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The Role of Genetics in Complement Mediated TMA

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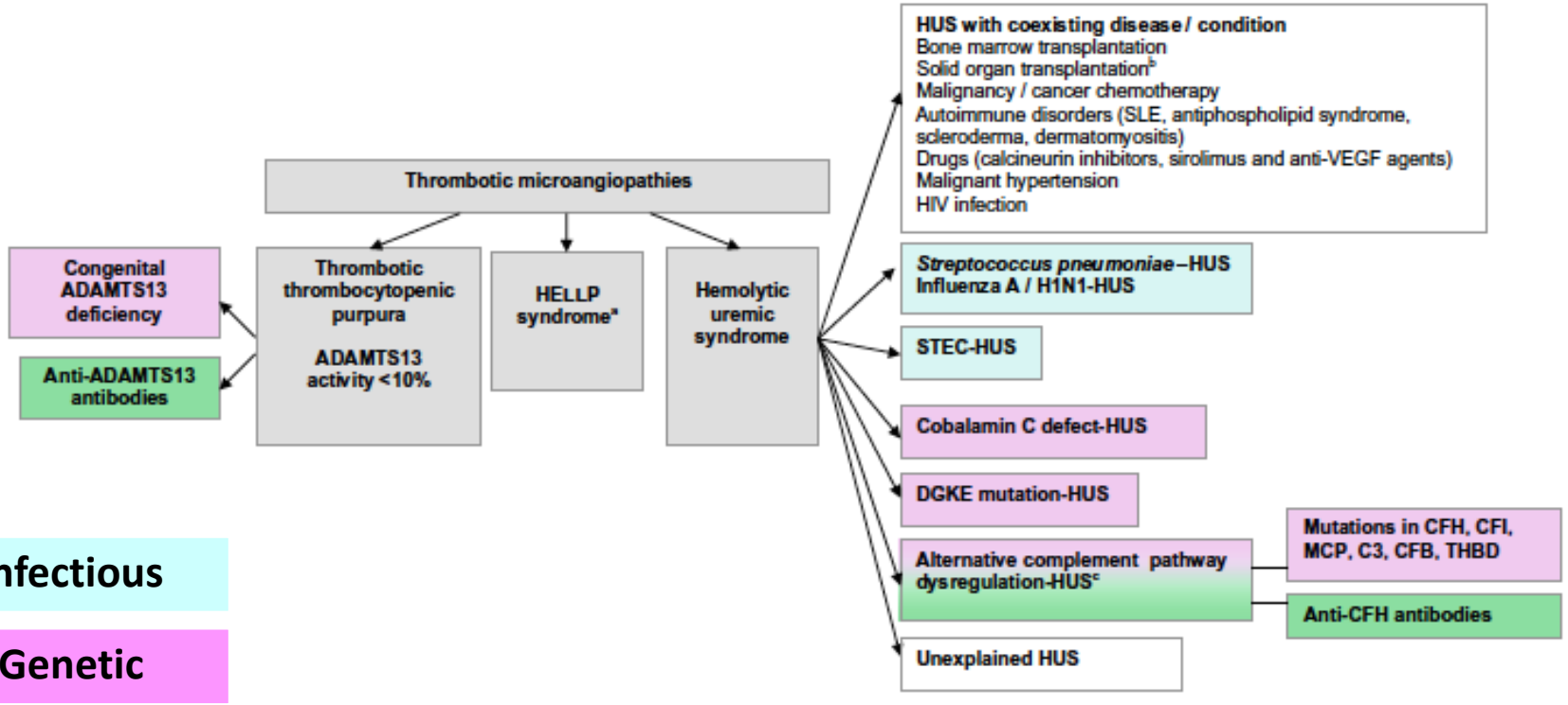
aHUS registry

ERKReg
The European Rare Kidney Disease Registry

European Reference Center for Rare Kidney Diseases

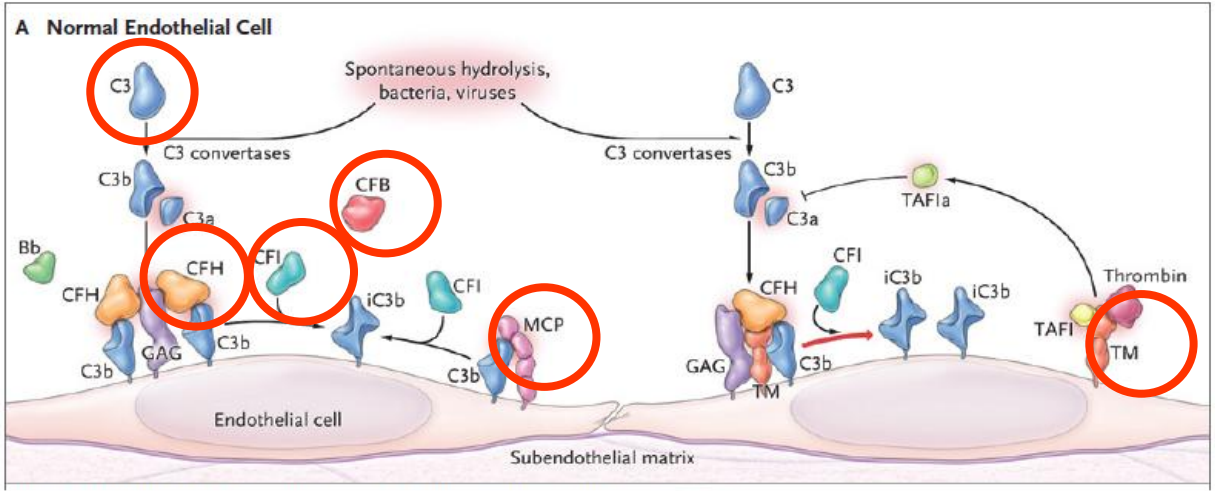
ERKNet
The European
Rare Kidney Disease
Reference Network

