Role of complement in paediatric TMA with pathogenic variants and anti-factor H antibodies

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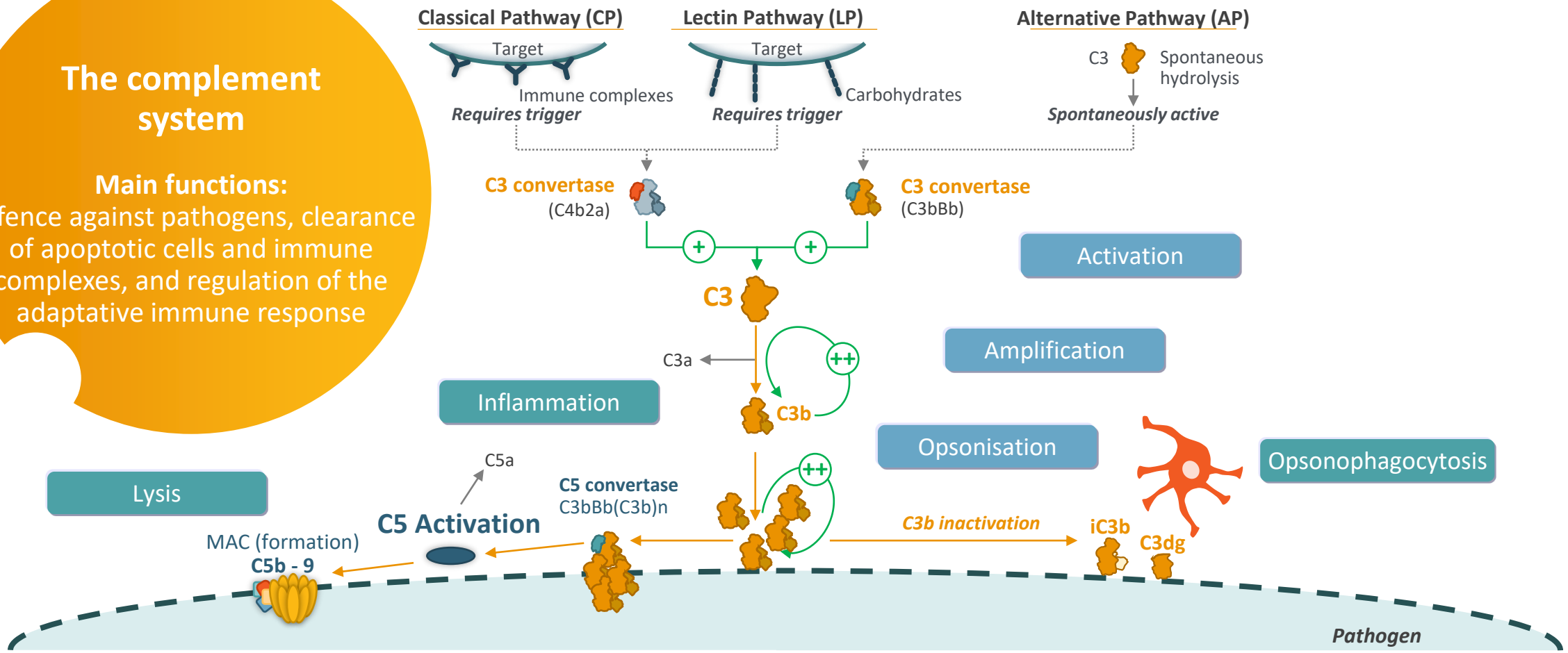
Disclosures

EGJ has received lecture fees from Alexion, Vifor, Sobi, Samsung and Astellas, and has been a consultant for Q32 Bio, Sobi and Arrowhead.

The Complement System

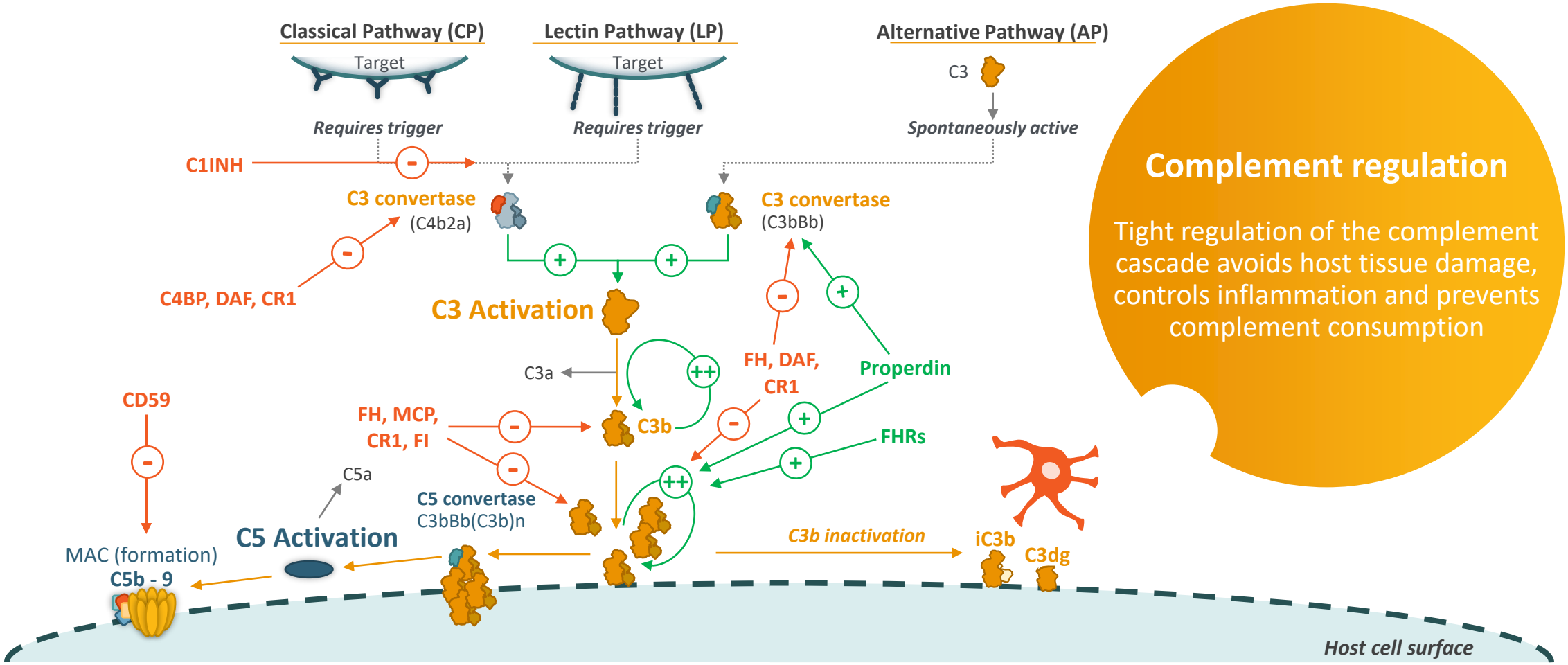
The complement system

Main functions:
defence against pathogens, clearance of apoptotic cells and immune complexes, and regulation of the adaptative immune response



C3, complement 3; C5, complement 5; MAC, membrane attack complex.

