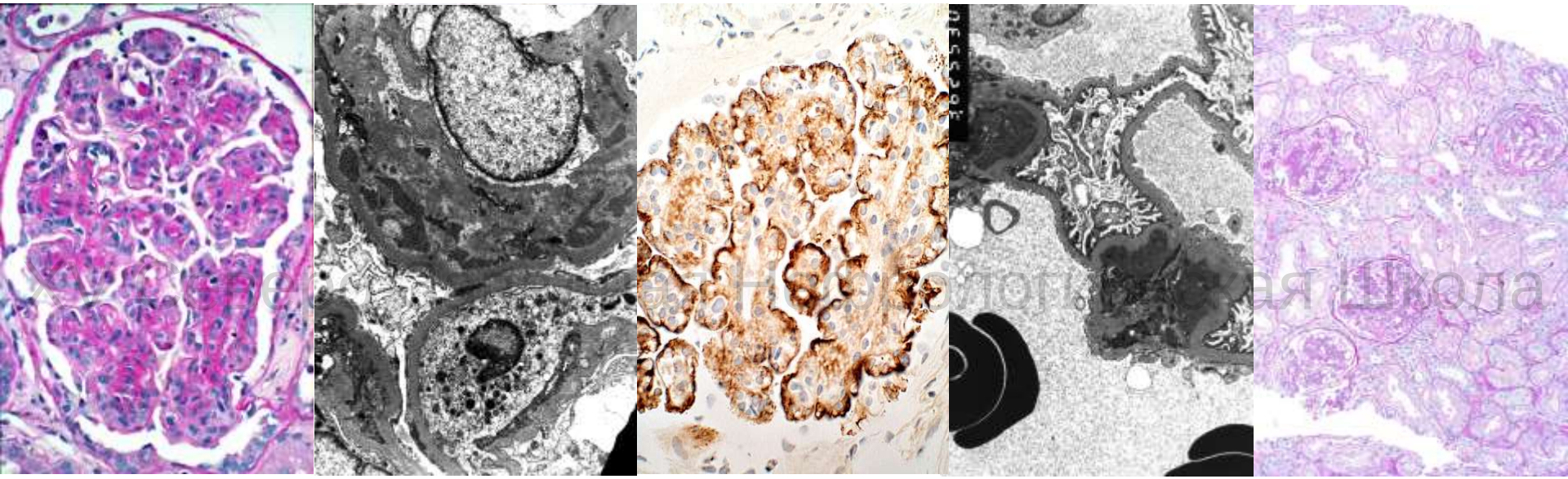
Membranoproliferative GN



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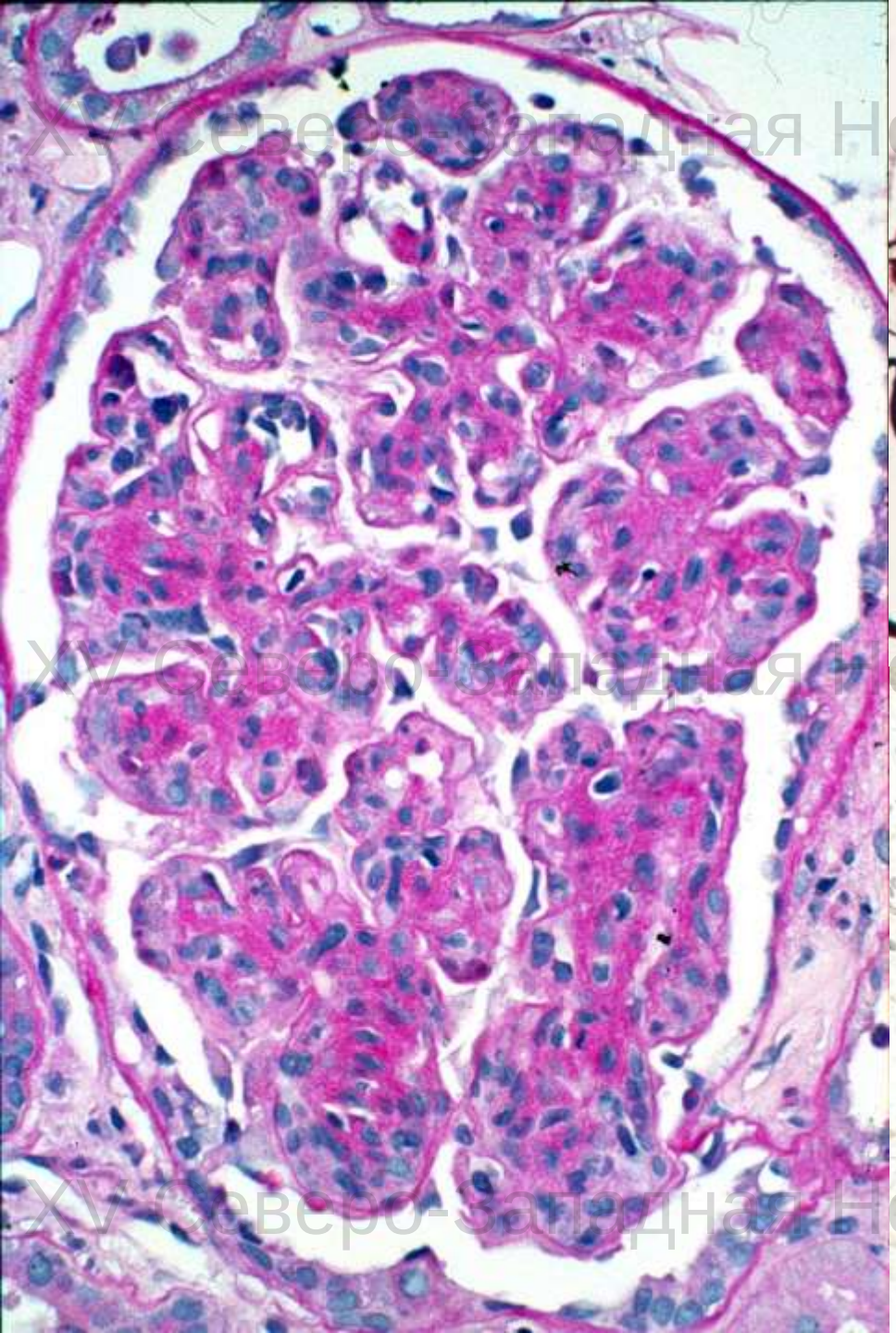

