Comment explorer un SHU atypique en 2008?

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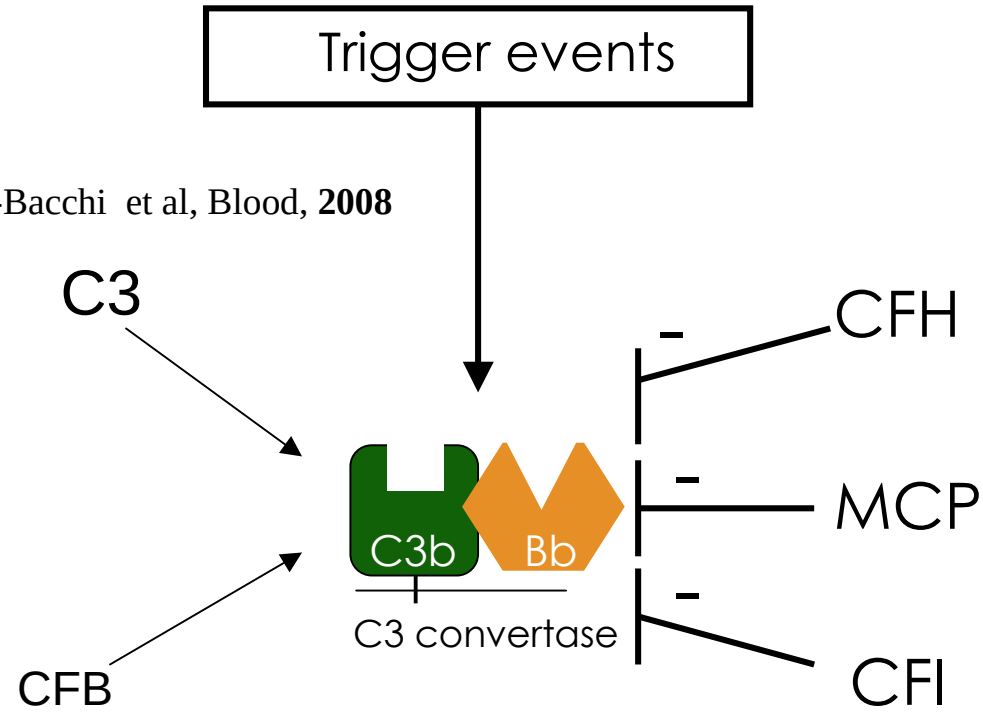
atypical HUS and complement

Fremeaux-Bacchi et al, Blood, **2008**



Goicoechea de Jorge et al. Proc Natl Acad Sci **2007**

- Warwicker et al. Kidney Int **1998**
- Caprioli et al . J Am Soc Nephrol 2001
- Dragon-Durey et al. J Am Soc Nephrol 2004
- Venables et al Plos Med 2007

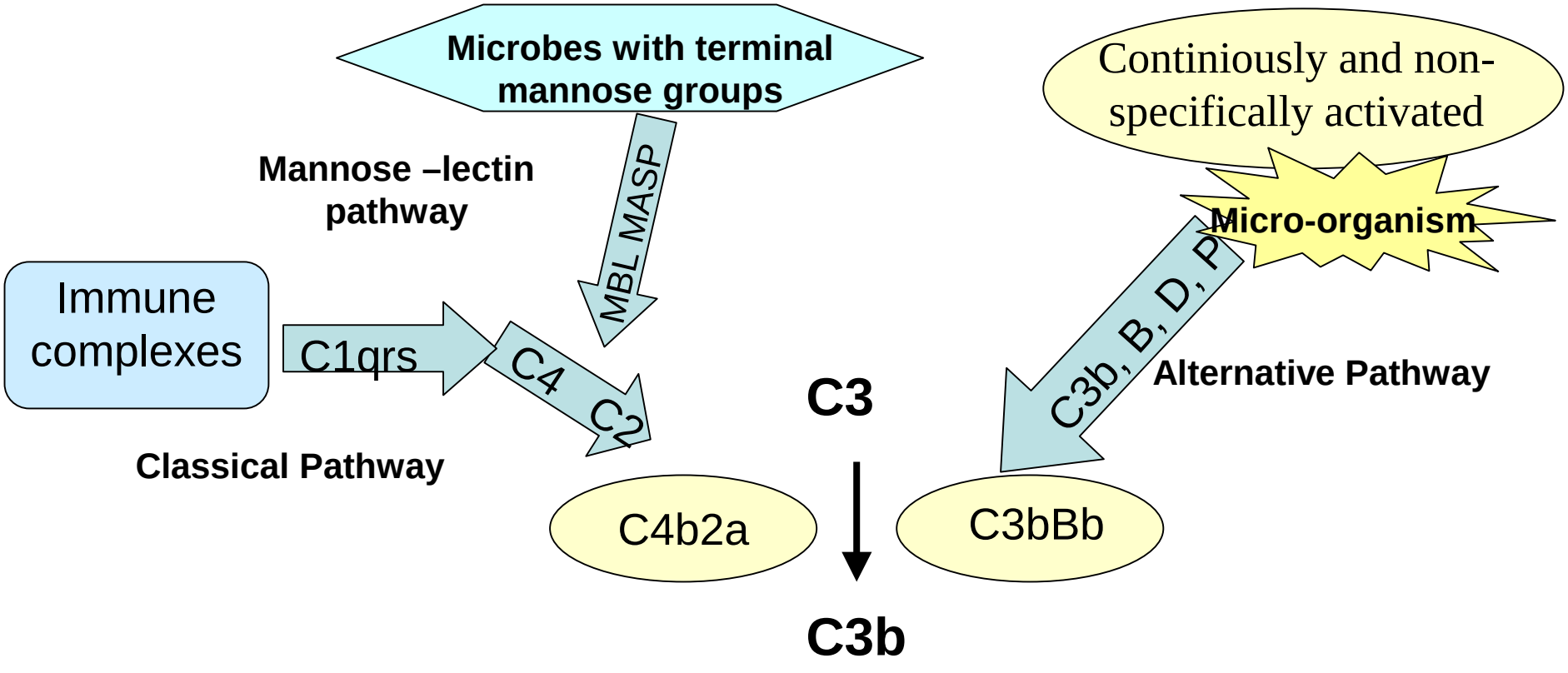
- Richards et al. Proc Natl Acad Sci U S A **2003**
- Noris, M et al. Lancet 2003
- Fremeaux-Bacchi et al. J Am Soc Nephrol 200

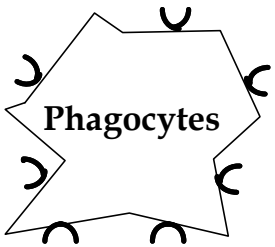
- Fremeaux-Bacchi et al. J Med Genet **2004**
- Kavanagh et al. J Am Soc Nephrol 2005