The Complement System is tightly regulated

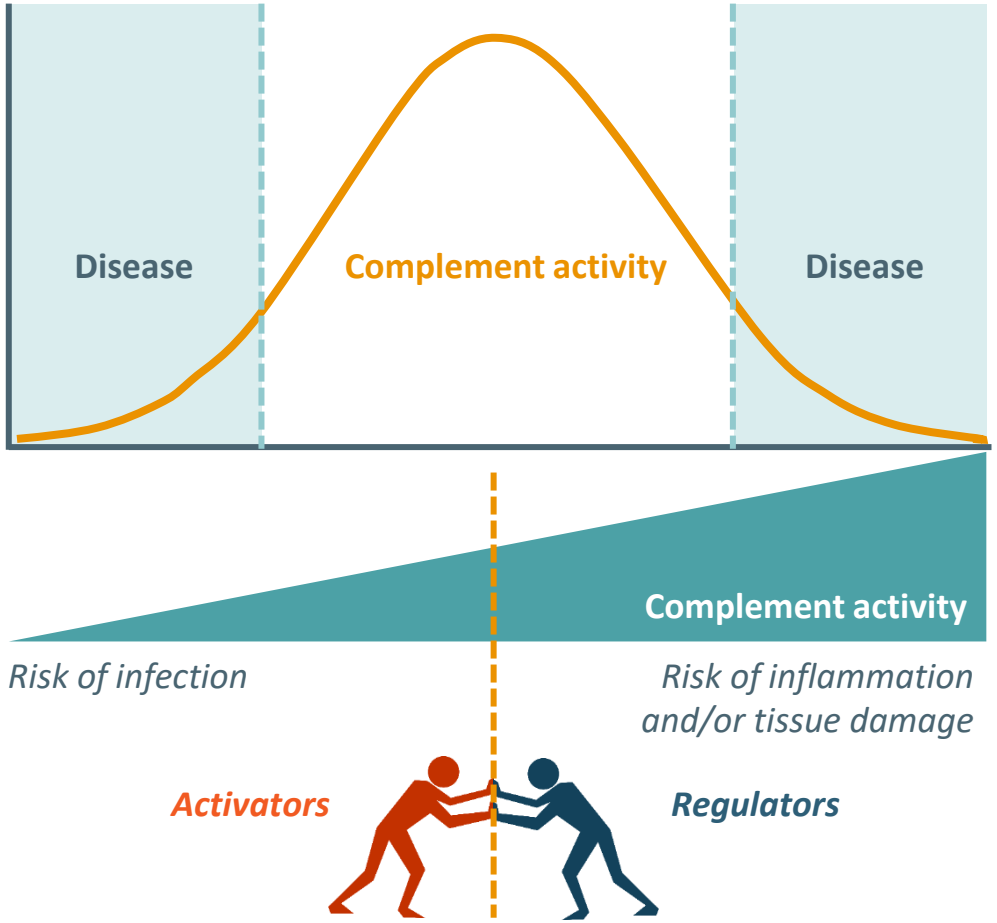


Complement regulation

Tight regulation of the complement cascade avoids host tissue damage, controls inflammation and prevents complement consumption

C1INH, C1 inhibitor; C4BP, C4 binding protein; CR1, complement receptor 1; DAF, decay accelerating factor; FH, factor H; FHR, FH-related protein; FI, factor I; MAC, membrane attack complex; MCP, membrane cofactor protein.

Complement activity is highly variable and determines disease susceptibility



Complement activity is heterogenous

Complement activation can be influenced by:

- Acquired factors
- Genetic variation
- Environmental factors

Complement abnormalities in complement-mediated TMA

In CM-TMA, abnormalities in **complement genes** are present in **approximately 40-60%** of cases

- **Variations in complement regulators**
  - *CFH: 15-30%*
  - *MCP: 10-15%*
  - *CFI: 5-15%*
- **Variations in complement activators**
  - *C3: 2-10%*
  - *CFB: 0-3%*
  - *CFHR1-5: 0-8%*

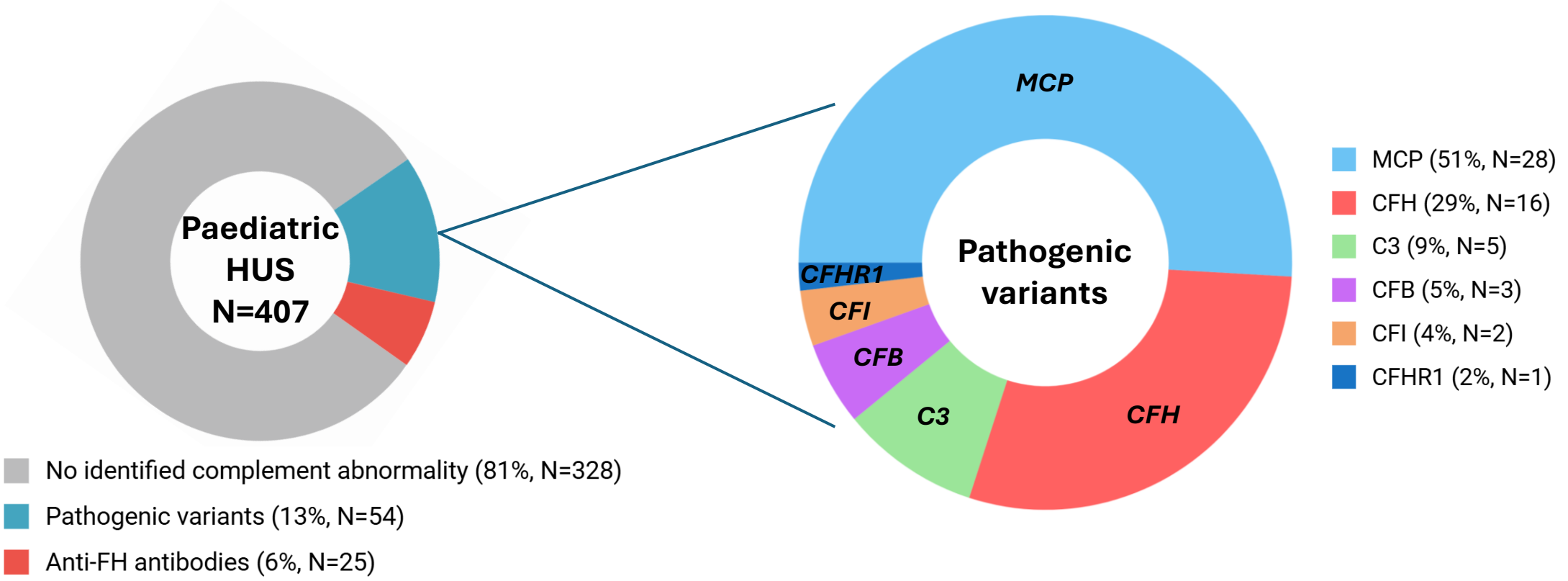
Acquired factors (**anti-factor H autoantibodies**) are present in many patients with CM-TMA