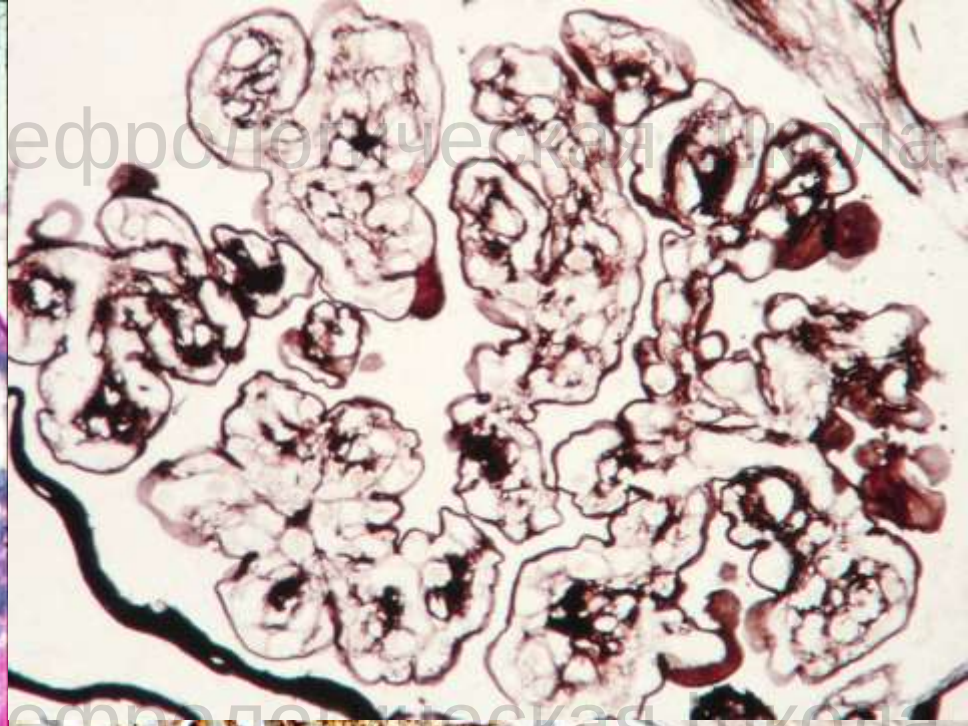

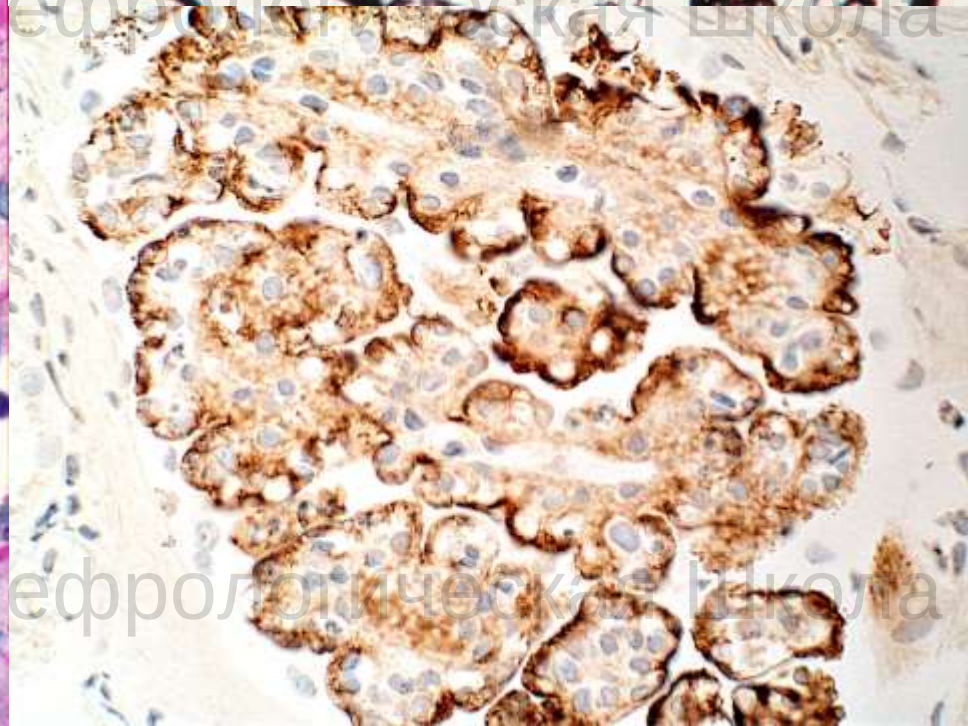

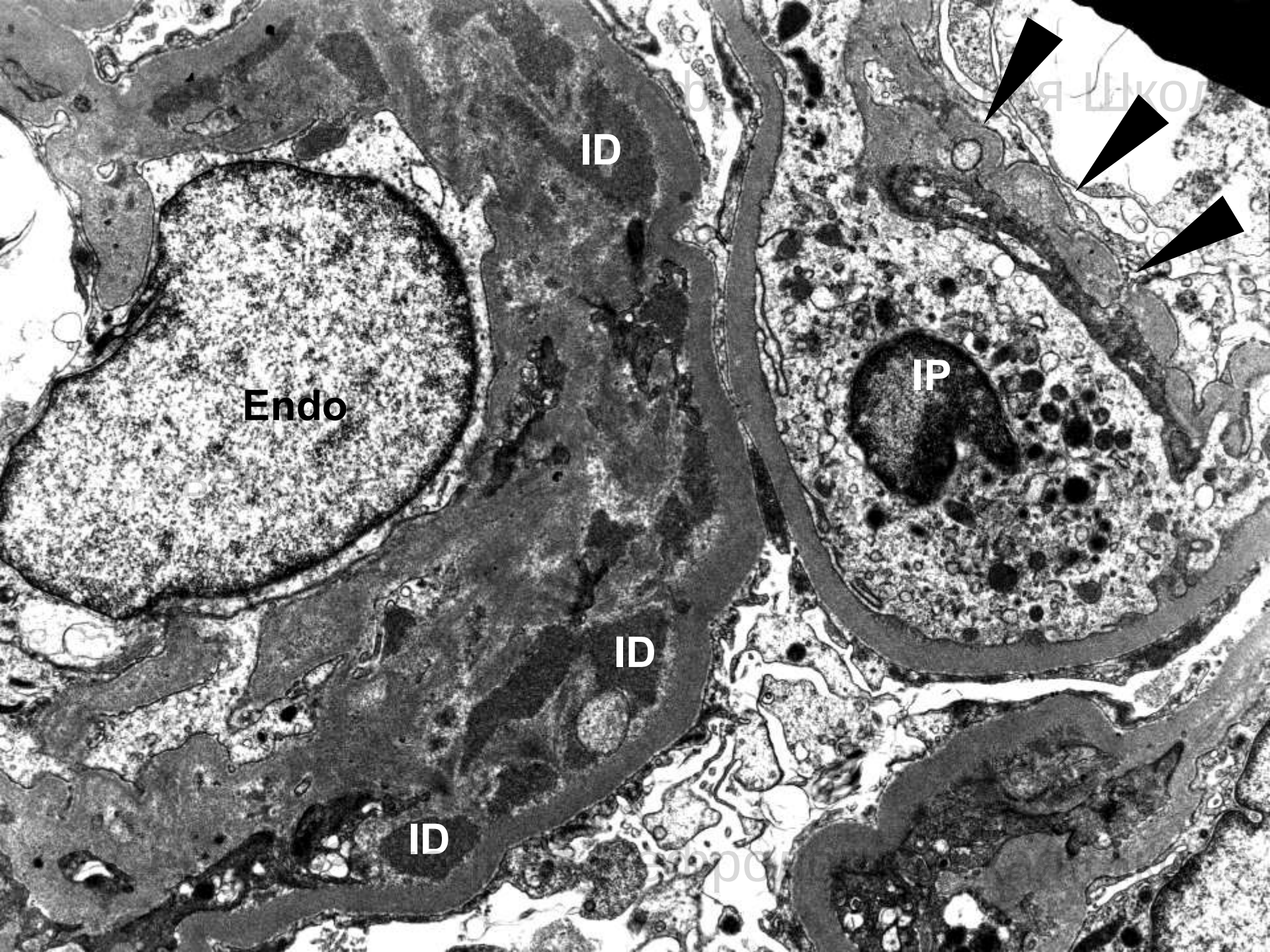
ID
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Membranoproliferative GN (MPGN)