5 European groups

Up to 900 patients

Complement System

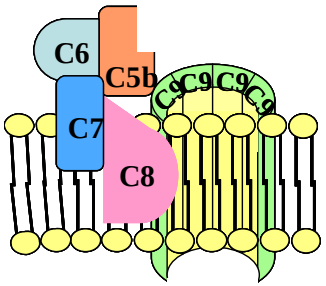




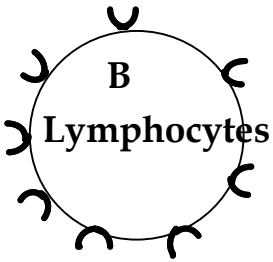
Opsonization and Phagocytosis

C3a
C4a
C5a

Inflammation



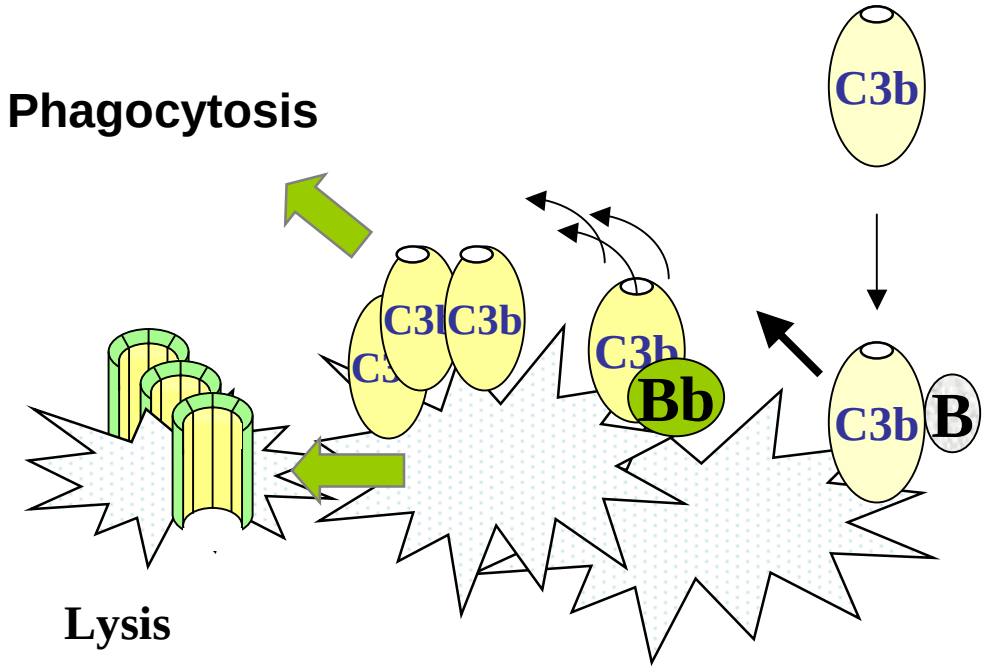
Lysis



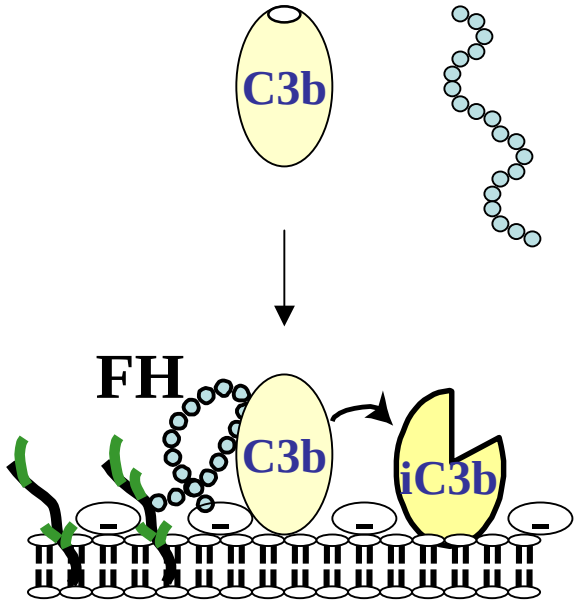
Link with adaptive Immunity

Alternative complement pathway activation on various surface

Microbial surface



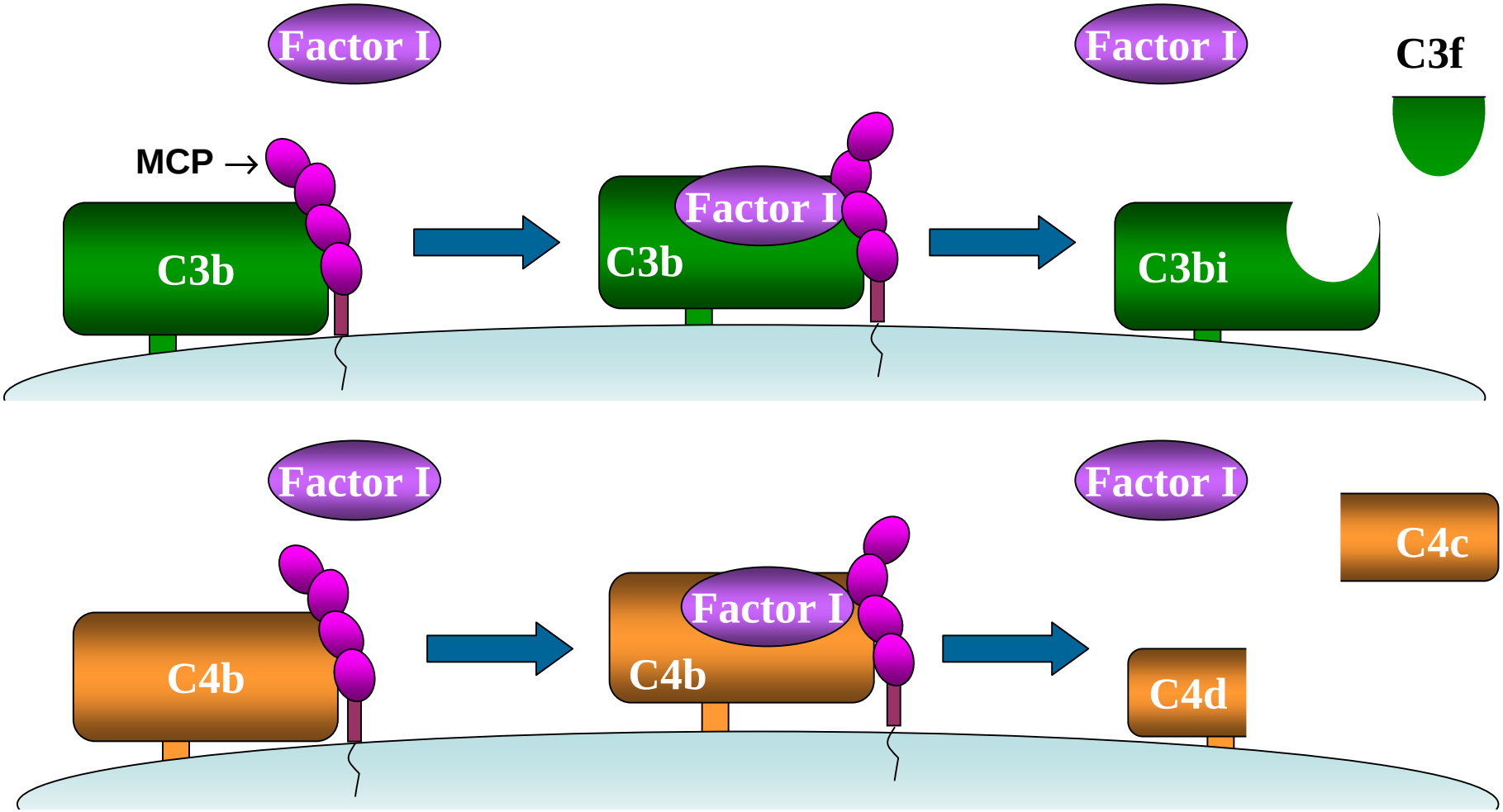
Host cell membrane



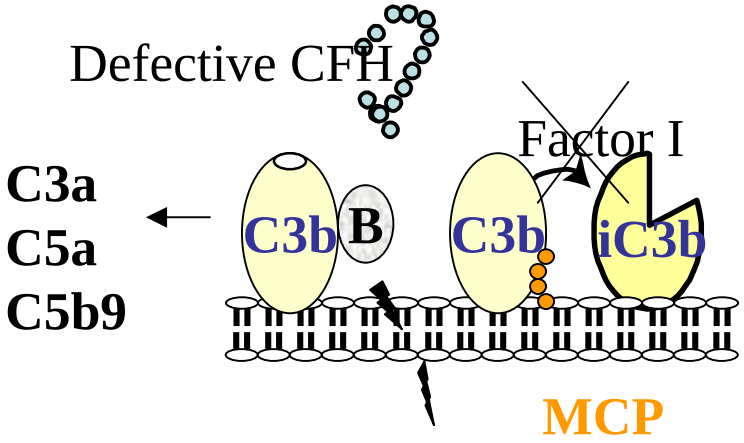
Presence of negatively charged cell surface polyanions (heparin, sialic acid, GAGs)

Complement activation

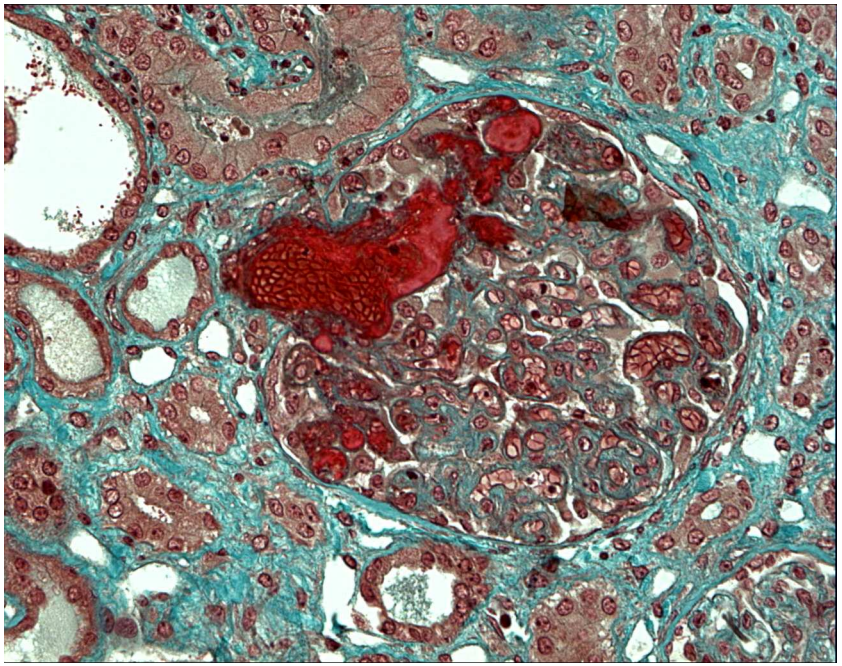
Complement Inactivation


Factor I
Factor I
C3f
MCP →
C3b
Factor I
C3b
C3bi
Factor I
Factor I
C4c
C4b
Factor I
C4b
C4d

aHUS is emerging as a paradigm of disease resulting from inefficient protection of the host endothelial cells surfaces in the setting of complement activation.



Damage by complement attack



CFH mutations in atypical HUS

🗁**1981, Thompson et al : HUS and Factor H deficiency (1994, Pichette, 1998, Ohali; 1998, Rougier)**

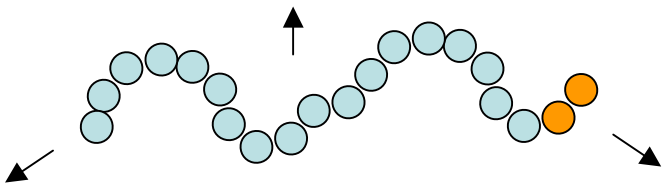
🗁**1998 (Warwicker)** : Genetic studies using linkage analysis in 3 families without Factor H deficiency: RCA Locus; identification of heterozygous nucleotide substitution in the SCR 20 in one of them.