The reported prevalence of autoantibodies varies widely due to heterogeneity and difficulty in detection:

- **Anti-factor H antibodies**: 6-50% (depending on geographical areas)

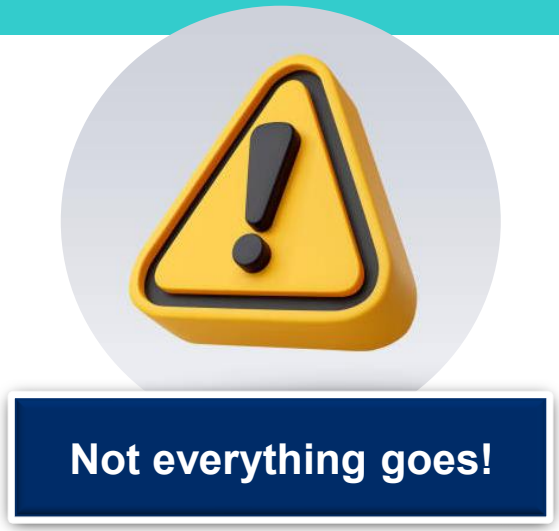
Complement abnormalities in paediatric TMA

- Paediatric cases from the Spanish HUS Registry: 407 patients



Unpublished data

Molecular basis of CM-TMA



Pathogenic variants:

- Loss-of function in complement regulators: *CFH, CFI, MCP*
- Gain-of-function in complement activators: *C3, CFB, CFHRs*

Common gene variants:

- Non-pathogenic *per se*, but they contribute to the risk of developing aHUS in the presence of a pathogenic variant or an aHUS-associated trigger.
- aHUS-associated common variants: *CFH-H3* and MCP_{GGAAC} haplotypes.

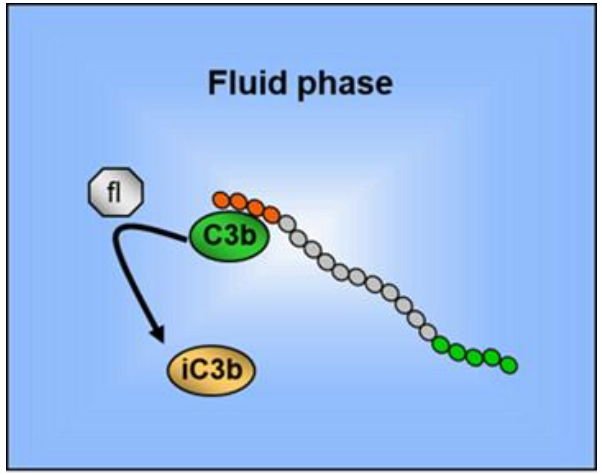
Autoantibodies:

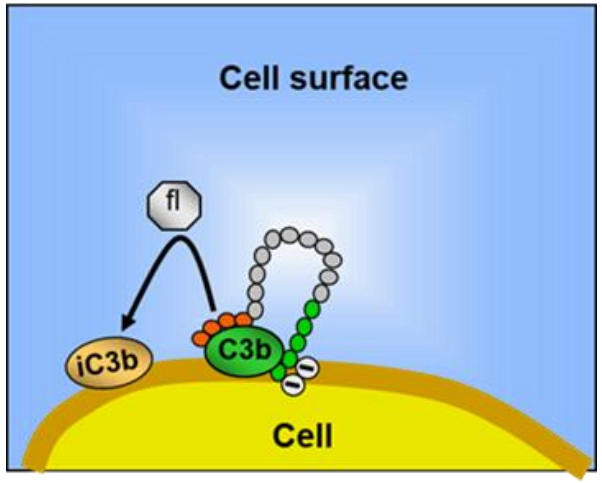
- Anti-factor H antibodies (usually against the C-term and in the presence of Del.*CFHR3-CFHR1*)

Overlap of risk factors between different diseases

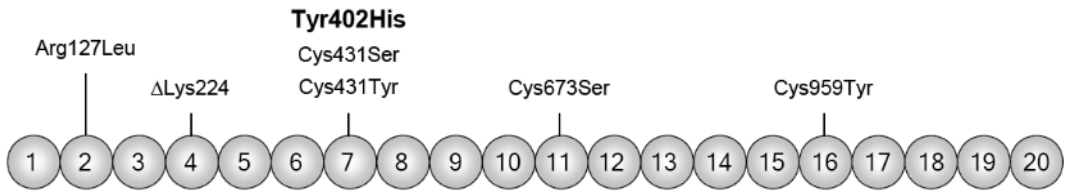
	aHUS	C3 Glomerulopathy		IgA Nephropathy	AAV
		C3GN	DDD		
Genetic factors					
• *Mutations*	*CFH* *MCP* *CFI* *CFB* *C3* *CFHR1*	*CFH* *MCP* *CFI* *CFB* *C3* *CFHR1* *DGKE*	*CFH* *MCP* *CFI* *CFB* *C3* *CFHR1*	*CFH* *CFHR5*	*CFH*
• *Polymorphisms*	*CFH* *MCP* *CFHR1* *CFHR3*	*CFH* *CFHR1* *CFHR3* *CFHR5*	*CFH* *CFHR1* *CFHR3* *CFHR5*	*CFHR1* *CFHR3* *CFHR5*	*C3* *CFB*
Autoantibodies	Factor H	Factor H C3Nef	Factor H C3Nef	IgA	ANCAs
Environmental Factors	Infection IST Cancer therapies Oral contraceptives Pregnancy Childbirth, etc…	Infection	Infection	Infection	Infection Silica Drugs