Light microscopy

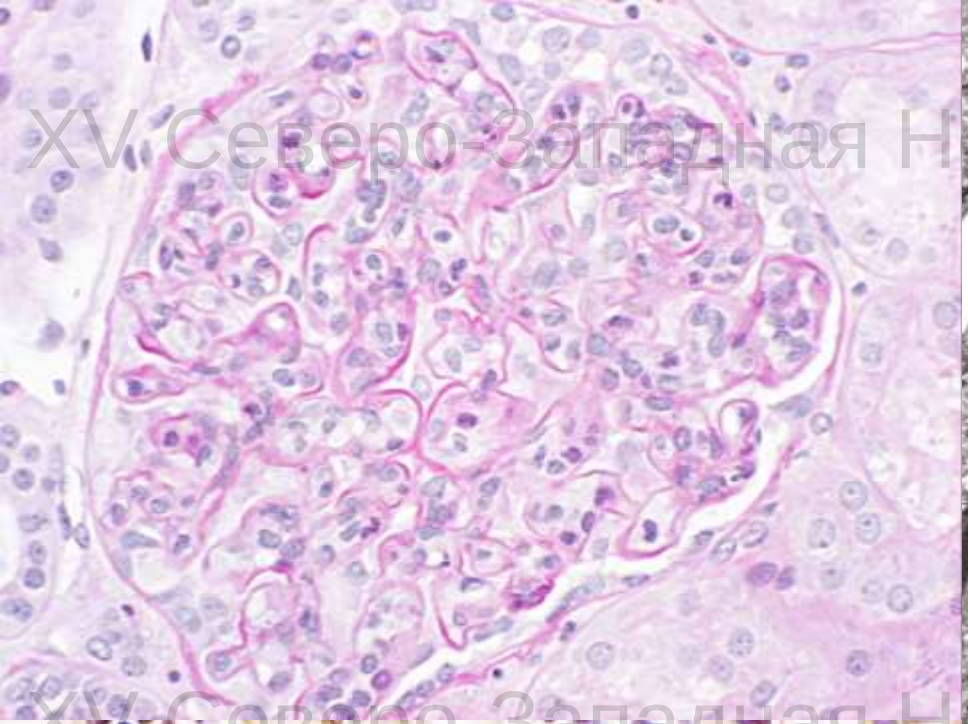
- "Lobulation" of the glomerular tuft
- Mesangial/endocapillary proliferation
- BM thickening, remodelling with double contours

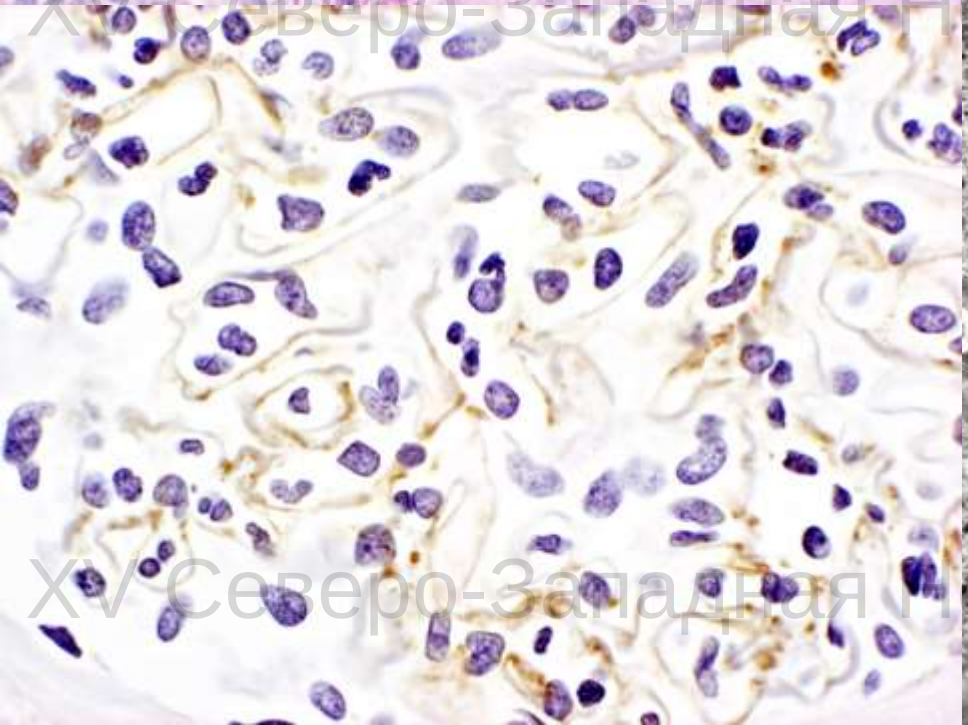
Immunohistology

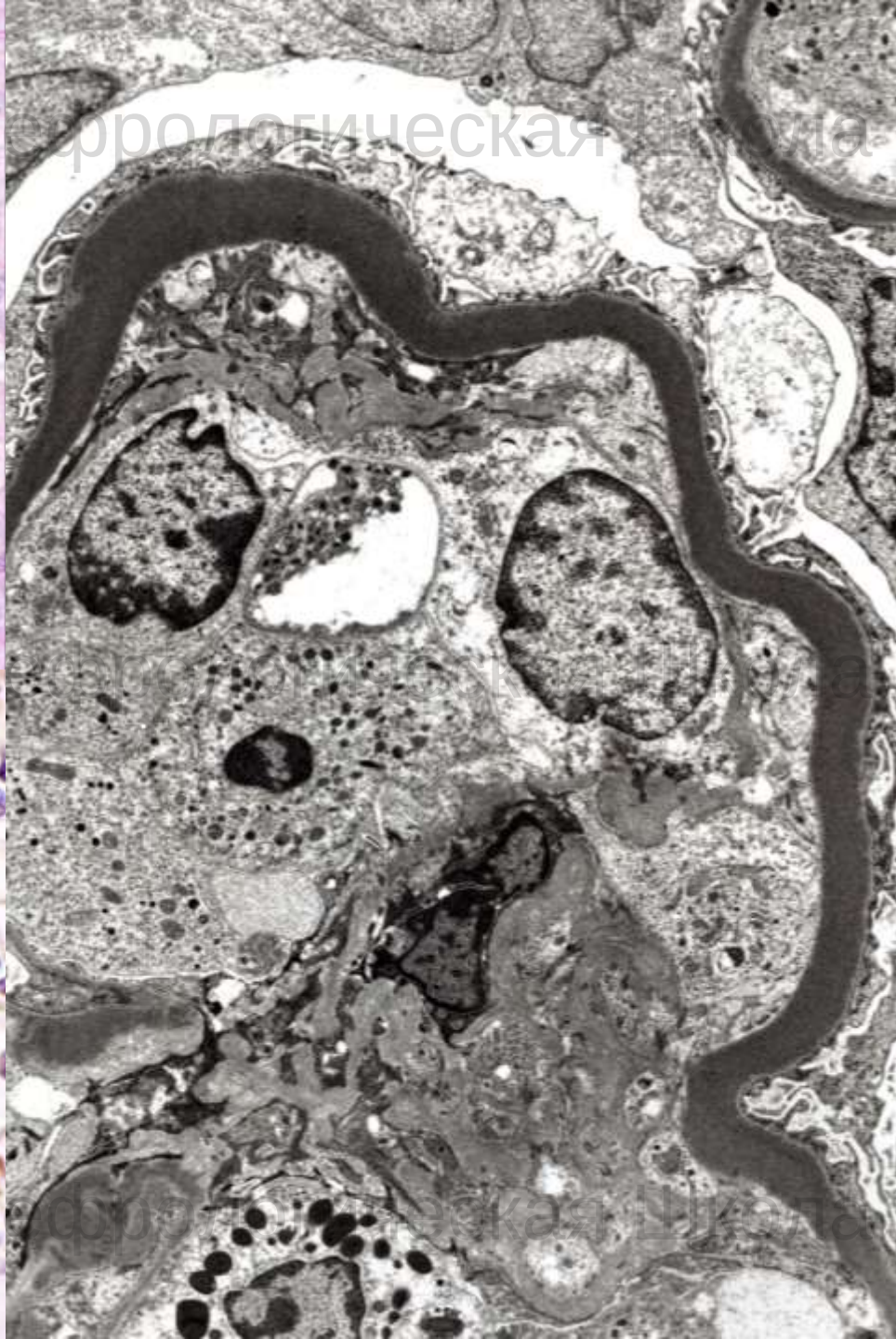
- Variable amounts of IgG, IgM, C1q with sometimes dominant C3