Spectrum of Etiologies in TMA/HUS



Loirat et al. Pediatr Nephrol 2015

Complement Dysregulation in aHUS



Noris and Remuzzi, New Engl J Med 2009; 361:1676-87

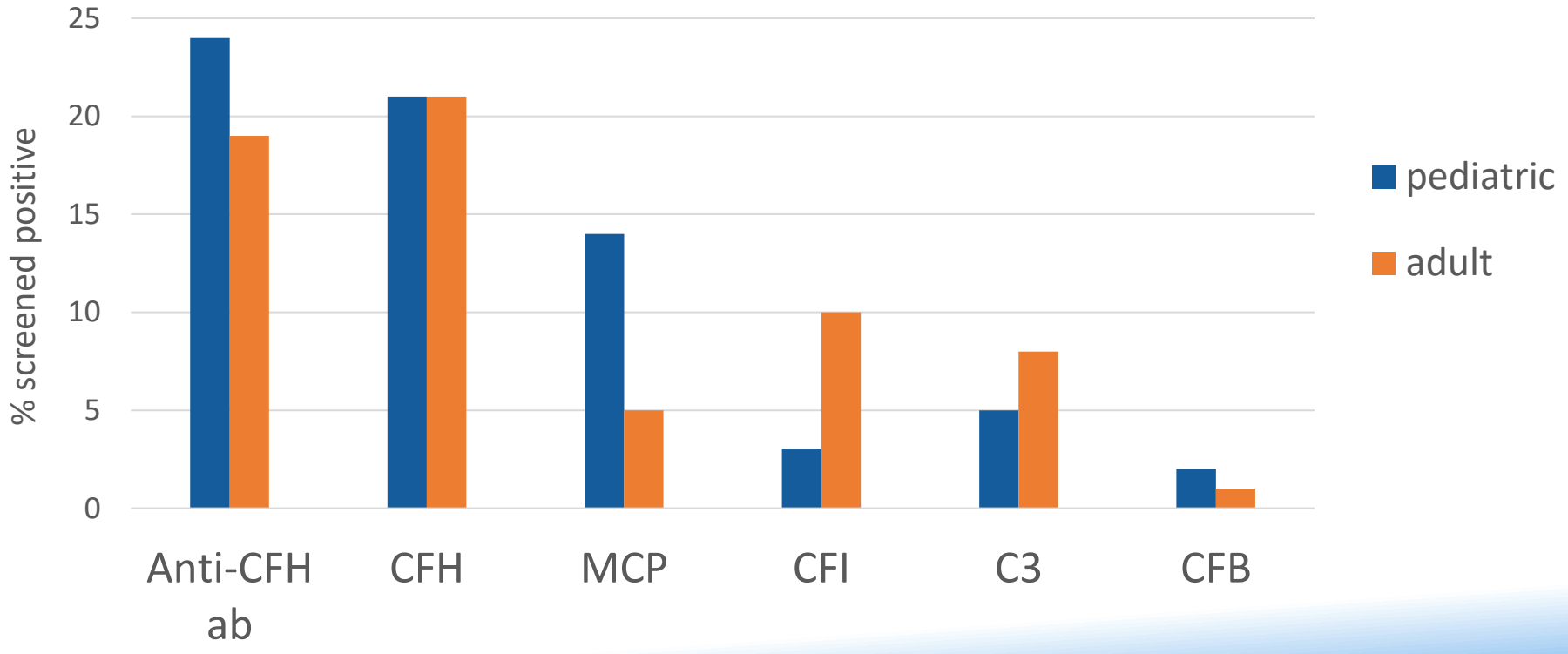
50-60 % explained by mutations in CFH, CFI, MCP, C3, CFB, TMBD

-> autosomal dominant transmission with incomplete penetrance

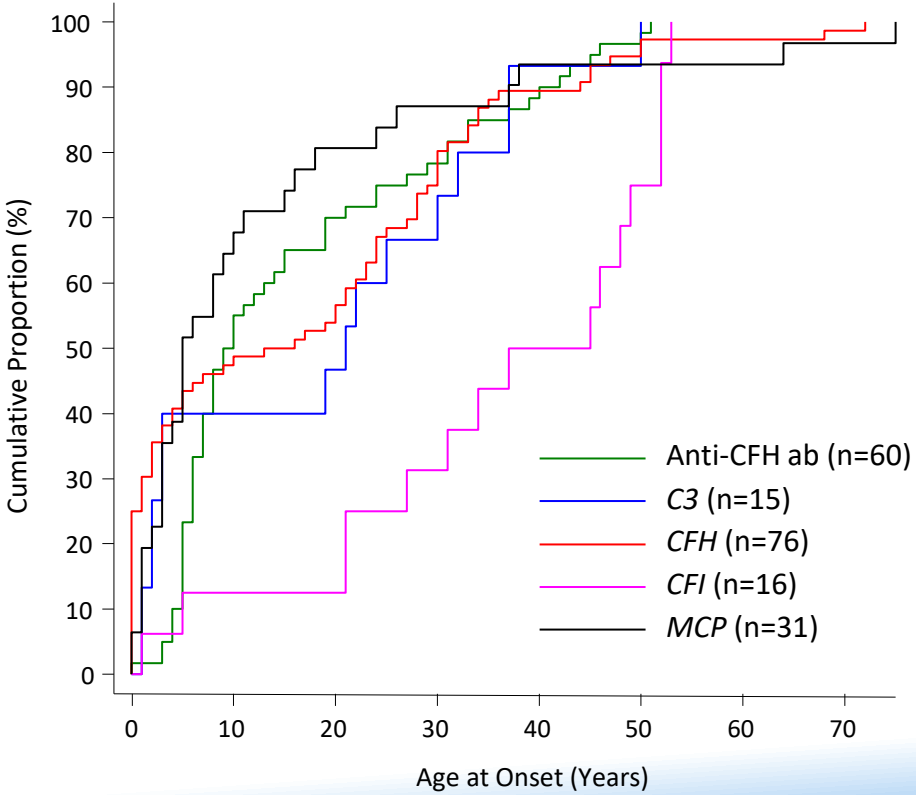
15-25% explained by factor H autoantibodies