Distinc factor H mutations associate with CM-HUS and C3G





C3G



Mutations cause FH deficiency and complement dysregulation in fluid phase

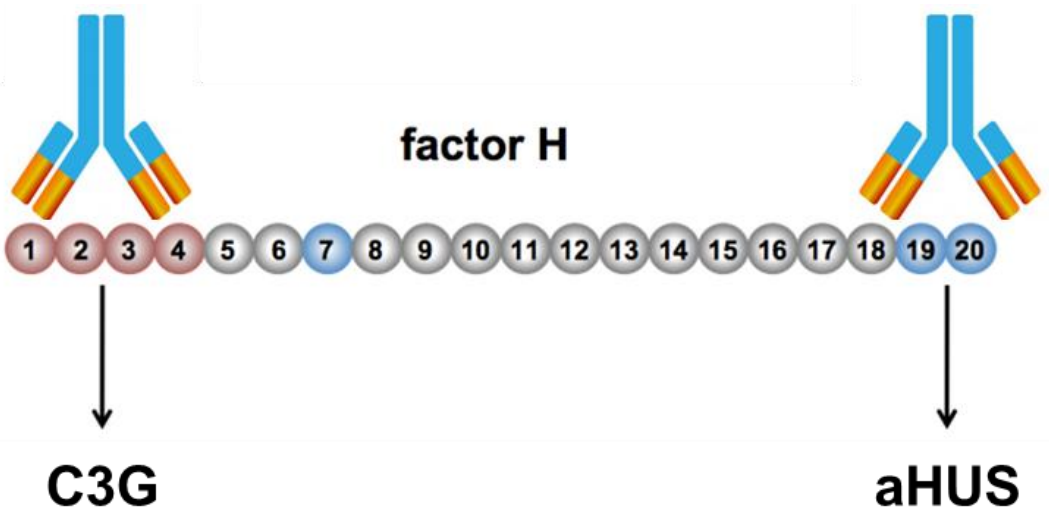
aHUS

Altered complement regulation on cell surfaces, without affecting plasma FH and C3 levels

S. Rodríguez de Córdoba and E. Goicoechea de Jorge. 2008. *Clin. Exp. Immunol.* 151:1-13

Acquired drivers in CM-HUS and C3G

Acquired factor	aHUS	C3G
C3 nephritic factor	No	Yes
Anti-factor H autoantibodies	Yes	Yes



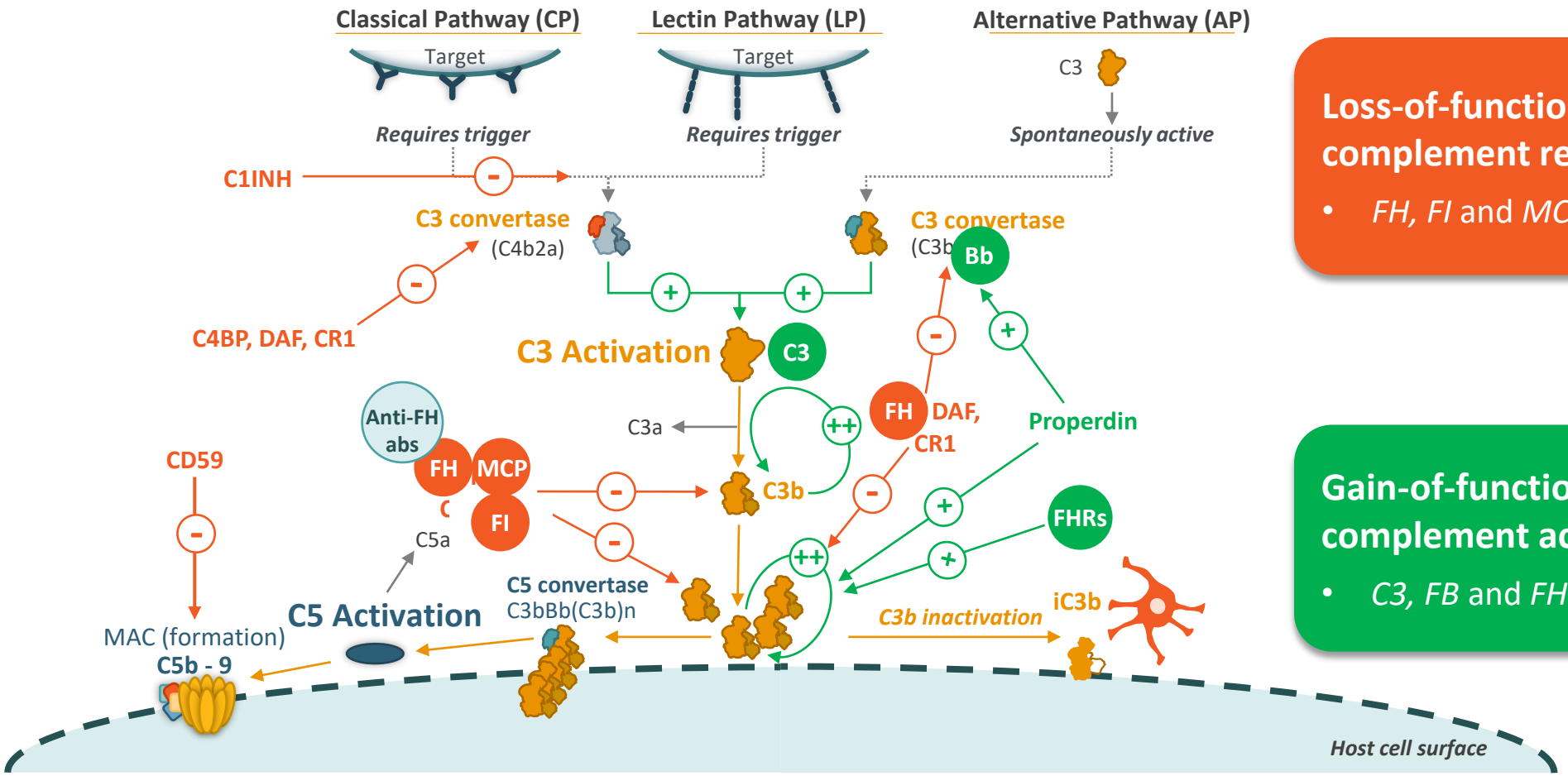
S. Rodríguez de Córdoba and E. Goicoechea de Jorge. 2008. *Clin. Exp. Immunol*. 151:1-13