Electron microscopy

- Subendothelial Immune deposits
- BM double contours (mesangial Interposition)
- (Intramembranous dense deposits (MPGN TypeII))
- (other patterns of deposits (MPGN Type III))







Membranoproliferative GN (MPGN)

Etiology

- **"Primary/idiopathic"**

- **Associated with other diseases**

  Viral infections (Hepatitis-B,-C, HIV....)
  Bacterial infections ("shunt nephritis", endocarditis, syphilis)
  Auto-immune diseases (SLE, rheumatoid arthritis)
  Monoclonal gammopathy

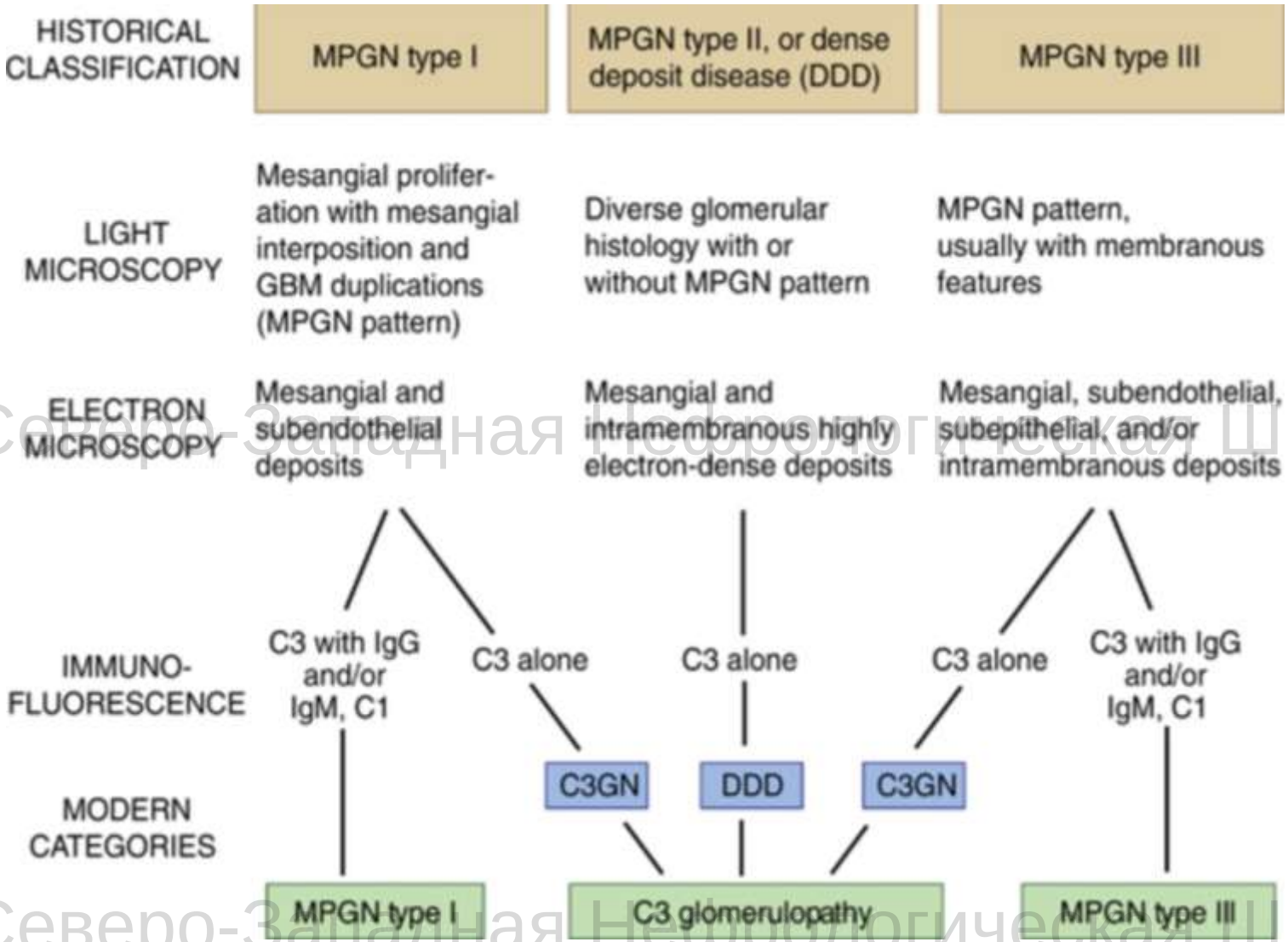
Pathogenesis

Glomerular immune-complex depsition (IgG, IgM, complement components)

and/or

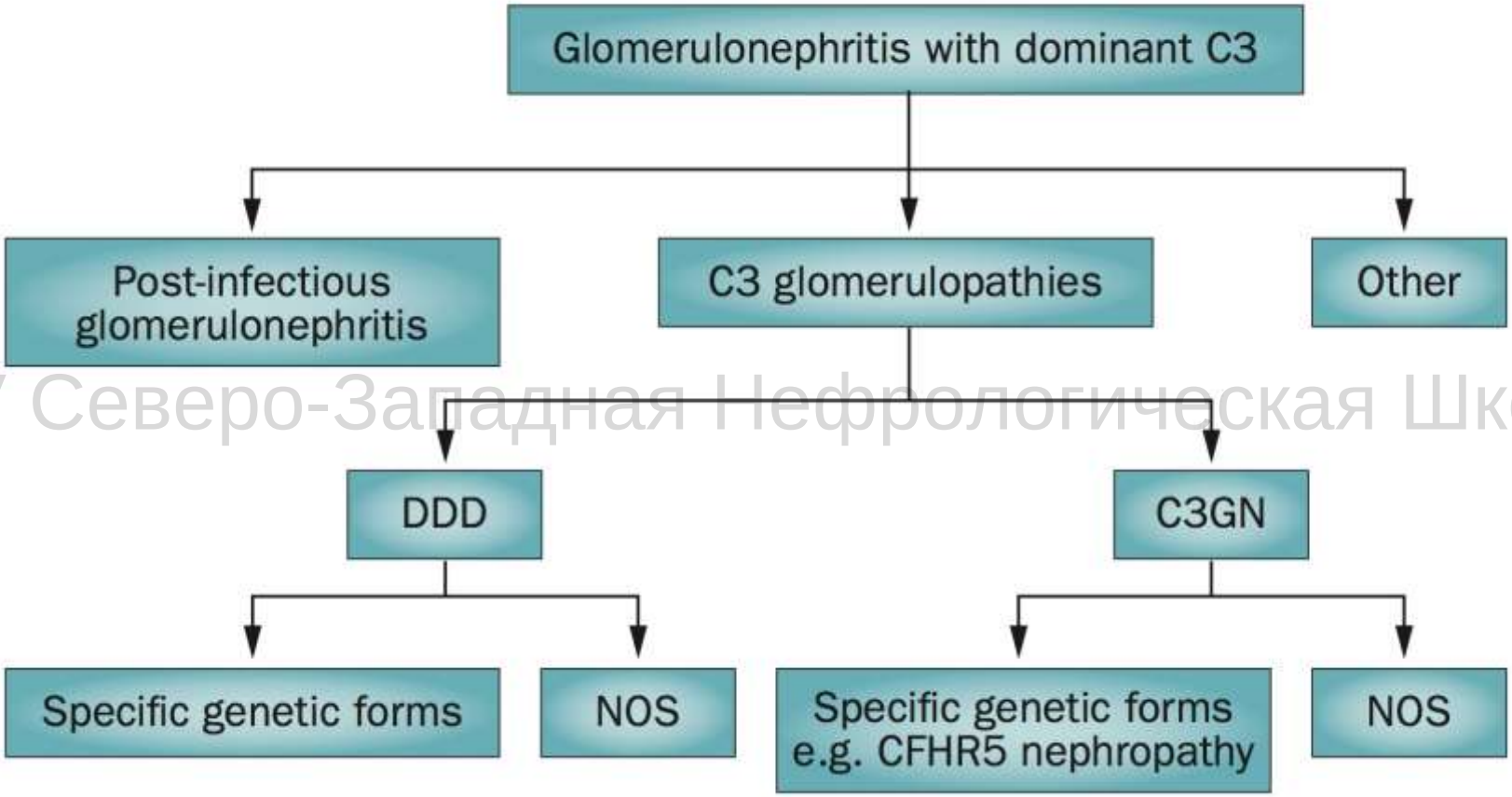
Defective control of complement activation leading to exessive accumulation of C3 (fist acknowledged in DDD)