✓**Atypical HUS associated with no evidence of Factor H deficiency**

🗁2008 Up to 100 mutations in CFH gene

- Homozygous and heterozygous mutations
- Mutations clustering in the C-terminal domain of the protein (SCR 16-20)
- The frequency of Factor H-associated HUS between 20%-30%
- With or without low C3 level/ With or without low Factor H
- Genetics screening

Destabilization of tertiary or quaternary structure



Defect in C3b/C3d binding

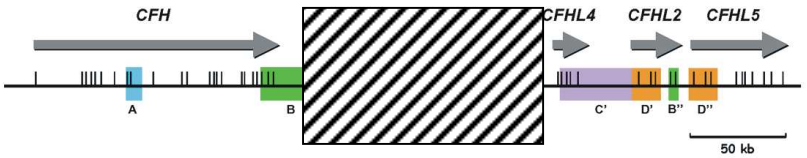
Defect in C3b and heparin binding

Factor H antibody associated HUS (30 cases)

In all patients :

- Non shigatoxin-related HUS and absence of abnormalities at the genetic analysis of Factor H, Factor I and CD46 genes
- Presence of anti-Factor H IgG detected by ELISA

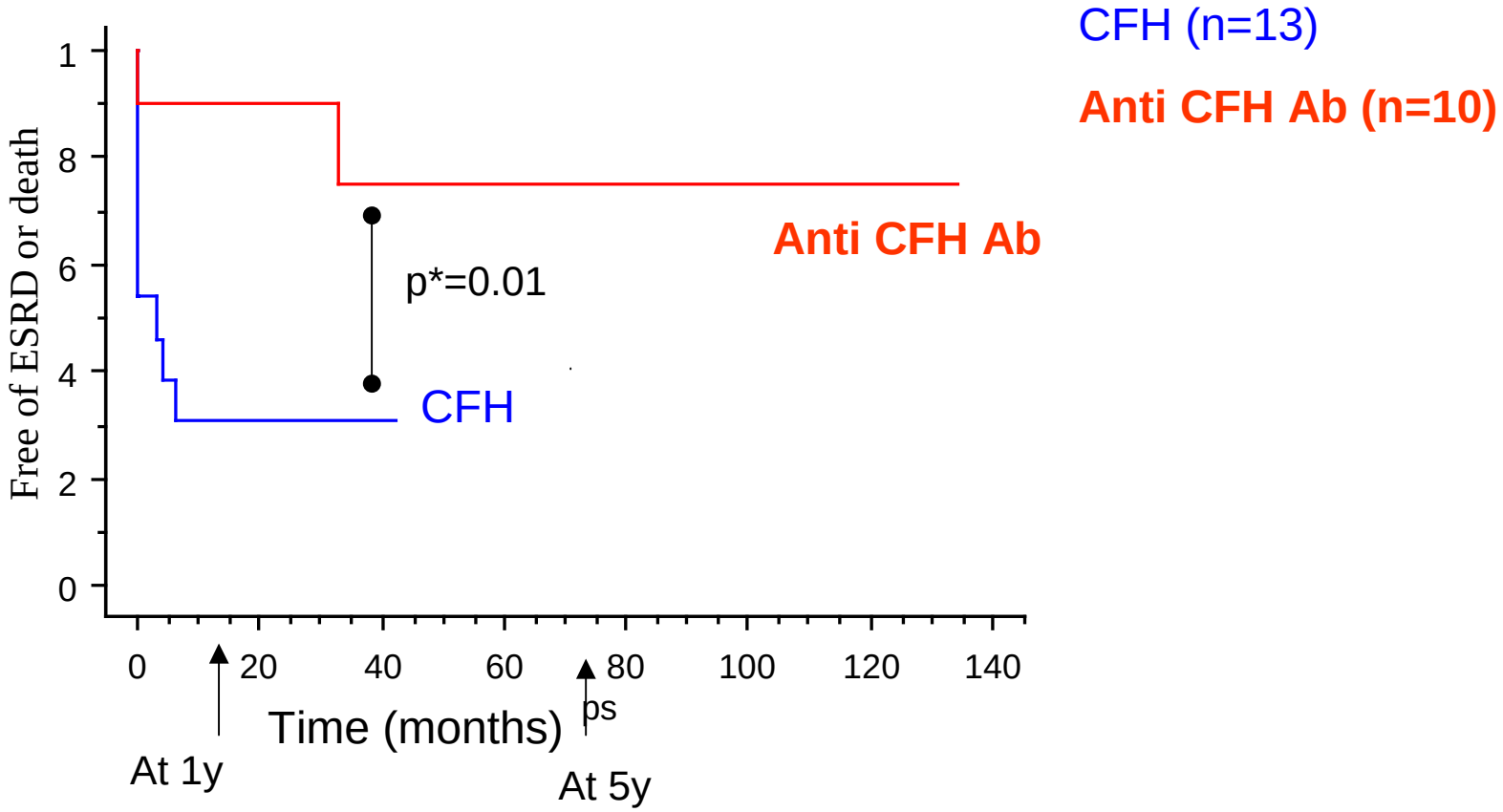
- Outcome :
  - Relapsing form one episode HUS
    - No recurrence
    - ESRD at the first shot
- Association with CFHR1 deletion



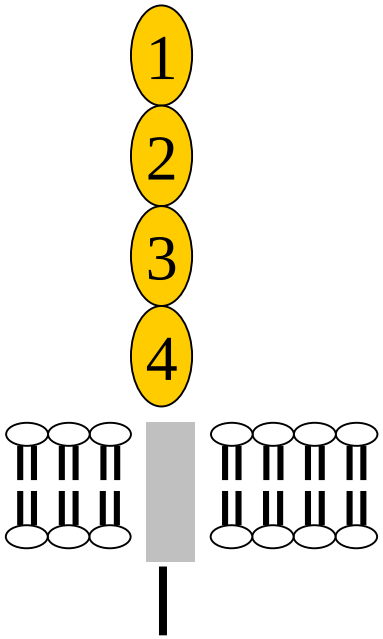
Dragon-Durey, JASN, 2006 ;Jozni, Blood, 2007

Longer overall kidney function among patients with CFH Ab than patients with CFH mutation

French Cohort



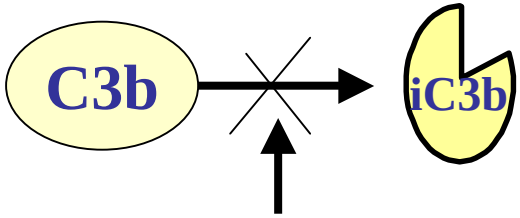
MCP (CD46)