Common gene variants differently associated with disease

		C3G (n=89)		aHUS (n=640)		AAV (n=87)		IgAN (n=106)	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
CFH Haplotypes	H1	**1.454 (1.005-2.105)**	**0.047**	0.824 (0.645-1.053)	0.122	0.850 (0.559-1.292)	0.447		
	H2	0.846 (0.544-1.317)	0.459	0.882 (0.673-1.156)	0.363	0.929 (0.589-1.466)	0.753		
	H3	1.392 (0.929-2.084)	0.109	**1.583 (1.219-2.055)**	**0.0006**	1.140 (0.735-1.768)	0.557		
	H4a	**0.442 (0.232-0.843)**	**0.013**	0.899 (0.654-1.235)	0.510	1.176 (0.709-1.951)	0.531		
	H4b	0.920 (0.449-1.884)	0.819	1.079 (0.699-1.666)	0.732	0.760 (0.340-1.700)	0.504		
	H5	0.236 (0.168-2.163)	0.437	0.871 (0.442-1.717)	0.690	0.932 (0.296-2.933)	0.904		
	H6	0.126 (0.007-2.167)	0.153	**0.268 (0.099-0.724)**	**0.009**	**3.607 (1.465-8.881)**	**0.005**		
Del.CFHR3-CFHR1	*Deletion*	**0.577 (0.357-0.933)**	**0.025**	0.993 (0.781-1.263)	0.957	0.858 (0.494 - 1.491)	0.5870	0.5 (0.29-0.84)	0.01
C3 alleles c.304 C>G (R102G)	C	**0.679 (0.467-0.988)**	**0.043**	0.993 (0.781-1.263)	0.957	0.858 (0.494 - 1.491)	0.5870		
	G	**1.472 (1.012-2.141)**	**0.043**	1.007 (0.792-1.280)	0.957	1.166 (0.671 - 2.025)	0.5870		
MCP Haplotypes	GGC	1.006 (0.674-1.502)	0.976	**1.468 (1.132-1.903)**	**0.004**	0.814 (0.484-1.369)	0.4373		
	AAT	0.963 (0.667-1.391)	0.841	**0.746 (0.586-0.949)**	**0.017**	0.864 (0.540-1.383)	0.5419		
	Others	0.859 (0.478-1.543)	0.611	0.890 (0.613-1.293)	0.541	1.225 (0.627-2.394)	0.5524		
CFB alleles	R	1.449 (0.976-2.151)	0.067	1.077 (0.871-1.331)	0.495	**1.822 (1.185-2.802)**	**0.006**		
	Q	0.695 (0.404-1.195)	0.189	0.936 (0.707-1.240)	0.646	0.646 (0.365-1.142)	0.102		
	W	0.755 (0.455-1.254)	0.277	0.942 (0.719-1.235)	0.667	**0.501 (0.279-0.898)**	**0.020**		

Tortajada et al., *Kidney International*, 2017.
Lucientes-Continente et al. *Kidney International*, 2024.
Goicoechea de Jorge, unpublished data.

Complement abnormalities may lead to AP dysregulation



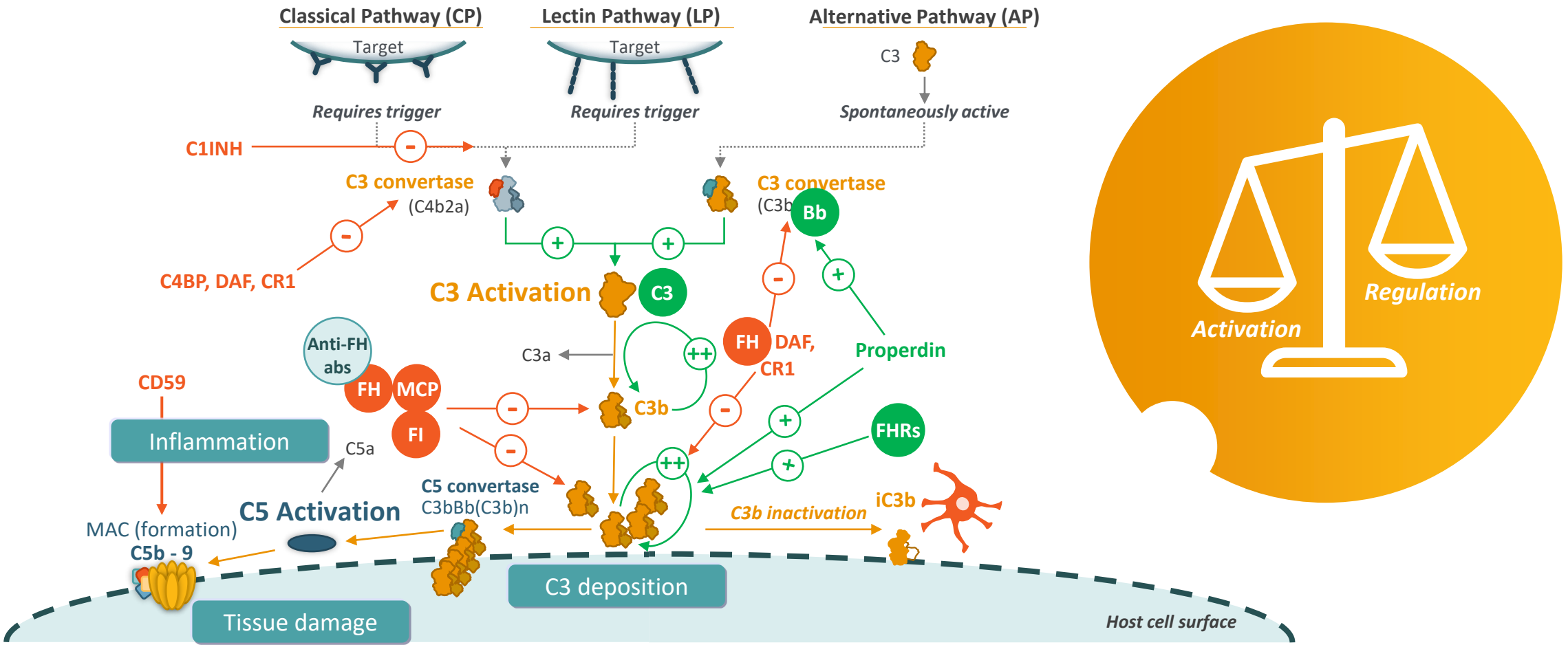
Loss-of-function variants in complement regulators:

- *FH, FI* and *MCP*

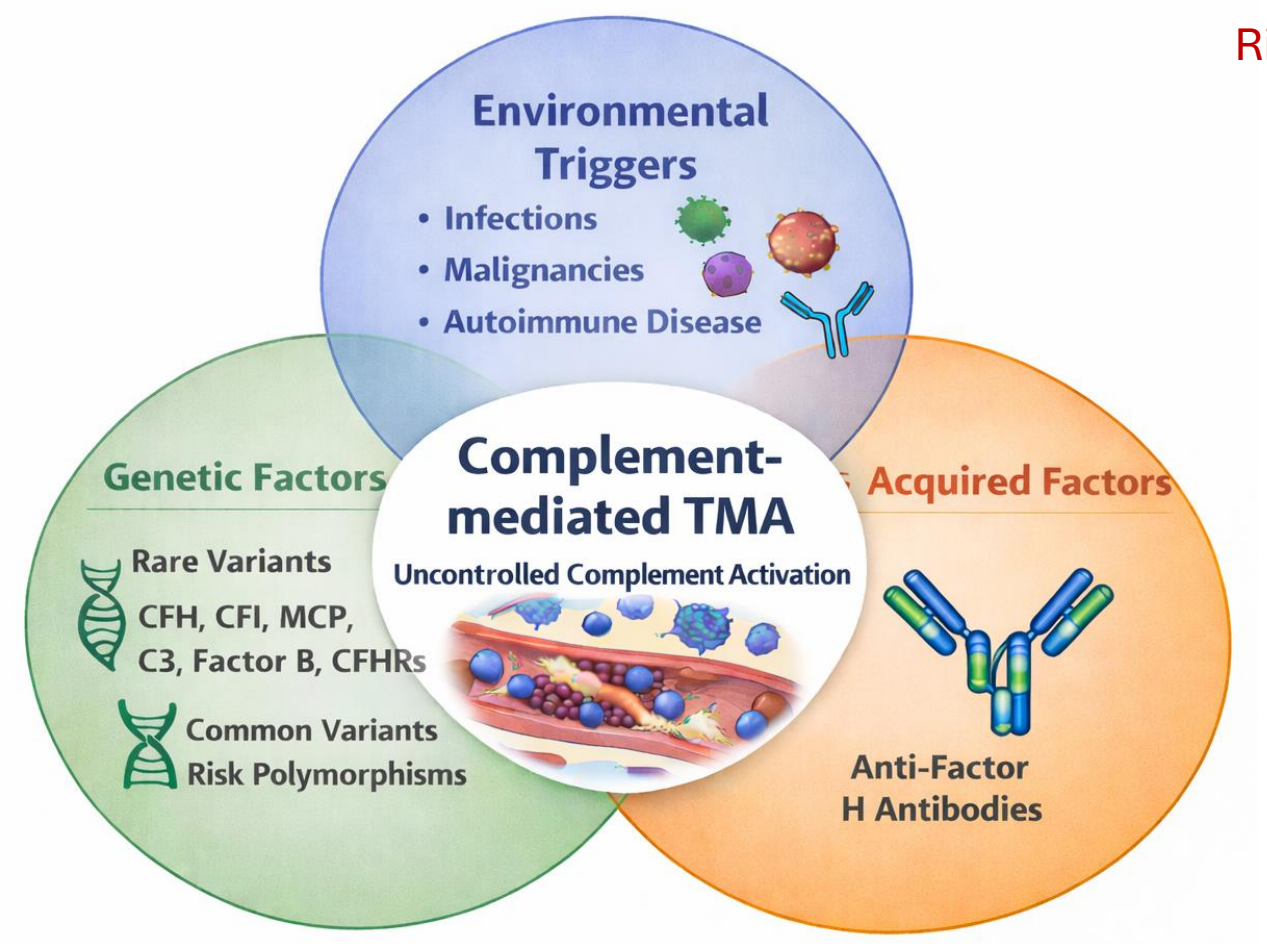
Gain-of-function variants in complement activators:

- *C3, FB* and *FHRs*

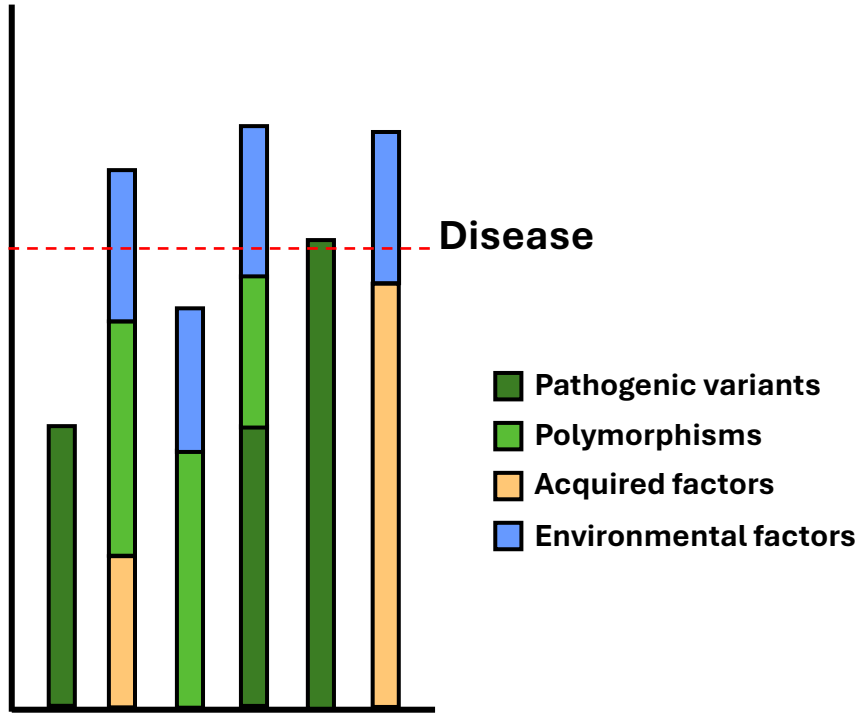
Complement abnormalities may lead to AP dysregulation