Membranoproliferative GN (MPGN)



D'Agati V. et al., Kidney Int 2012

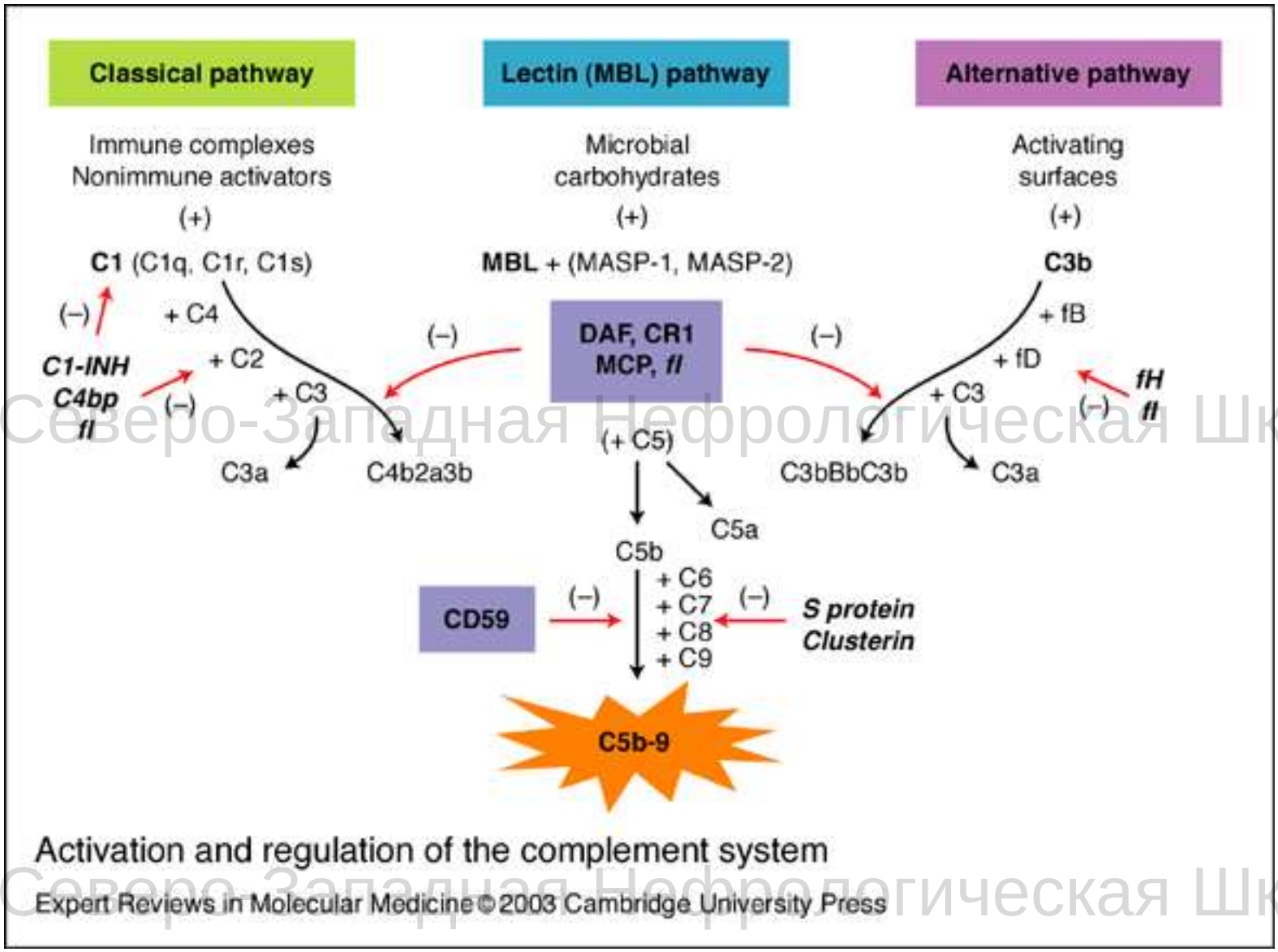
Diagnostic algorithm for C3-dominant glomerulopathy