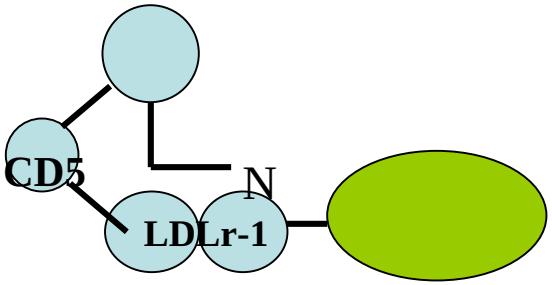
40 cas, 10% of patients

Richards et al; Noris et al, 2003
Fremeaux-Bacchi, 2006
Caprioli et al, 2006

Factor I



Defects in proteolytic inactivation of C3b

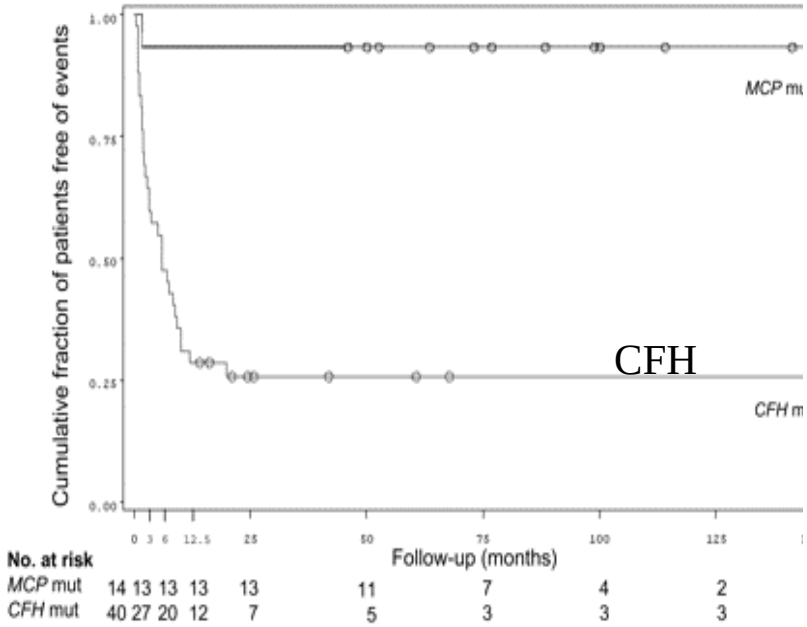


20 cas, 5% of patients

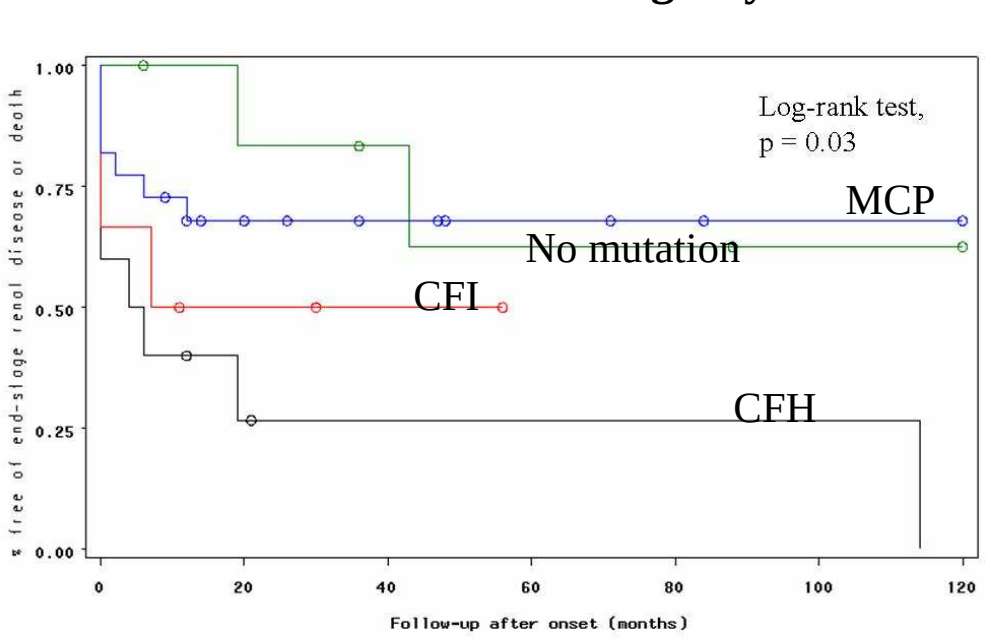
Frémeaux-Bacchi et al, 2004
Kavanah et al, 2005
Caprioli et al, 2006

RENAL SURVIVAL ACCORDING TO COMPLEMENT MUTATION

Italian Registry



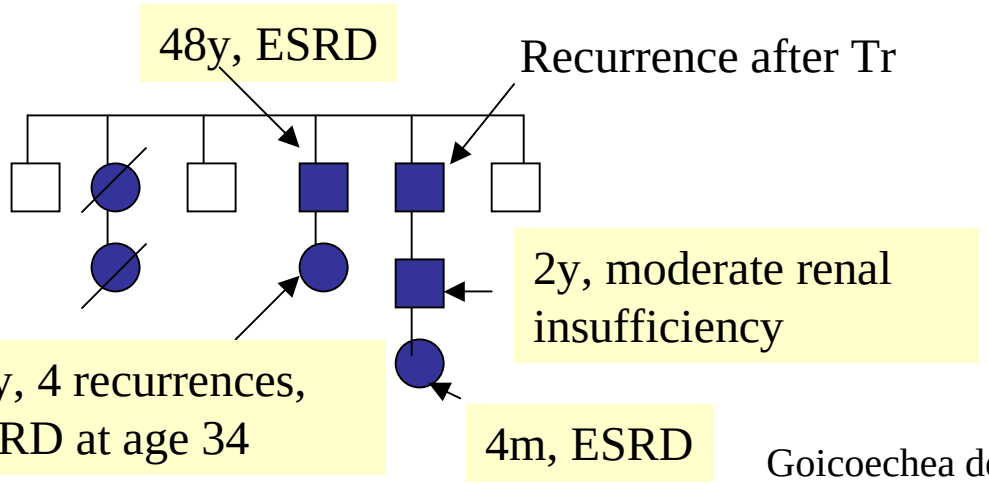
French Pediatric Registry

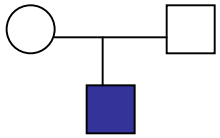


Caprioli et al, Blood, 2006

Sellier-Leclerc et al, JASN, 2007

Mutations in complement factor B are associated with aHUS





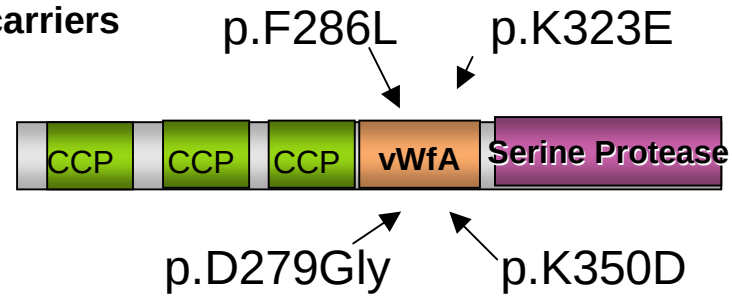
4m, several recurrences, ESRD 2 y later

De novo mutation

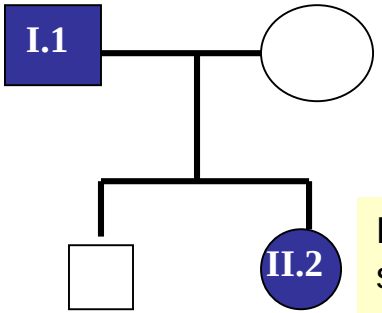
Goicoechea de Jorge E et al PNAS. 2007 Jan 2;104(1):240-5.

4/11 individuals were heathly carriers

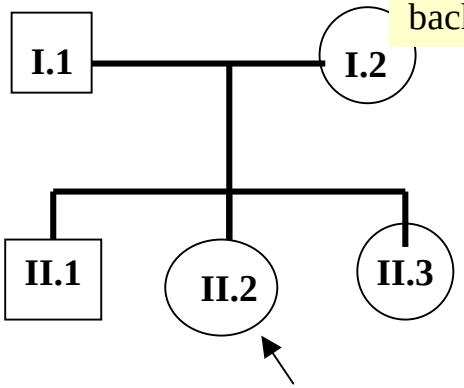
HUS (53y), ESRD
Trx 1 recurrence (5 months)
Tr 2 recurrence (day 15)



Girl, HUS (1m), ESRD (4m)
Renal Transplantation (19m) with HUS recurrence at day 15
back to dialysis at 6.4y



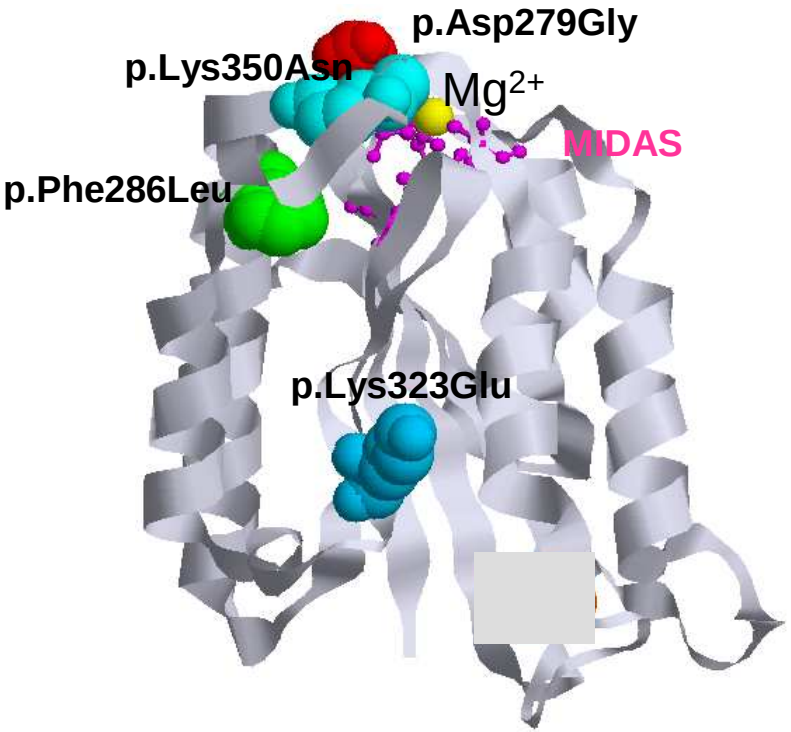
HUS (33y), no sequellea under plasmatherapie (2y)