Most Common Causes of aHUS

444 cases screened



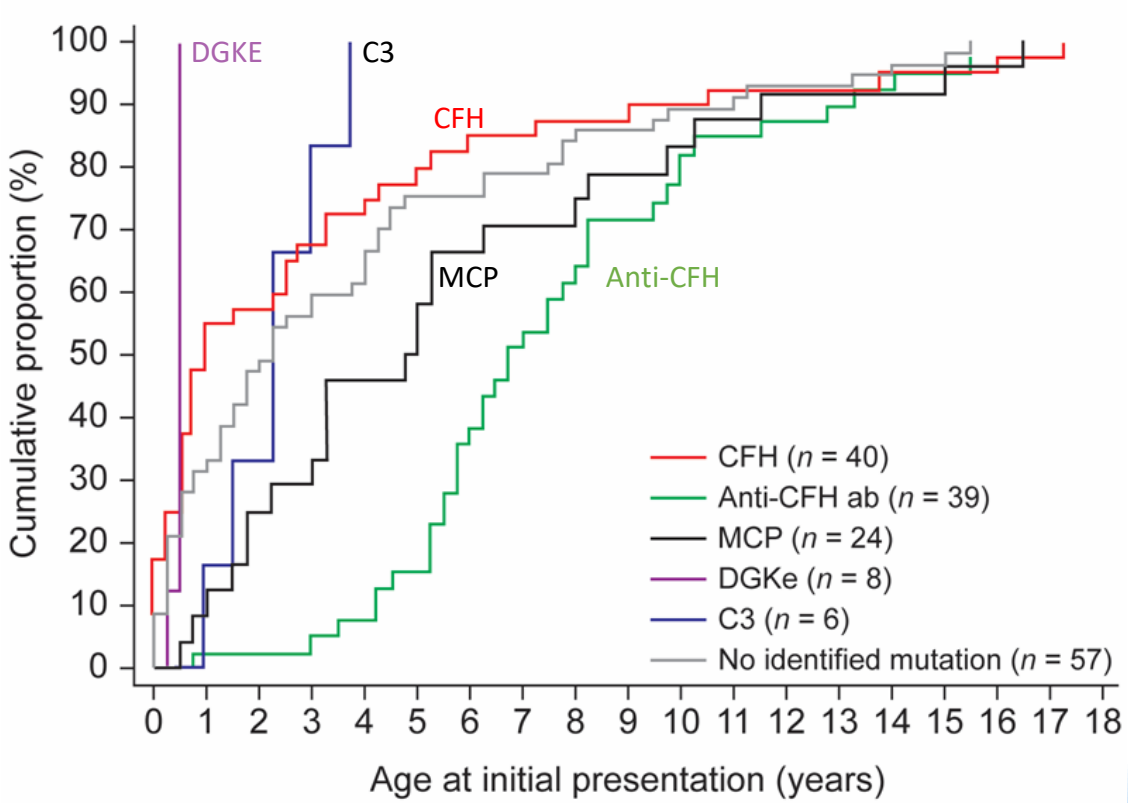
Age at Onset by Complement Disorder



Mutation	Median Age at Onset (Years)
MCP	7.2
C3	7.7
Anti-CFH abs	8.4
CFH	18.5
CFI	34.3