C3 glomerulopathy: consenus report

Pickering M. et al, Kidney Int 2013

Complement activation pathways



Activation and regulation of the complement system

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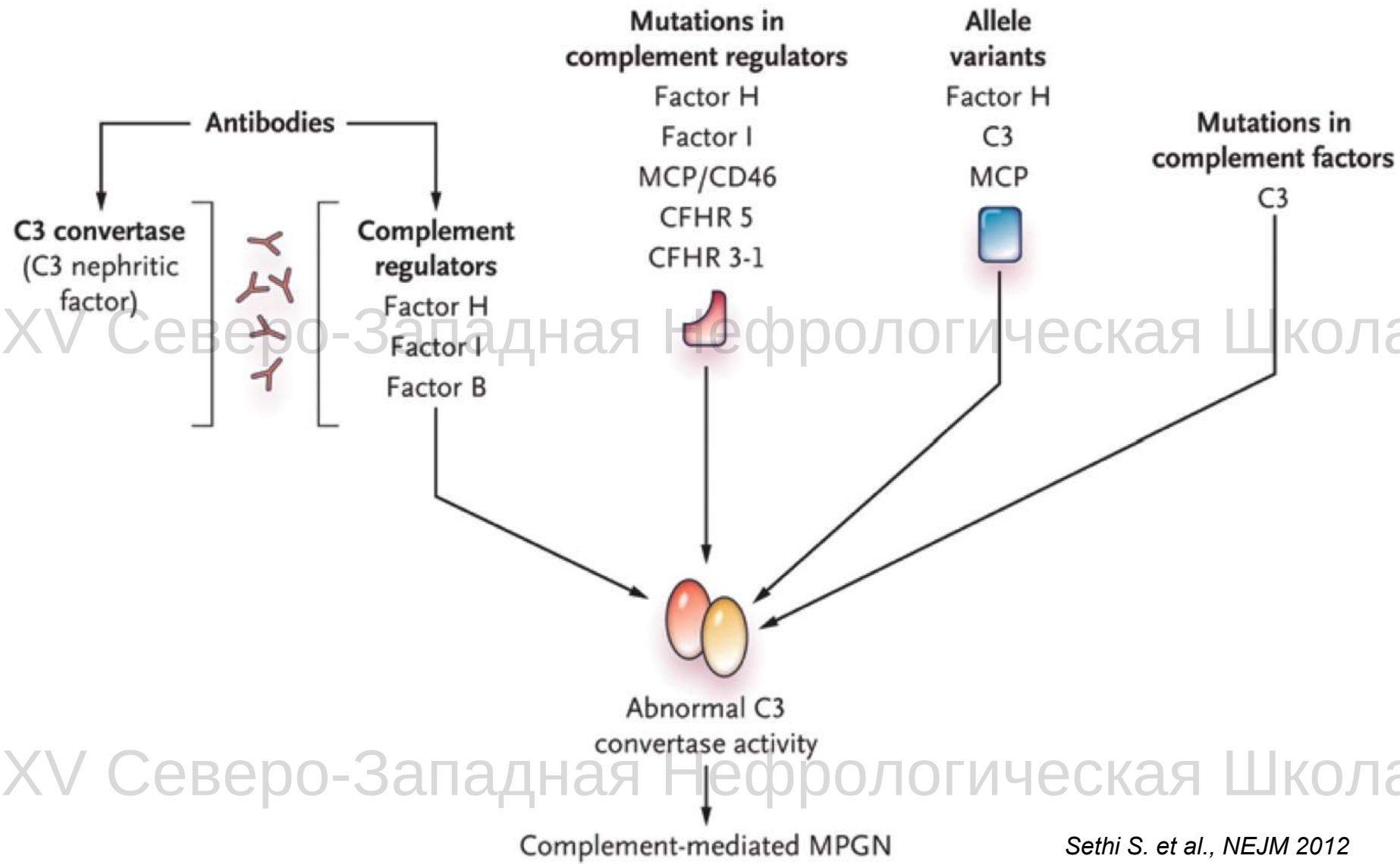
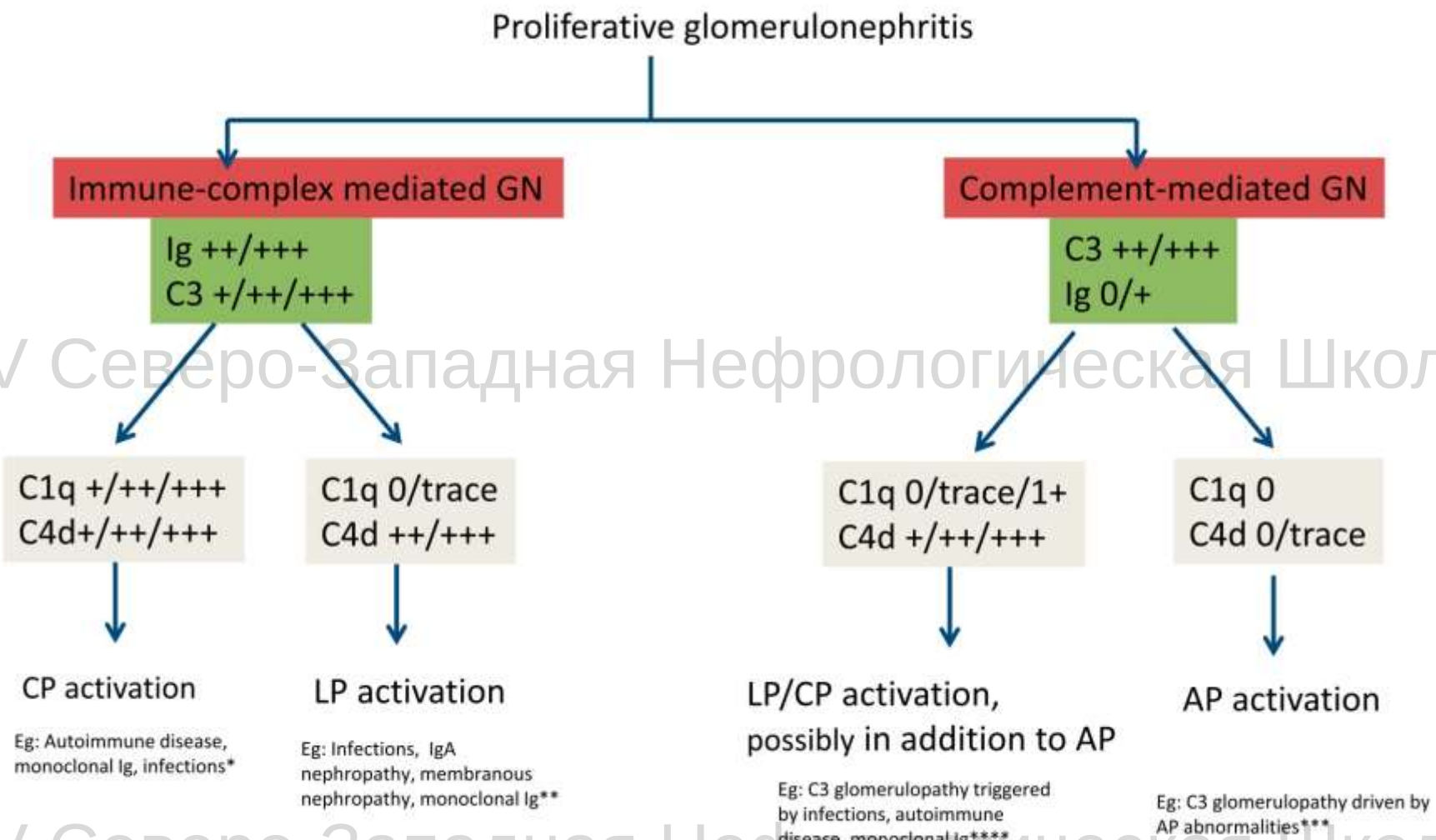
Molecular mechanisms of inadquately regulated AP



Sethi S. et al., NEJM 2012

C4d staining as diagnostic aid in C3 glomerulopathy



Sethi S. et al., JASN 2015

Complement investigations in C3 glomerulopathy

Tests/measurements recommended in all patients

- **Serum C3 and C4**
- **C3 nephritic factor (C3NeF)**
- **Complement factor H (CFH)**
- **Serum paraprotein**
- **Screening for CFHR5 mutation**

Further testing should be considered on a case-by-case basis as they require expert interpretation and/or clinical validation

•Measurement of serum factor B, C5, C3 activation, C3adesArg, C5 activation, soluble C5b-9
•Measurement of anti-factor H autoantibodies anti-factor B autoantibodies
•Mutation screening of complement regulatory and activation genes (e.g., CFH, CFI, CD46, C3, CFB)

European complement network: http://www.ecomplement.org

C3 glomerulopathy: consenus report ***Pickering M. et al, Kidney Int 2013***

C3 Glomerulopathies

C3 Glomerulonephritis

Dense Deposit Disease (formerly MPGN II)

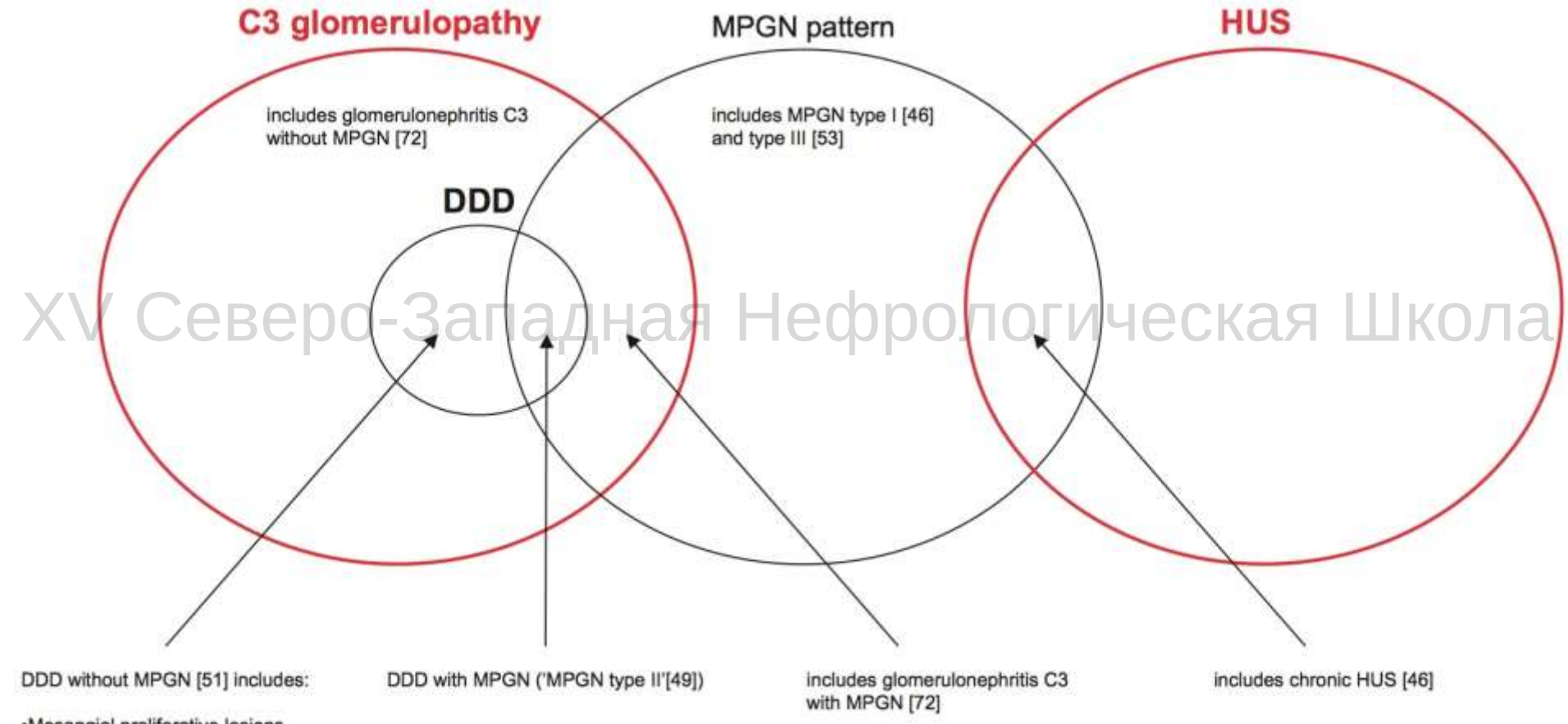
Familial C3 glomerulopathies (i.e. CFHR5 mutation)