De novo mutation

French cohort

Four mutations in Factor B lead to a gain of function in patients with aHUS

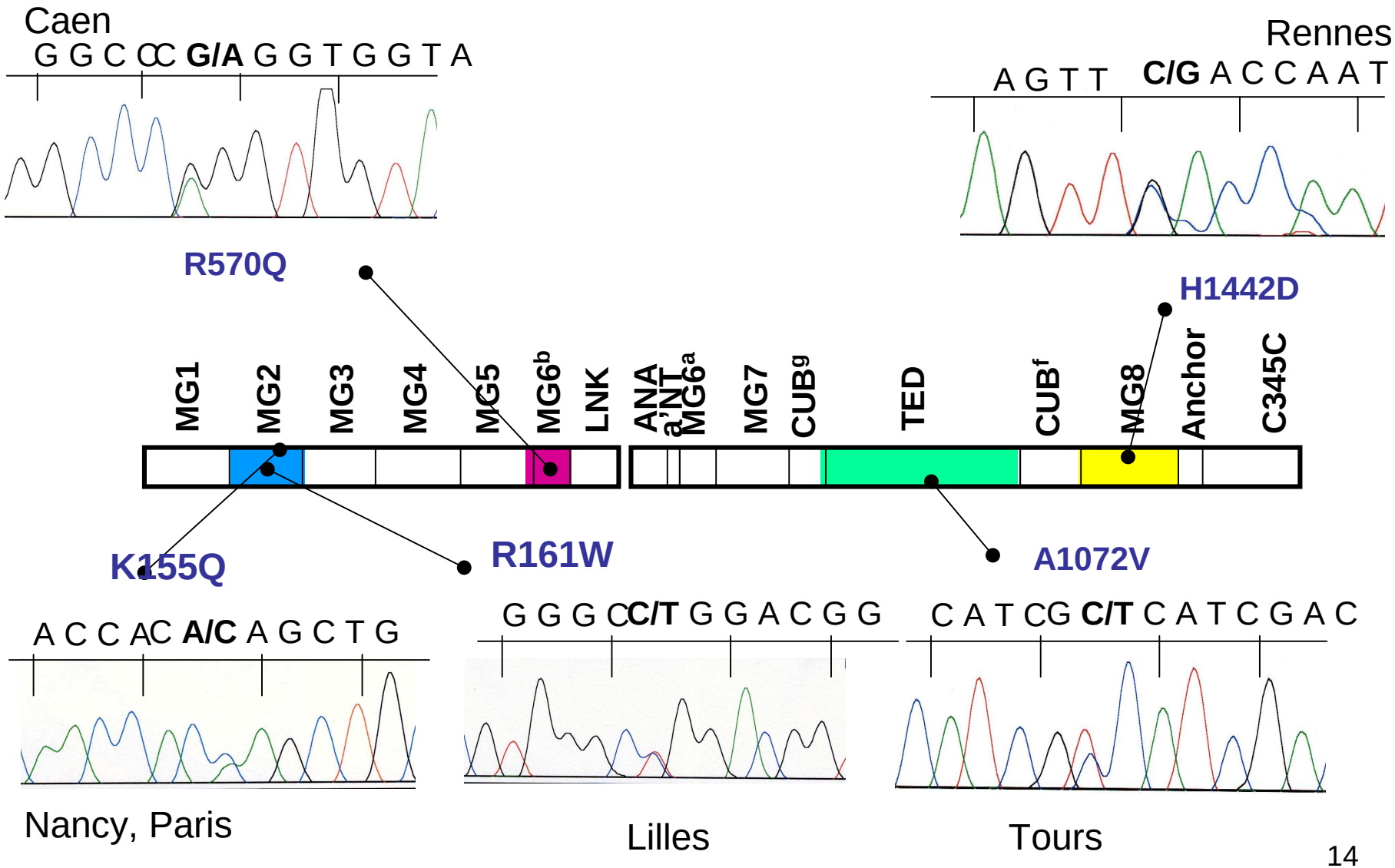


vWF domain

All mutations are in the CFB VwfA domain

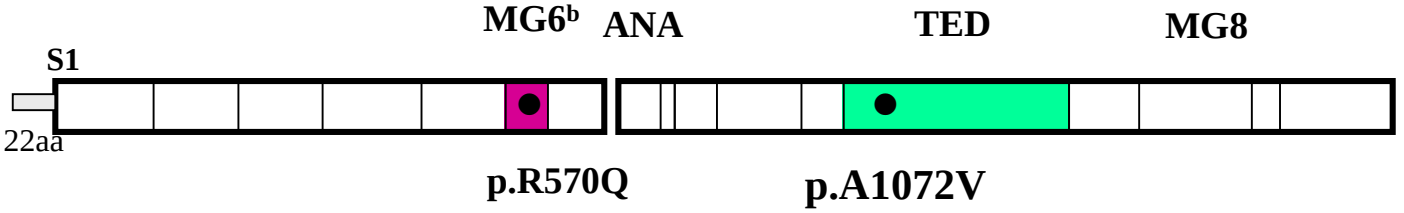
	Binding C3b	Formation C3bBb	Resistance to decay	Gain of function
p.D279G	more efficient	more efficient	YES	YES
p.K350D	more efficient	more efficient	NA	YES
p.F286L	more efficient	rapid spontaneous decay		YES
p.K323E	no change	no change	Yes	YES

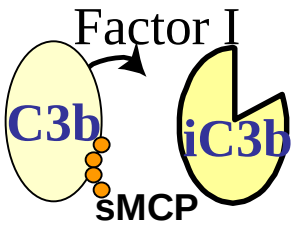
Mutations in C3 are associated with aHUS

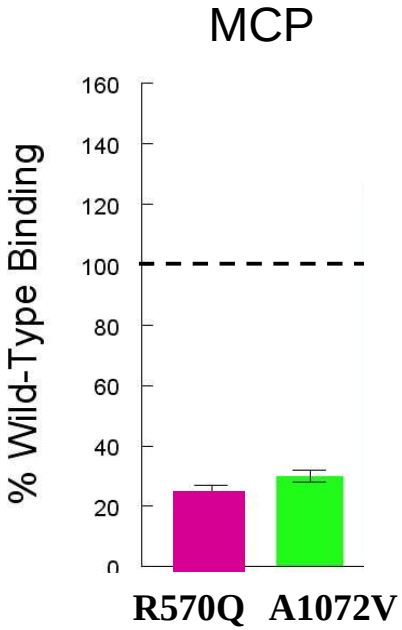


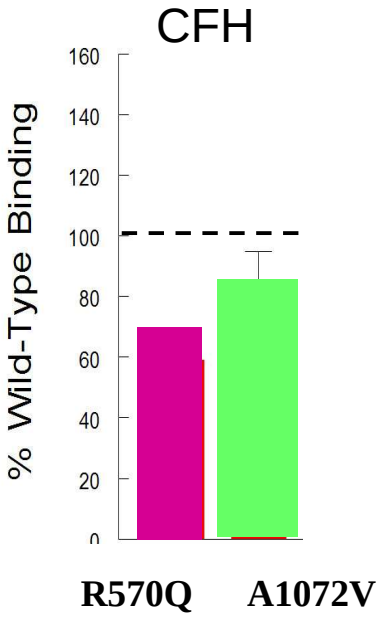
Fremeaux_Bacchi et al, 2008

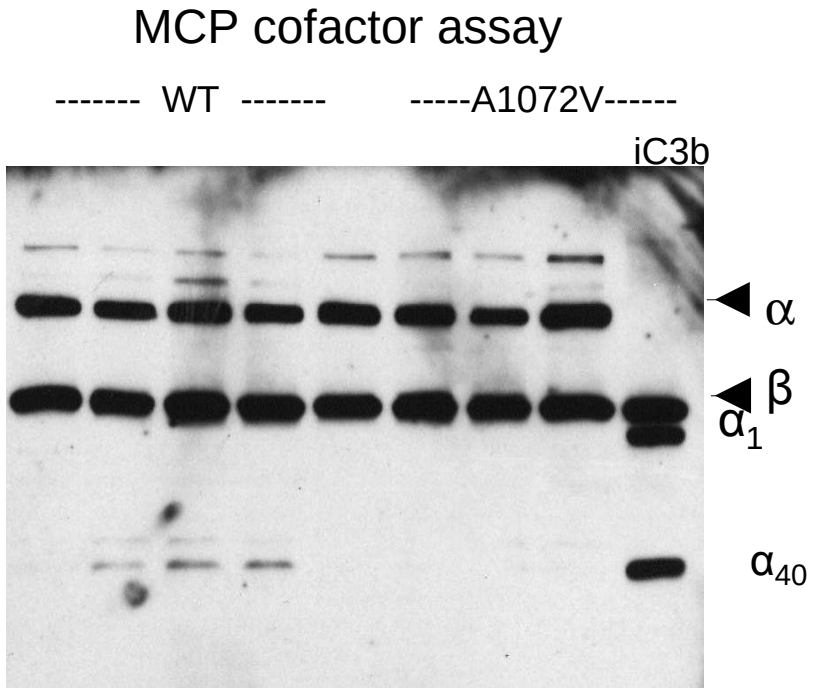
Mutations in C3 lead to decrease the binding to MCP and CFH and cofactor assay











aHUS and Complement

French multicentric project

PHRC National, 2005-2008 et 2008-2011

Clinical features: HUS (non-*E. coli* associated origin; no criteria for secondary HUS)

Retrospective and prospective **recruitment (00-06)**

Biological analyses:

- Protein level: C3, C4, Factor B (FB), Factor H (FH) and Factor I (FI) and MCP (CD46) expression; Anti Factor H antibodies
- Genetic level: exon-specific sequence analysis of Factor H, MCP, Factor I CFB and C3