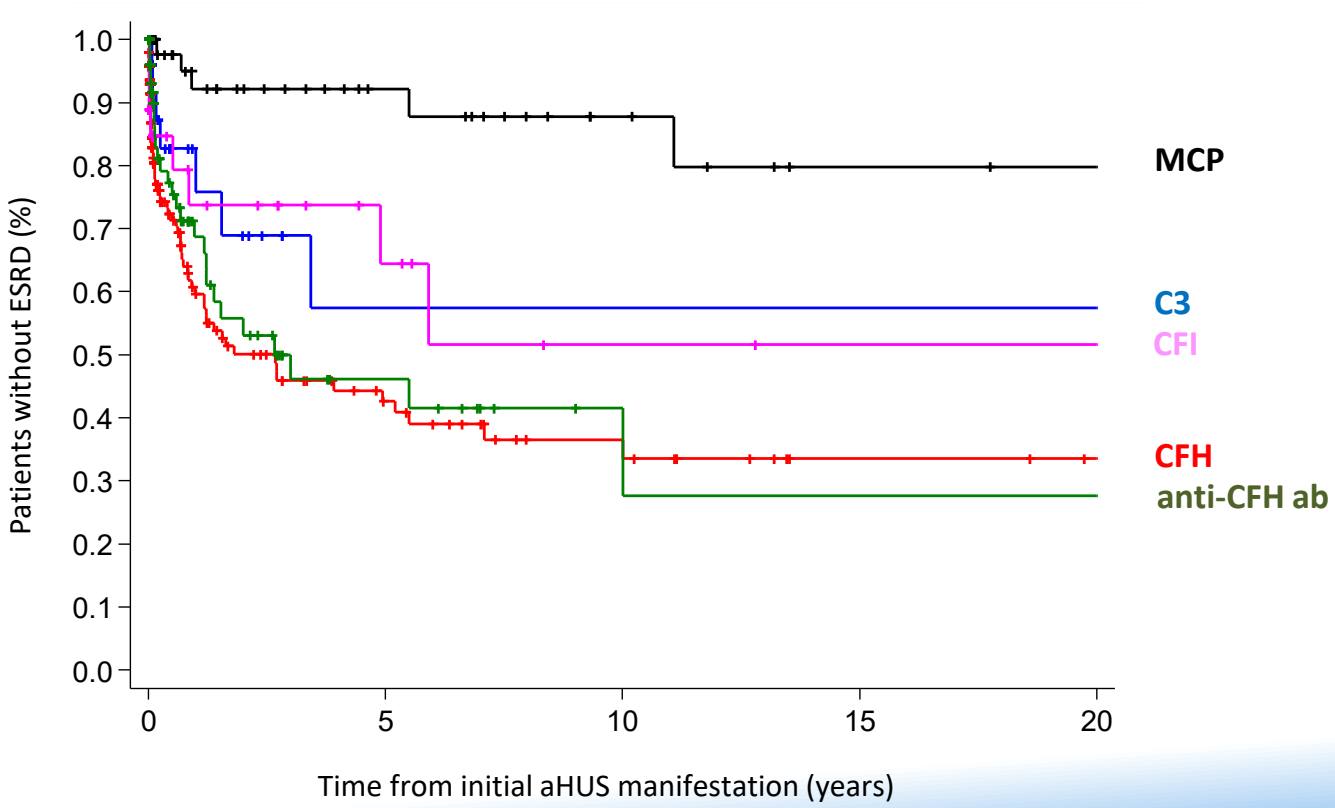
Schaefer et al. Kidney Int 2018

Pediatric Age at Onset by Complement Disorder



Schaefer et al. Kidney Int 2018

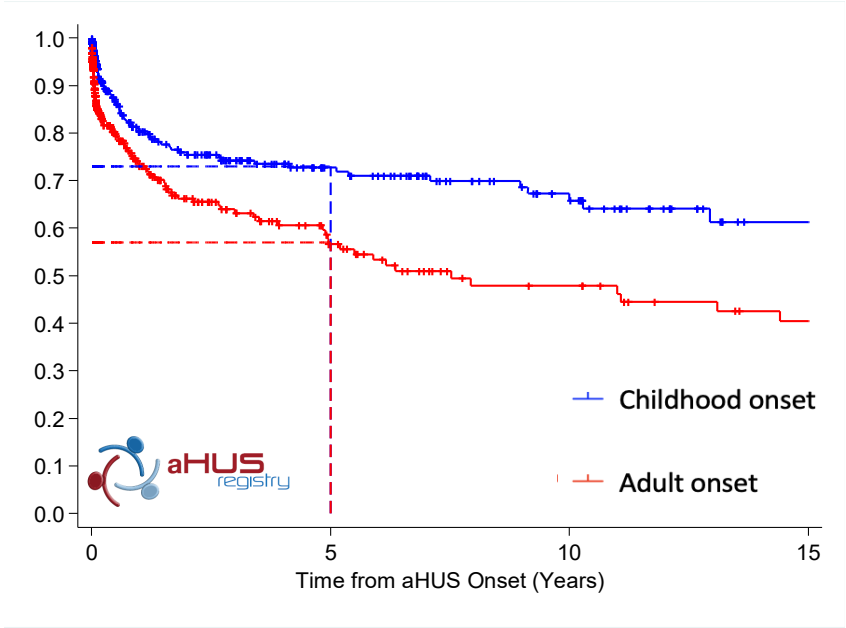
Natural History of aHUS by Complement Abnormality



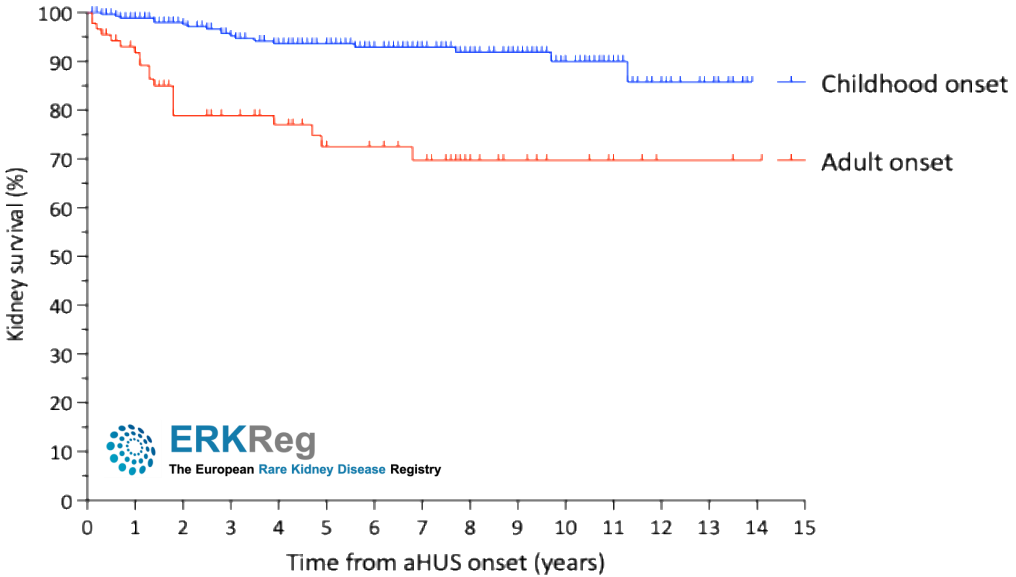
Schaefer et al. KI 2018

Transformation of Outcomes by C5 Inhibitor Treatment

Pre-C5i Era (before 2011)