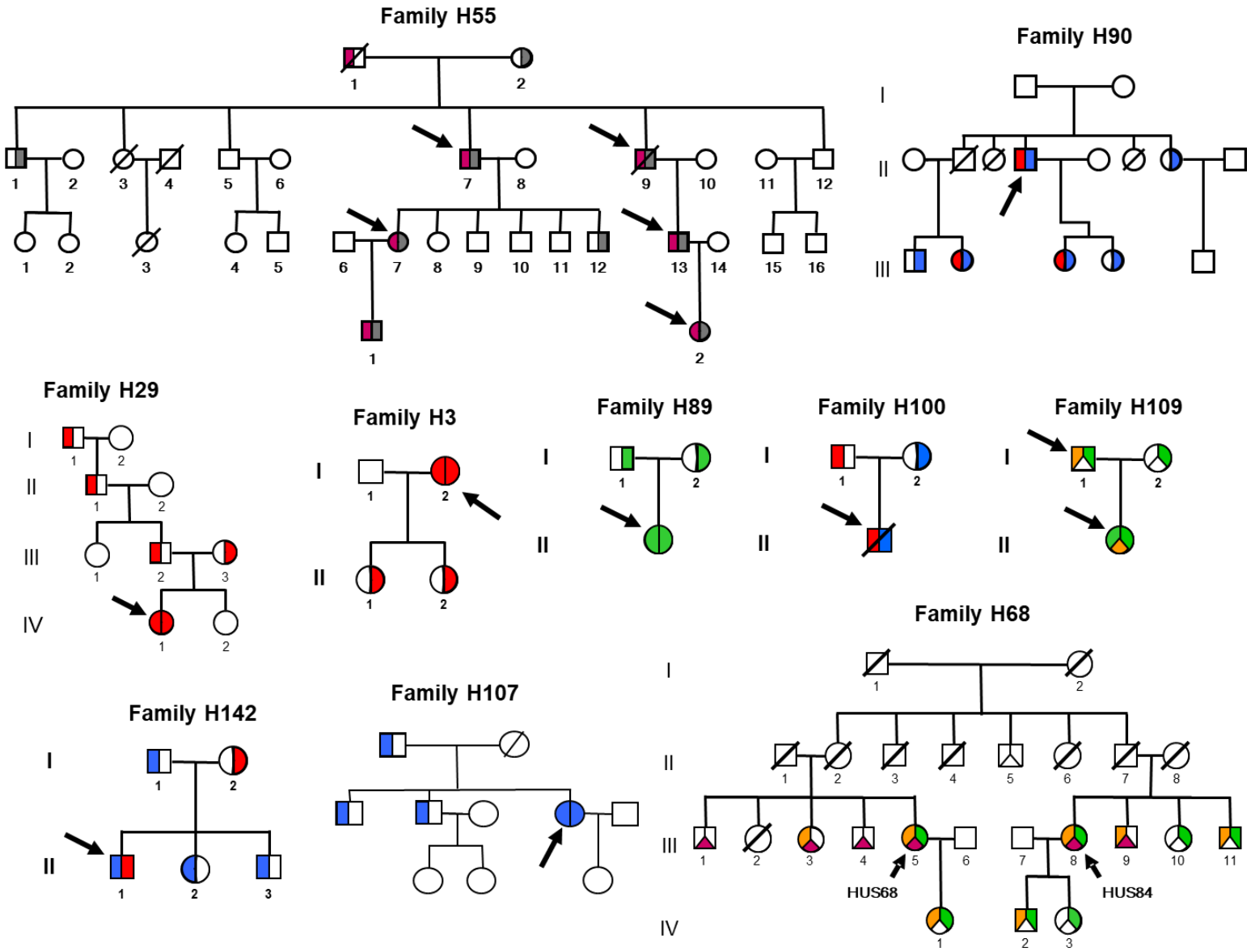
Complement-mediated TMA is a complex, polygenic multifactorial disease



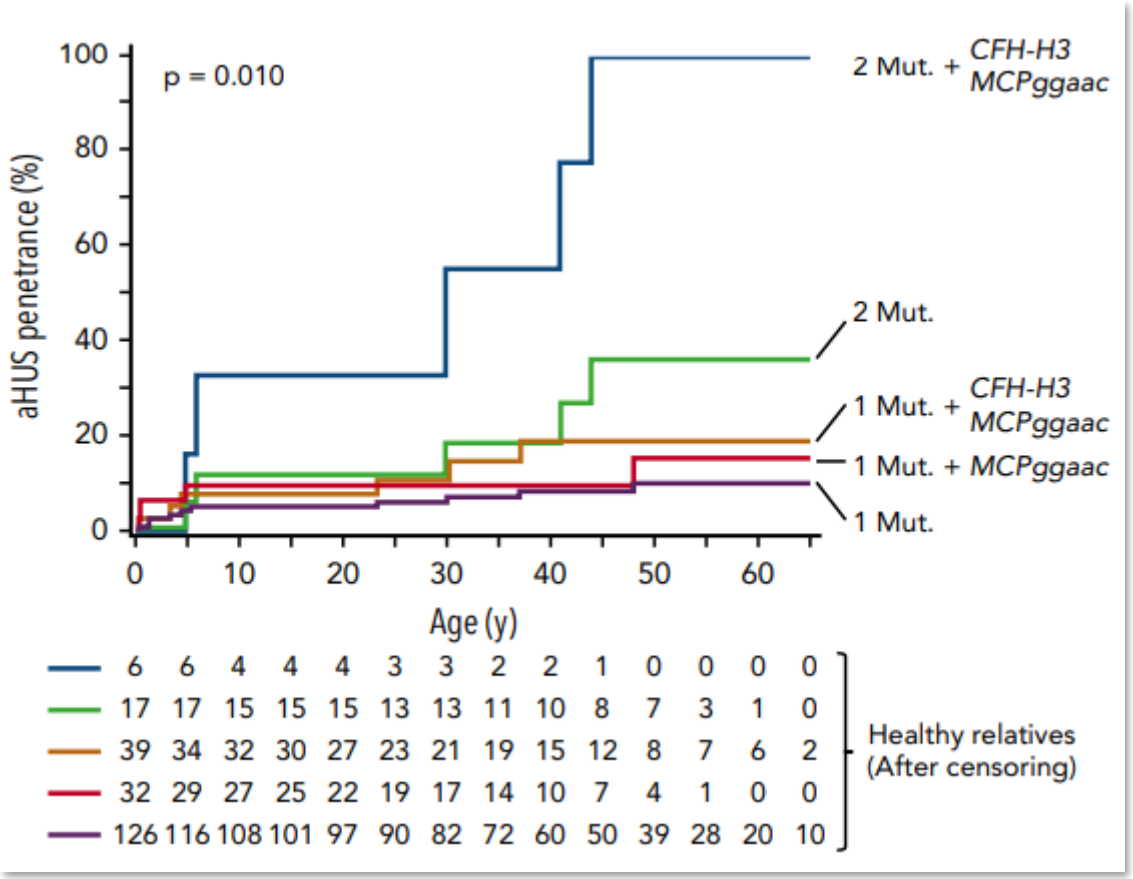
Risk factors are not causative, but predisposing factors