France
212 patients

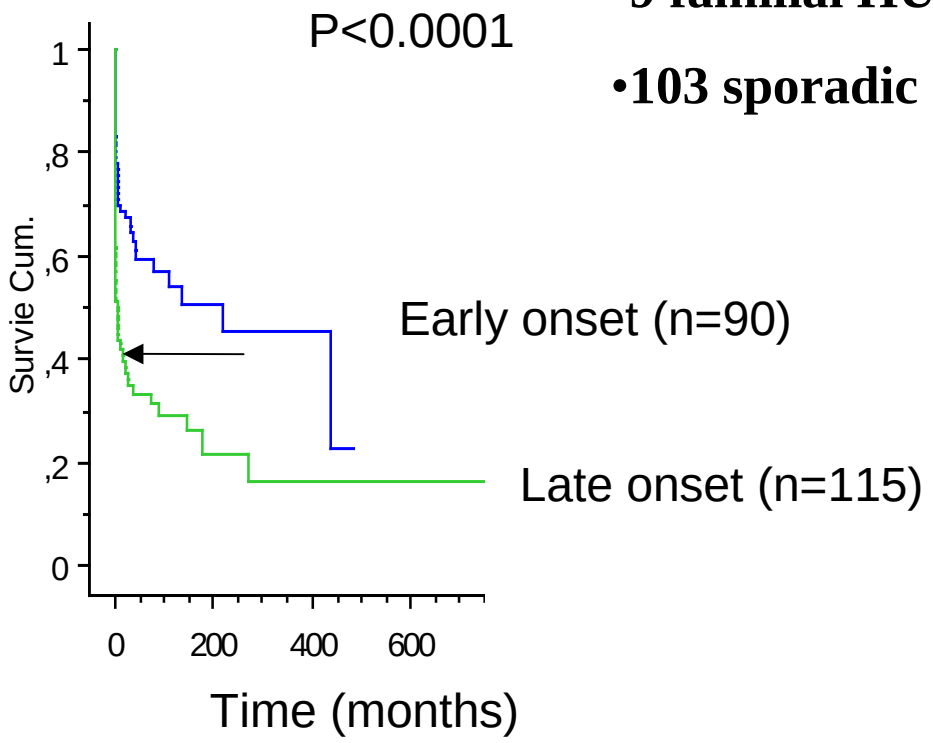
Pediatric Cohort
N=97 (89 pedigrees)

- **50 girls / 47 boys**
- **14 familial HUS (18%)**
- **75 sporadic cases**

Adult Cohort

N=115 (112 pedigrees)

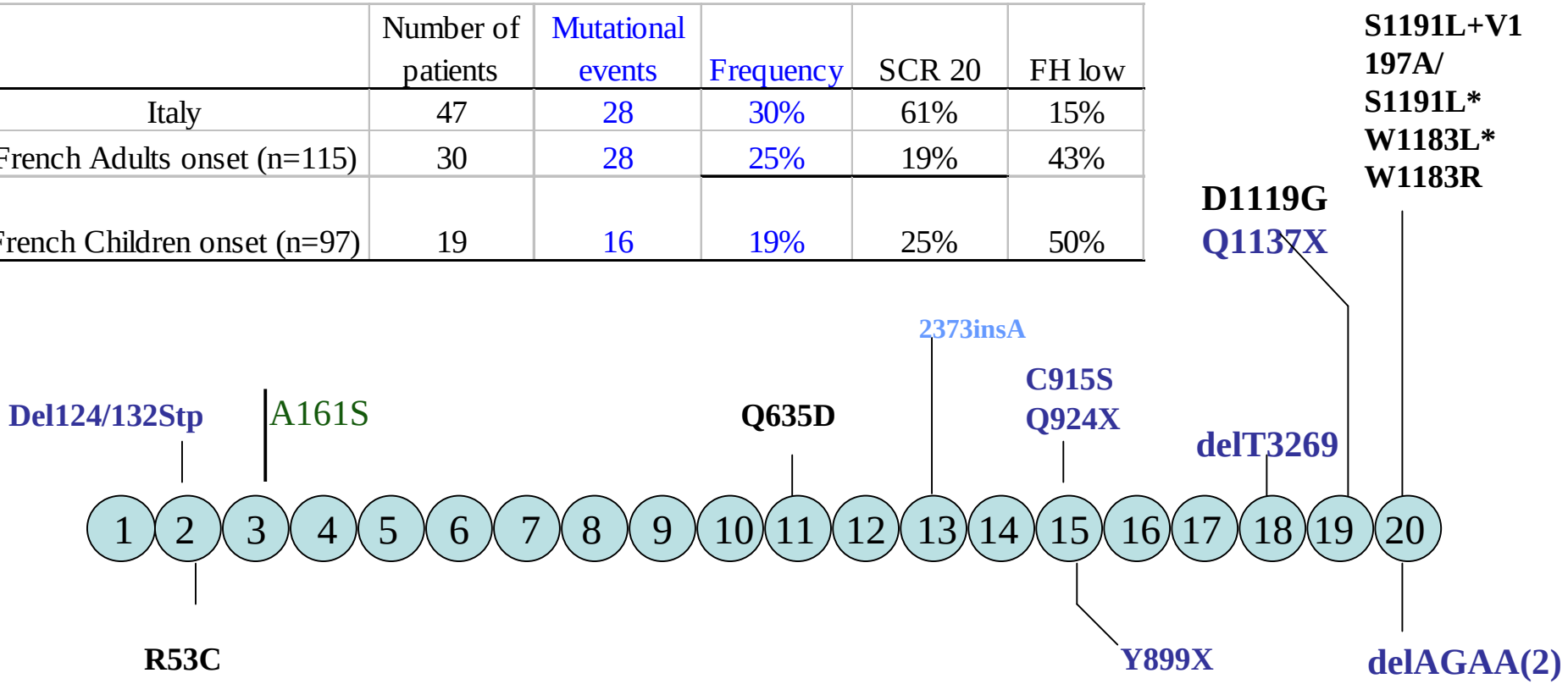
- **93 women / 22 men**
- **9 familial HUS (8%)**
- **103 sporadic cases**

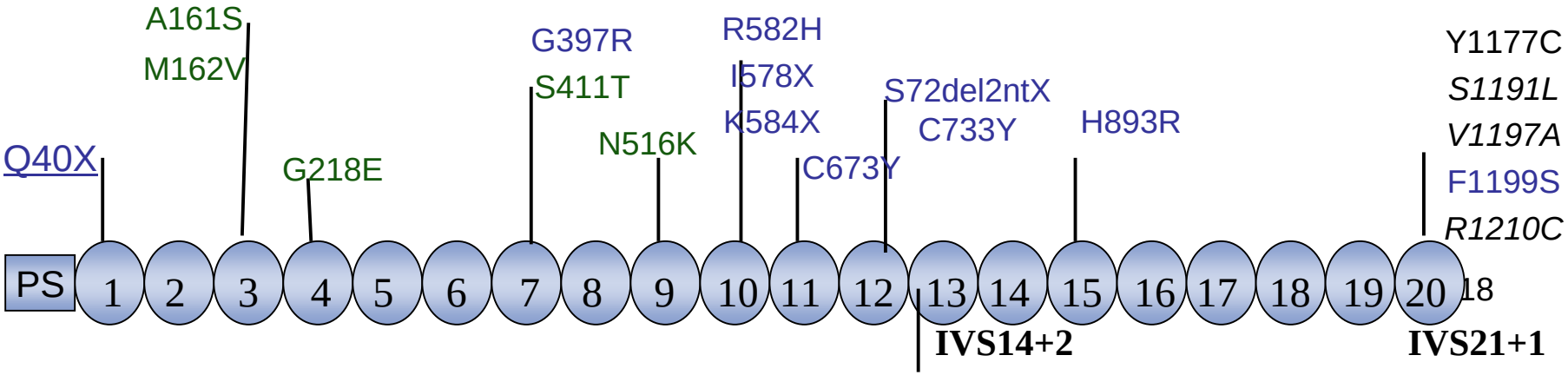


7 deces

CFH mutations in the French cohort

	Number of patients	Mutational events	Frequency	SCR 20	FH low
Italy	47	28	30%	61%	15%
French Adults onset (n=115)	30	28	25%	19%	43%
French Children onset (n=97)	19	16	19%	25%	50%