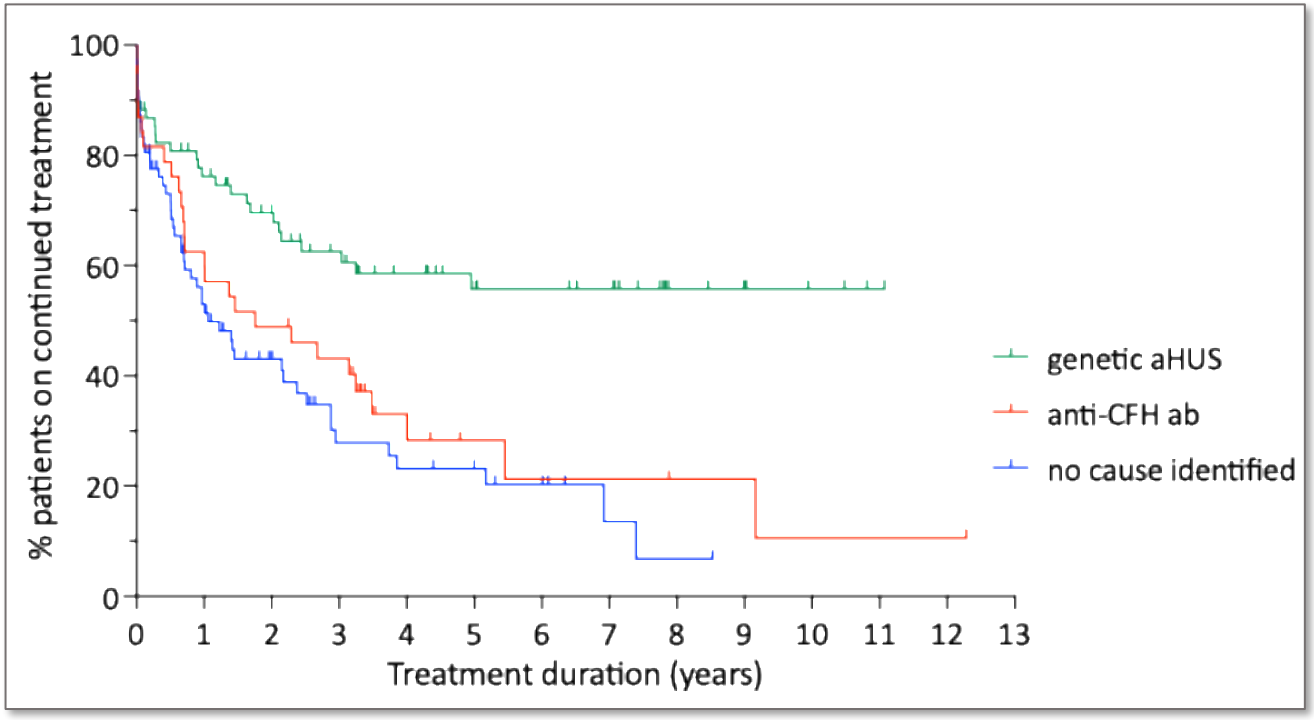
C5i Era (since 2011)



Practice Pattern: Duration of C5i Therapy

ERKReg
The European Rare Kidney Disease Registry

162 aHUS patients treated with Eculizumab or Ravulizumab



Vujovic et al. Lancet eClinicalMedicine 2025

Treatment Duration by Affected Gene

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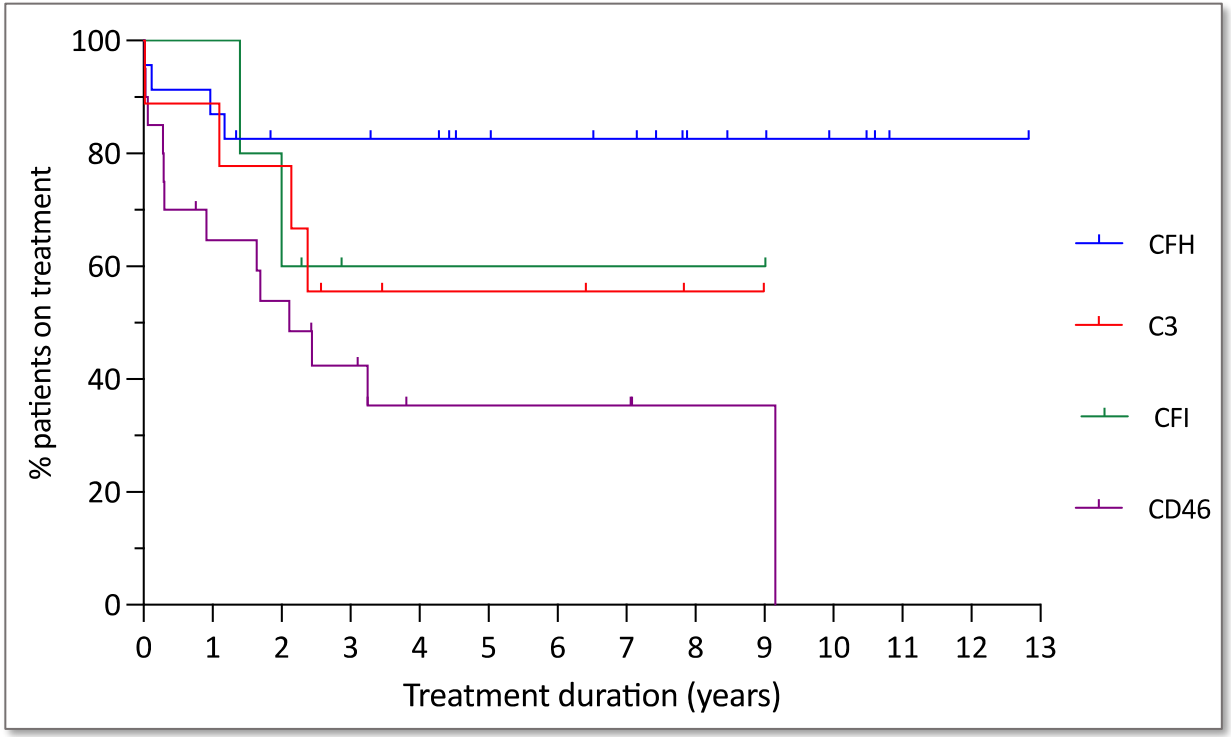