The penetrance of the disease is incomplete



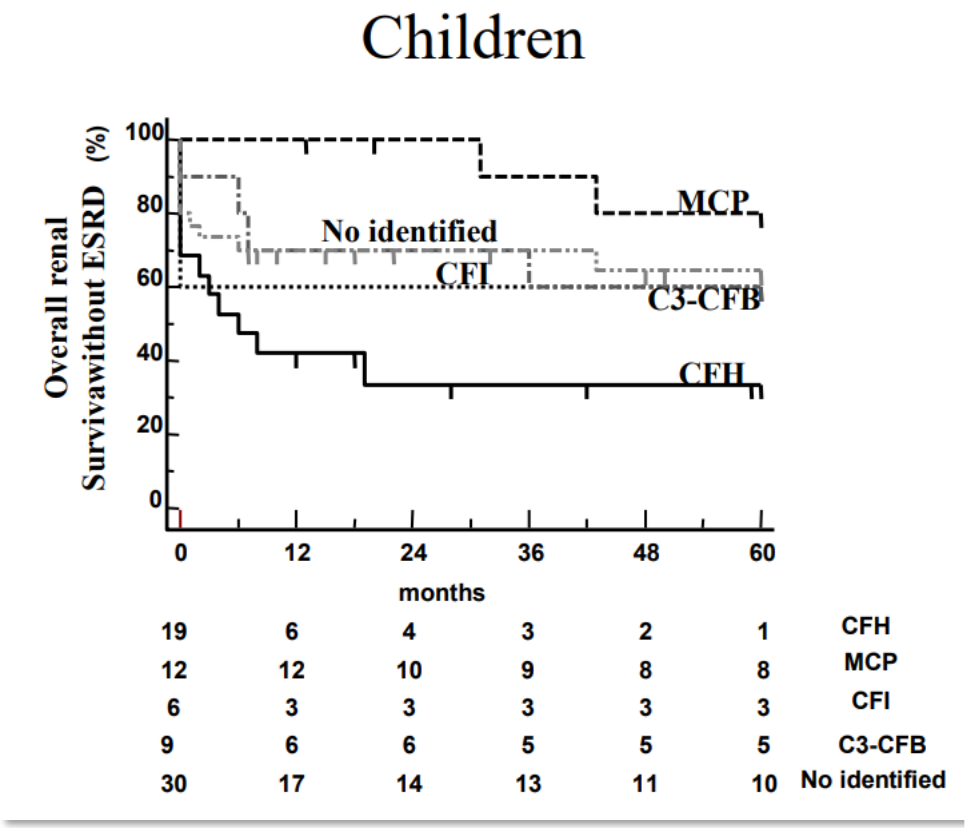
The risk of developing CM-TMA increases with the genetic load



aHUS penetrance in relatives

	Carriers	Affected / Total	Penetrance (35y)	Max. Penetrance (y)
Pedigrees 1 mutation	No mutation	0/152	-	-
	Mutation	10/126	**6.8%**	**9.6% (48y)**
	Mutation only	0/36	-	-
	Mutation + *CFH-H3*	0/19	-	-
	Mutation + *MCPggaac*	4/32	**9.4%**	**15% (48y)**
	Mutation + *CFH-H3* + *MCPggaac*	6/39	**14.5%**	**18.8% (37y)**
Pedigrees 2 mutations	No mutation	0/23	-	-
	1 mutation	0/46	-	-
	2 mutations	5/17	**18.6%**	**36% (44y)**
	2 mutations only	0/3	-	-
	2 mutations + *CFH-H3*	0/5	-	-
	2 mutations + *MCPggaac*	0/3	-	-
	2 mutations + *CFH-H3* + *MCPggaac*	5/6	**56%**	**100% (44y)**

Impact of complement abnormalities in kidney survival



Fremeaux-Bacchi *et al.* CJASN, 2013

Pediatric patients with *CFH* mutations are associated with poorer renal survival, whereas abnormalities in *MCP* are associated with the best prognosis

Renal survival in pediatric and adult CM-TMA

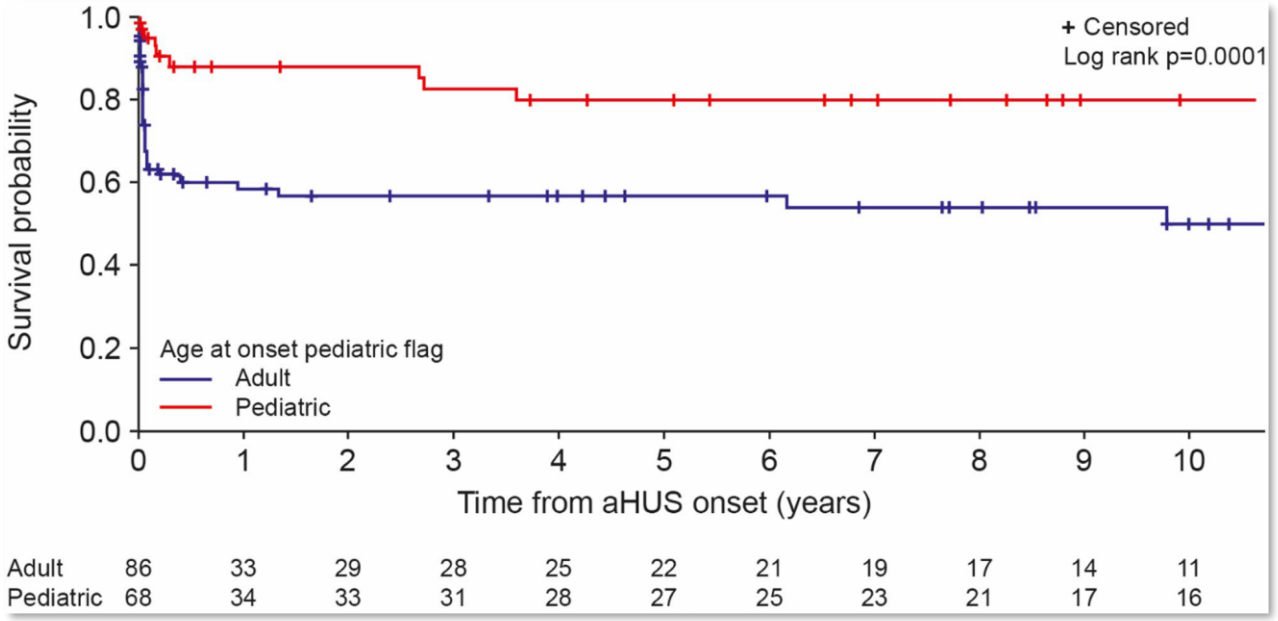
Gilbert *et al. BMC Nephrology* (2025) 26:434
https://doi.org/10.1186/s12882-025-04321-x

BMC Nephrology

RESEARCH Open Access

Demographics and baseline disease characteristics of UK patients within the global aHUS registry

Rodney D. Gilbert[1*], Imad Al-Dakkak[2], Clare Boothe[3], Timothy E. Cobb[3], Daniel P. Gale[4], Sian Griffin[5], Stephen D. Marks[6,7], Marie Scully[8], Mohan Shenoy[9], Aoife Waters[10] and Neil S. Sheerin[11]



- **The probability of ESKD-free survival at one and five years was significanly better in paediatric patients compared with adults.**

Gilbert *et al.* BMC Nephrology, 2025, 26:434

Thank you for your attention!!