Atypical postinfectious GN

Other “atypical” GN types?

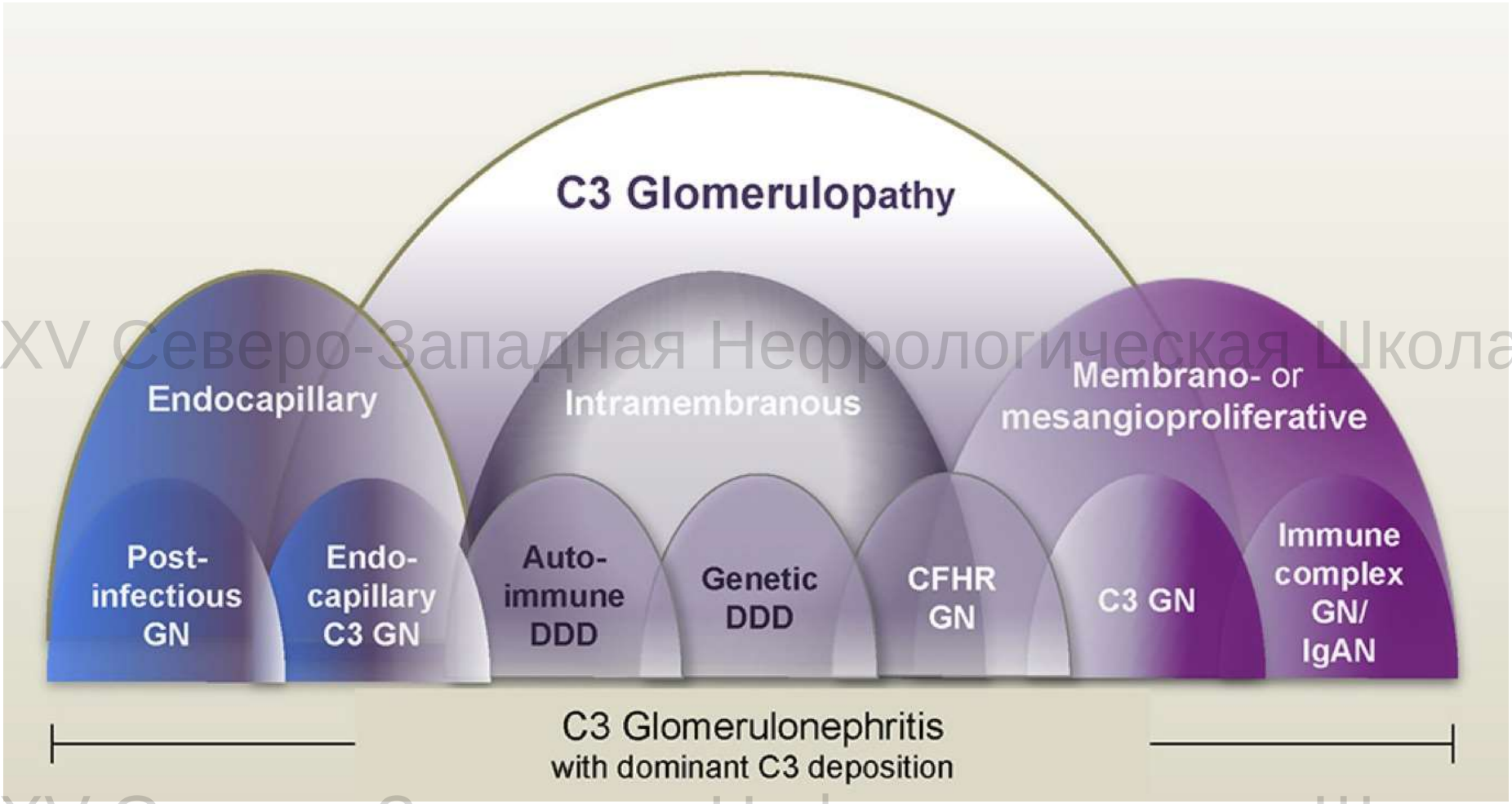
(Thrombotic microangiopathy)

Renal diseases associated with AP dysregulation



Pickering M.C. et al., Clin Exp Immunol 2008

Morphological patterns of C3 Glomerulopathies



Zipfel P.F. et al., Mol Immunol 2015

Laboratory findings in differnt types of MPGN pattern of injury

Table 2
Clinical and laboratory findings in different histology groups.