Vujovic et al. Lancet eClinicalMedicine 2025

Post-C5i Withdrawal Relapse Risk

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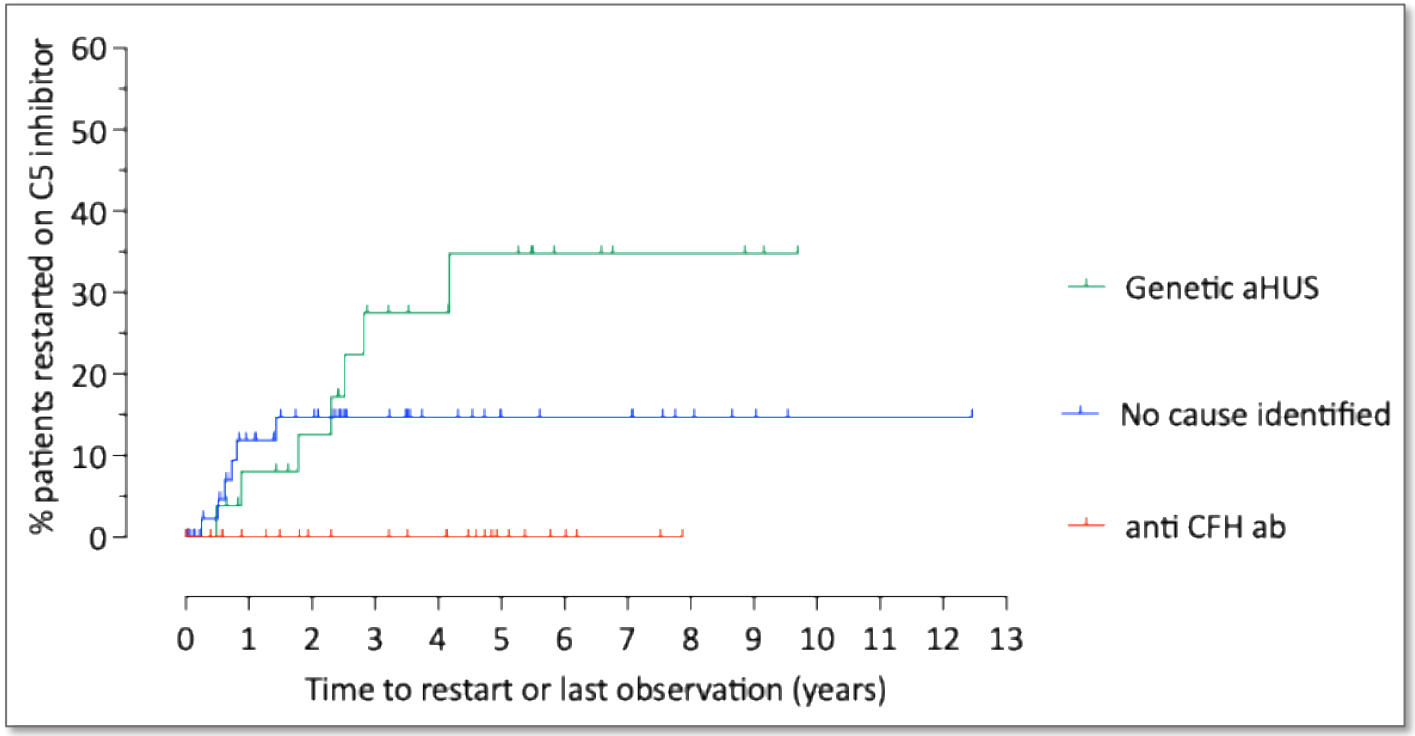
The European Rare Kidney Disease Registry