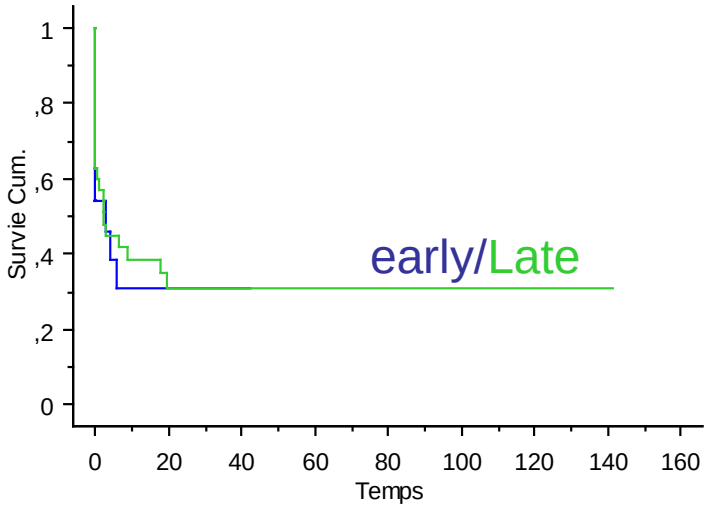


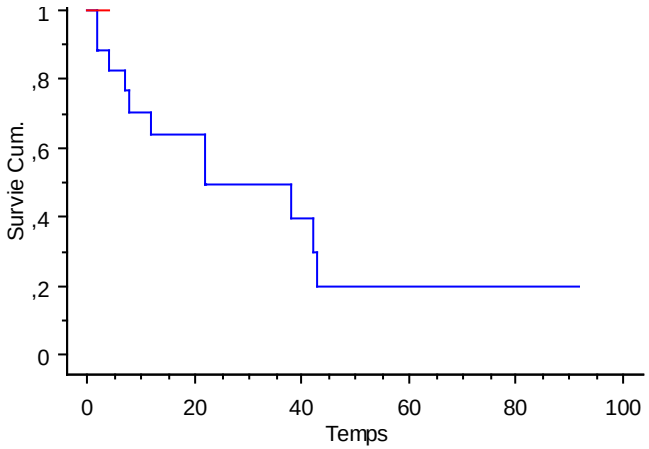


Factor H-associated HUS

- Penetrance approxymately 50%
- Triggers : Pregancy, infections

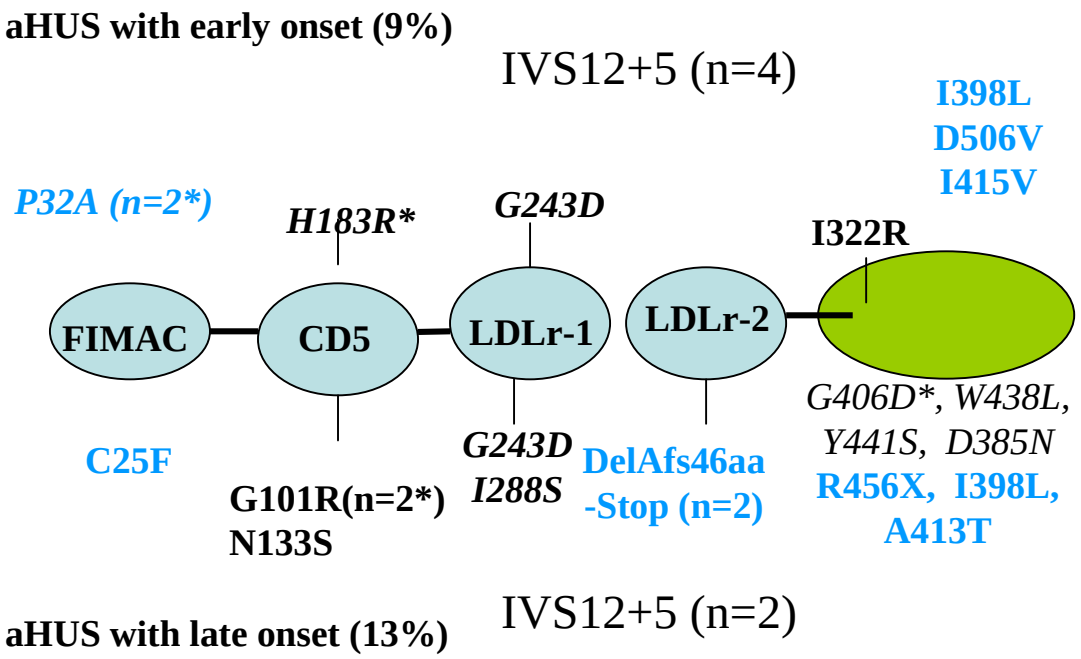
Outcome of Renal Transplantation



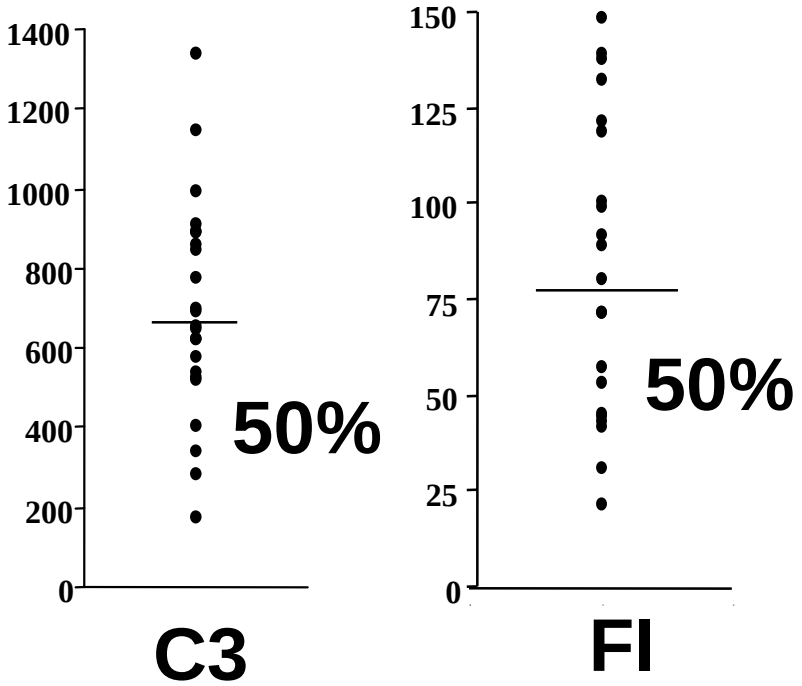


N=17 grafts

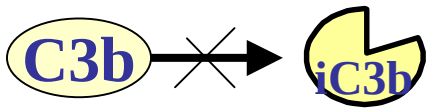
CFI mutations in the French cohort



Biological evaluation



8 CFI mutations and defects in proteolytic inactivation of C3b

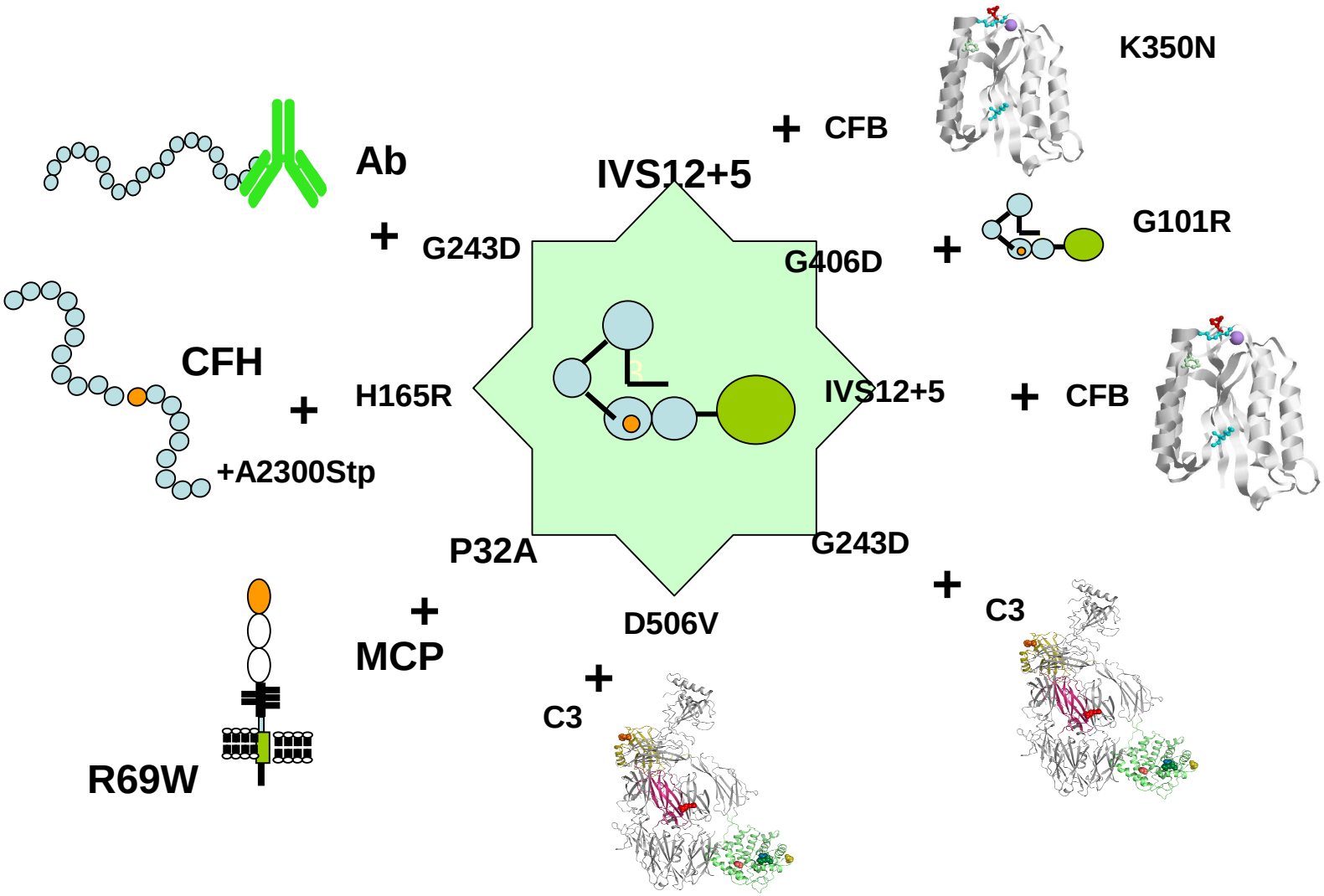


In 2008

21 patients

- No familial cases
- Disease onset: 1 m to 50y
- One flare without sequellea or Initial ESRD

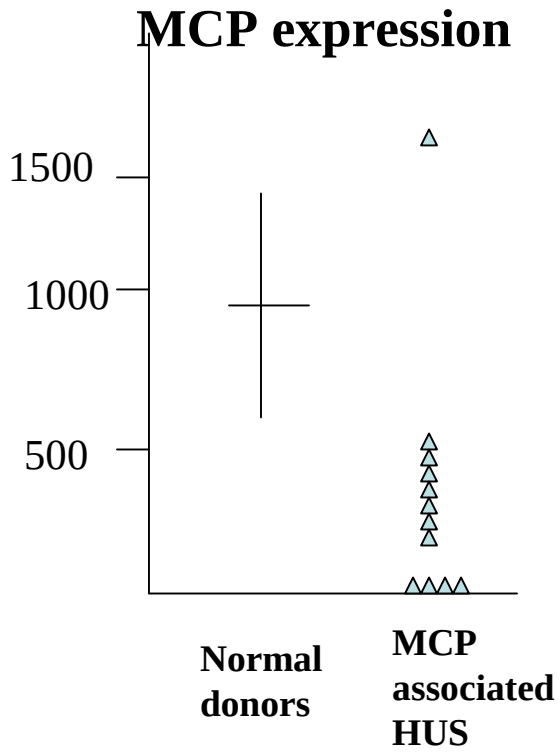
Multiple susceptibility factors in patients with CFI mutation (27%of CFI mutations)