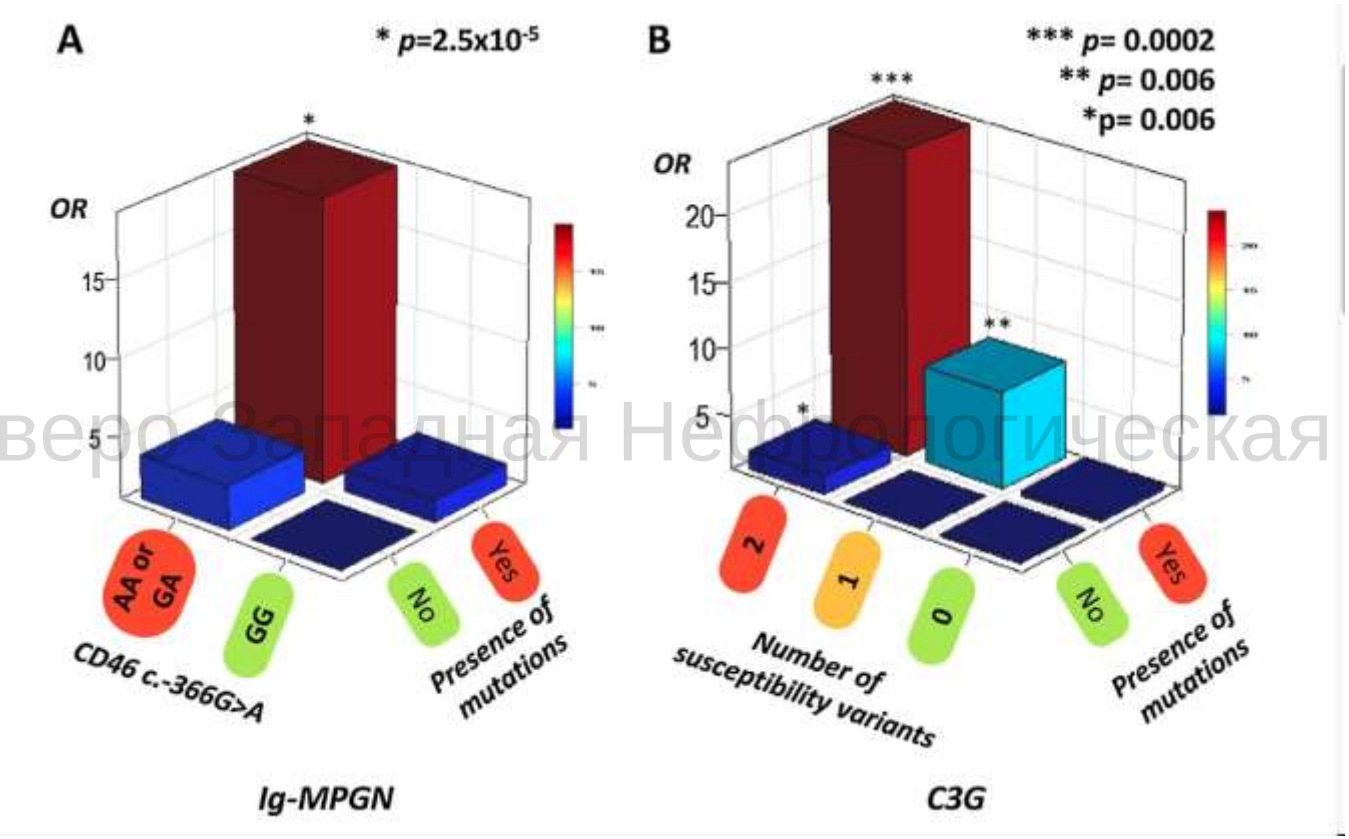
	Ig-MPGN	C3G		
			DDD	C3GN
N	67	73	21	52
Gender (% males)	51%	41%	38%	42%
Data at onset				
Age (*y*)—mean (SD)	20.1 (±15.2)[a]	15.0 (±11.9)[a]	15.9 (±11.4)	14.6 (±12.1)
Microhematuria	86%	86%	90%	84%
Gross hematuria	35%	38%	38%	38%
Proteinuria	88%	90%	86%	92%
Nephrotic syndrome	43%	29%	29%	29%
Renal impairment	27%[b]	14%	5%[b]	17%
Trigger event	31%	42%	41%	42%
C3NeFs positive	44%[e]	54%	78%[e,f]	44%[f]
Serum C3 (mg/dl)—Median (IQR)	45 (13–77)[c]	38 (15–73)	20 (9–46)[c,d]	44 (17–87)[d]
Serum C4 (mg/dl)—Median (IQR)	21 (12–29)	21 (17–27)	26 (20-29)	21 (17–25)
Low Serum C3 & normal C4	67%	74%	86%	69%
Plasma SC5b-9 (ng/ml)—Median (IQR)	515(286–1860)	417(228–1033)	353(252–623)	486(215–1140)
Mutation carriers*	17%	18%	14%	20%
Mutation carriers and/or C3NeFs*	56%	65%	83%	58%
Familiarity for nephropathy*	11%	14%	10%	16%

Nephrotic syndrome was defined as: 24-h proteinuria exceeding 3.5 g in adults or 40 mg/h/m2 in children together with albuminemia ≤3 g/L. Renal impairment was defined as abnormal serum creatinine levels. Familiarity for nephropathy was defined as the presence of at least one relative (up to 3rd degree) with biopsy-proven Ig-MPGN/C3G, or proteinuria and/or renal impairment without other apparent cause.

* Calculated in unrelated patients (64 Ig-MPGN, 21 DDD and 50C3GN).

Iatropoulos P. et al., Molecular Immunol 2016

Risk for MPGN and C3 GN increases with number of genetic variants



The presence of **mutations alone does not significantly increase the risk of Ig-MPGN or C3G**, **but it does so when combined with common susceptibility variants** (CD46 c.-366A in Ig-MPGN; CFH V62 and THBD A473 in C3G)

Iatropoulos P. et al., Molecular Immunol 2016

The phenotype of renal disease in AP control defects is variable might be determined by the type of trigger

Partial Complement Factor H Deficiency Associates with C3 Glomerulopathy and Thrombotic Microangiopathy

Katherine A. Vernon, Marieta M. Ruseva, H. Terence Cook, Marina Botto, Talat H. Malik, and Matthew C. Pickering

J Am Soc Nephrol 27: 1334–1342, 2016

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….subtotal FH deficiency associated with mesangial C3 accumulation consistent with C3G. Although there was no evidence of spontaneous thrombotic microangiopathy, the hepatocyte–specific FH–deficient animals **developed severe C5–dependent thrombotic microangiopathy after induction of complement activation within the kidney by accelerated serum nephrotoxic nephritis**. Taken together, our data indicate that subtotal FH deficiency can give rise to either spontaneous C3G or aHUS after a complement-activating trigger within the kidney and that the latter is C5 dependent.

The findings in this experimental model might provide an explanation for the **changes of phenotype from C3 GN to TMA or vice-versa in recurrent disease that we observed in five renal allograft recipients with defective AP control**.

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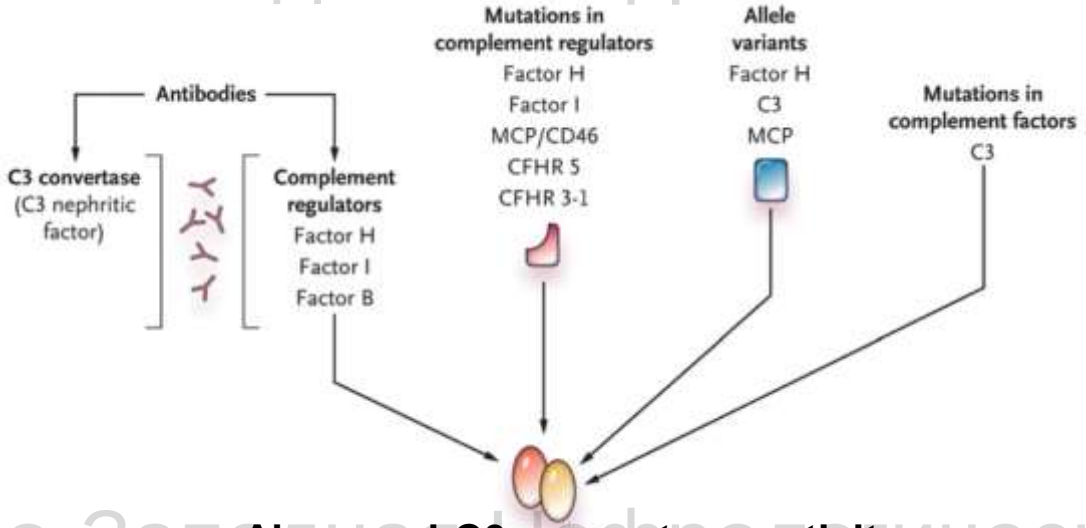
Pathogenesis of C3 related renal disease



Abnormal C3 convertase activity

Acquired triggers like infections, autoantibodies?, alloantibodies?, other pro-inflammatory conditions?

Induce renal disease and determine its phenotype

C3 GN | **IC-MPGN** | **TMA** | **other GN?**

Membranoproliferative GN (MPGN)

Summary

The conventional morphologic classification should be replaced by a pathogenesis based terminology

The spectrum of diseases and lesions associated with AP complement dysregulation is however not yet fully defined

Patients with C3 dominant glomerulopathies require systematic functional and genetic analyses of the complement system and its regulators.

AP dysregulation is a crucial pathogenic factor but phenotype and onset of disease are determined by additional “triggers“