Vujovic et al. Lancet eClinicalMedicine 2025

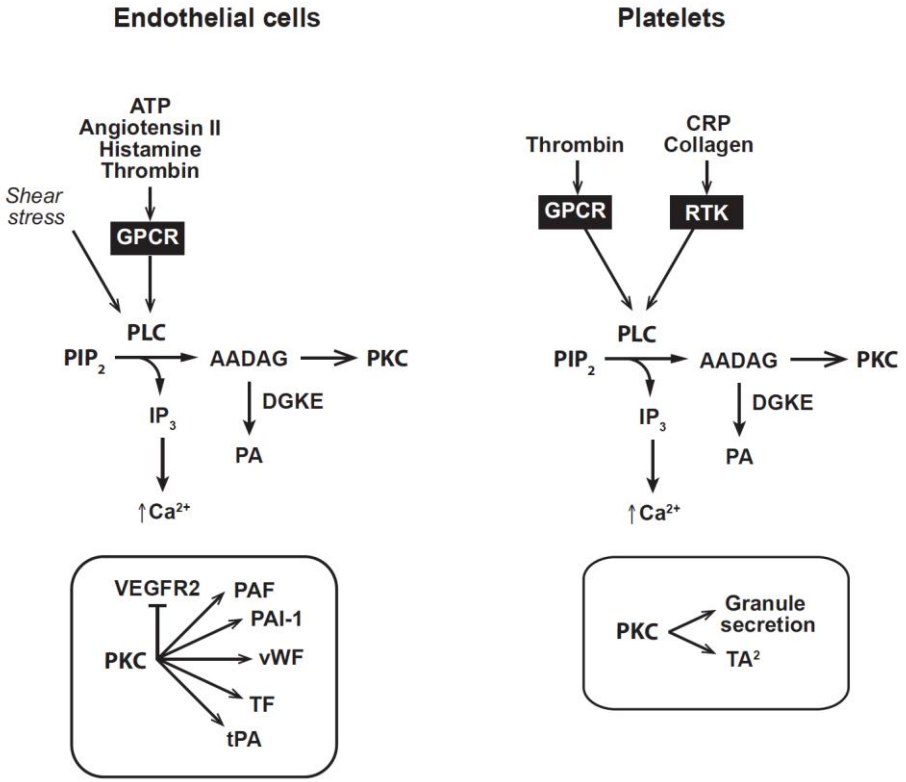
Post-C5i Withdrawal Relapse Risk by Affected Gene

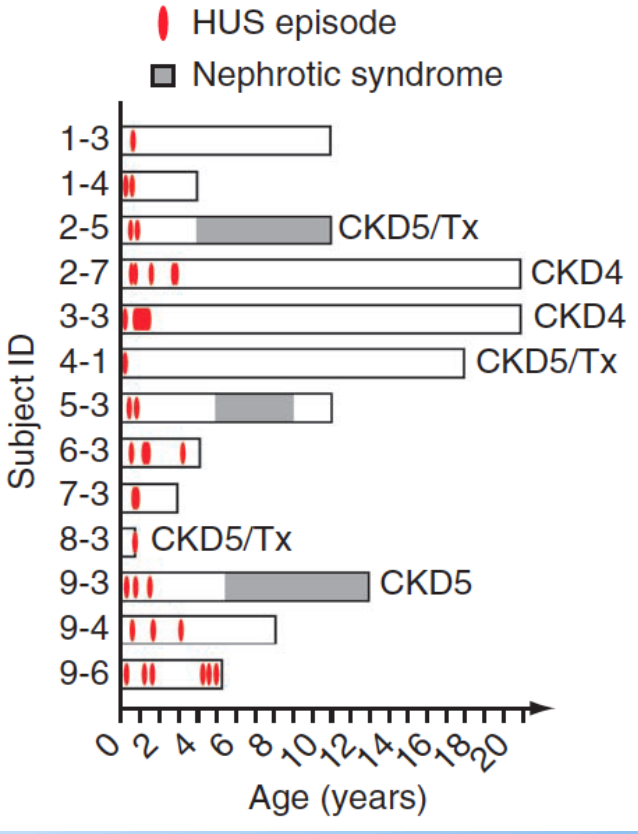
ERKReg
The European Rare Kidney Disease Registry

Affected gene	Post-discontinuation recurrence rate
CD46 (MCP)	3/13
CFH	1/4
C3	1/3
CFI	1/3
CFB	0/1
THBD	0/1

Vujovic et al. Lancet eClinicalMedicine 2025

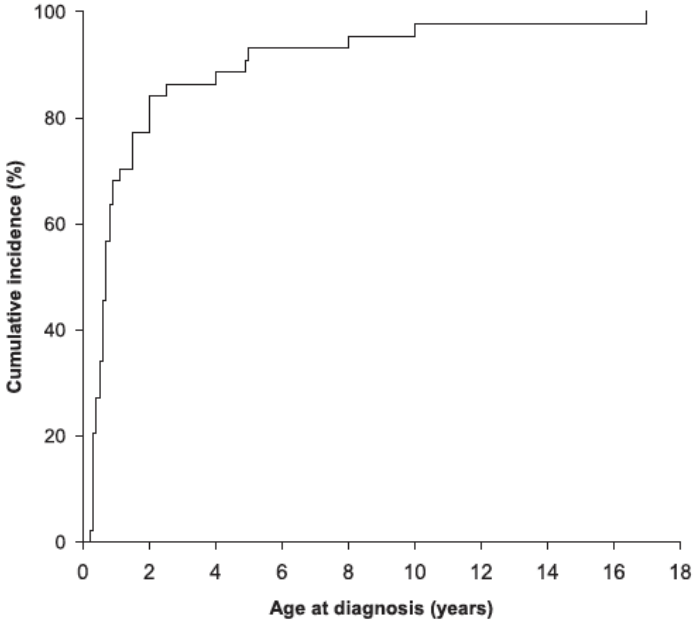
DGKE Nephropathy: Complement-Unrelated Genetic Form of aHUS

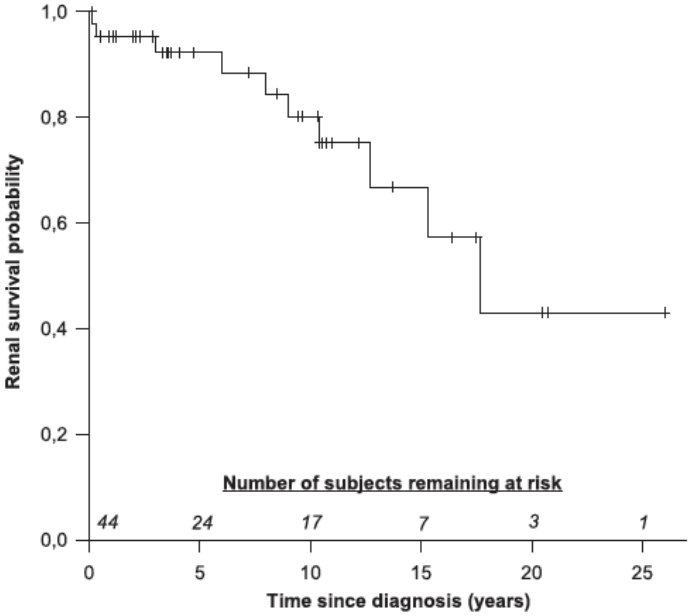




Lemaire M, et al. Nat Gen 2013

DGKE Nephropathy: Complement-Unrelated Genetic Form of aHUS

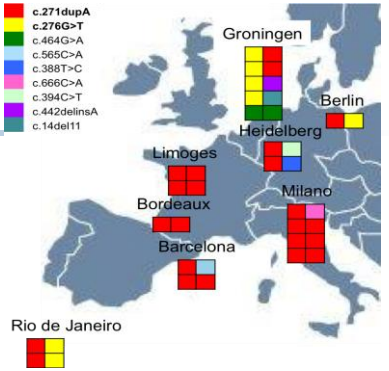




2 patients with documented relapses **while on Eculizumab** therapy

Azukaitis et al. JASN 2017

‘Metabolic’ aHUS: Cobalamin C Deficiency



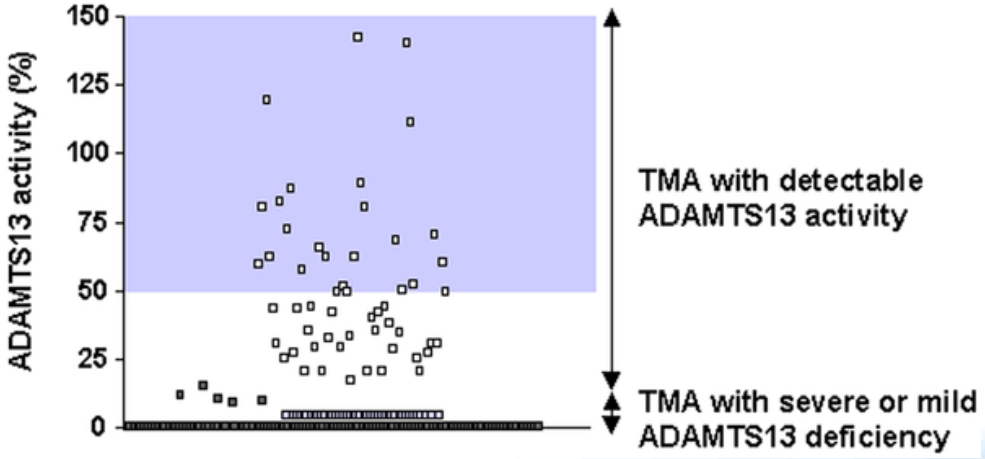
19 cases identified in ESCAPE Network:

- Age at onset: 7 days to 14 years (median 0.9 y)
- Phenotype: 10 isolated aHUS, 9 associated pulmonary hypertension
- Plasma homocysteine: **145** (53-207) uM (**nl <12**)
- Diagnosis: n=4 post mortem, n=3 6-19 y after 1st manifestation !
- Treatment: 14/19 Vit B12, folate supplementation
  1/19 Eculizumab, ineffective
- Outcome: 7 dead (5 without substitution therapy)
  4 CKD2-5, 2 post-transplant
  6 normal kidney function (all diagnosed and treated early)
  7/12 survivors with cognitive deficits

ADAMTS13 vWF Cleavage Protease Deficiency

Adults: Autoantibodies against ADAMTS13
Children: Autosomal recessive mutations in ADAMTS13 gene

Diagnosis: ADAMTS13 activity > 5 % of normal



Coppo P, et al. PLoS ONE 2010;5:e10208

Indications for Genetic Screening

NGS Screening
for CFH, CFI, CFB, C3, MCP, TM, DGKE recommended in:

- First aHUS episodes after ruling out STEC infection, ADAMTS13 deficiency, CbC deficiency and CFH antibodies

- **HUS relapse**
  Family history of non synchronous HUS
  Pregnancy/post-partum HUS
  de novo post-transplant HUS

- STEC-negative cases with ESKD as part of **pre-transplant workup**

Loirat et al. PN 2015

Relevance of Genetic Screening

- Establishing prognosis (risk of relapses, CKD progression)
- Genetic counselling to parents and family
- Decisions concerning kidney transplantation:
  - choice of donor
  - planning of post-transplant management
  - decision of combined kidney-liver transplantation
- Assessment of risks of treatment discontinuation

Loirat et al. PN 2015