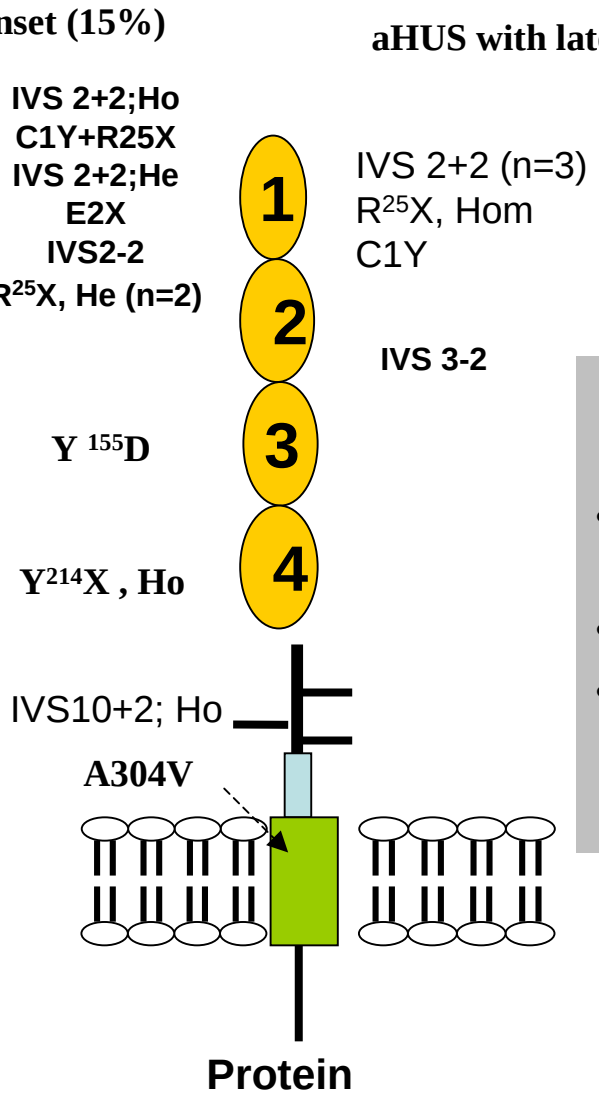


8 patients

Mutations in the MCP gene

Fremeaux-Bacchi 2006





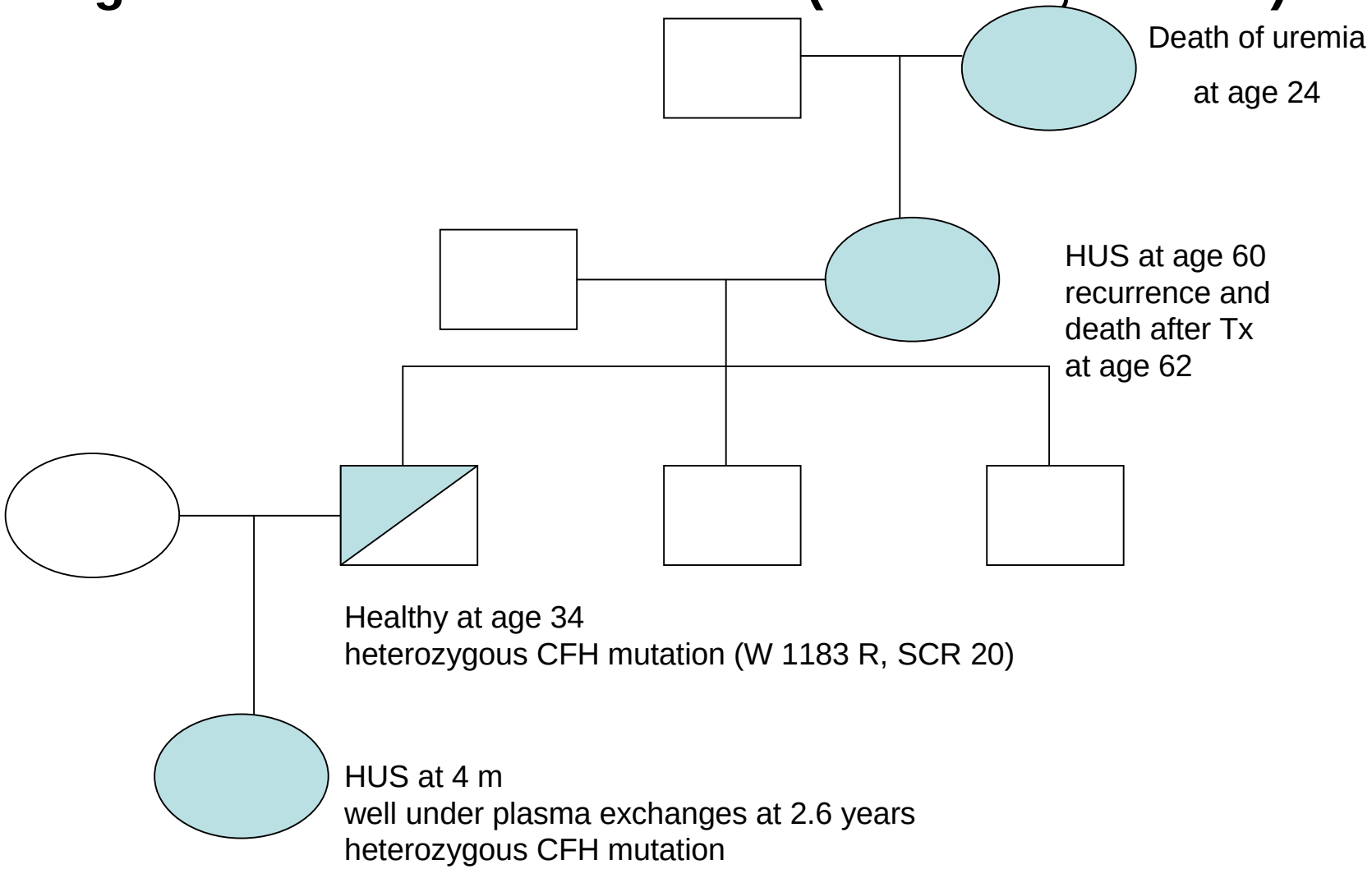
In 2008

19 patients

- 4 familial (5 cases) and 14 sporadic
- Disease onset: 2 to 41y
- Evolution : recurrences (2 to 20) or initial ESRD (adults onset)

INTRAFAMILIAL PHENOTYPE VARIABILITY

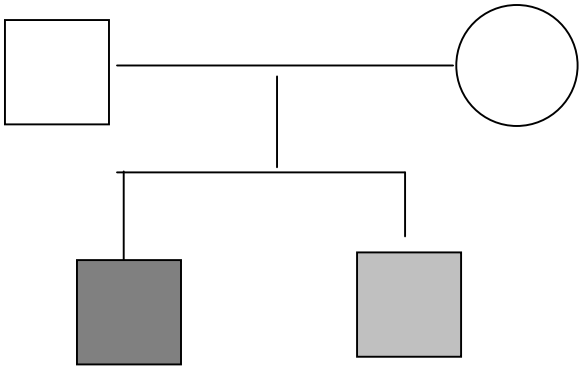
eg : aHUS with CFH mutation (W 1183 R, SCR 20)



Loirat

Incomplete identification in two families

(Paris)



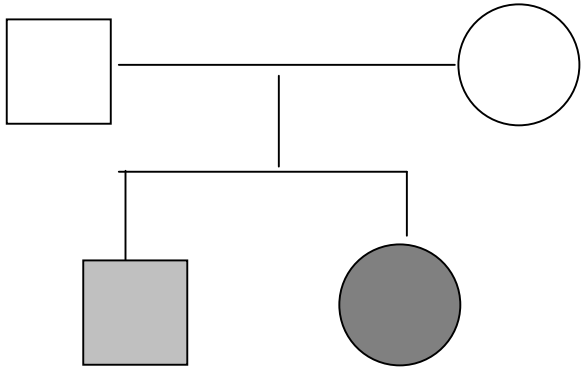
Severe outcome (5m)

One episode (6m)
No sequellea

G243D **CFI** No

K155Q **C3** No

(Nice)



One episode (4y)
No sequellea

Severe outcome 5m

No **CFH** **A161S**

✓The 2 families have other unknown genetic risk factor(s)

✓CFH, IF and C3 mutation might have unknown functionnal consequences playing the role of severity factors

✓ they could also correspond to rare polymorphisms (but they have not been identified in 100 controls)

Conclusions

	Familial	%	Sporadic	%
n	21		178	
Factor H	7	33	37	21
MCP	3	15	15	8
Factor I	-	-	23	13
C3	3	15	10	6
CFH antibodies	-	-	10	6
Multiple	-	-	10	6
Factor B	1	5	1	0
Explained	14	68	106	60
Unexplained	7	32	70	40

30 % des patients ont un C3 diminué

ADAMST13 **Comment explorer un SHU atypique en absence d'étiologie** **Verotoxine**

•CH50,C3, C4, Facteur B: Recherche des stigmates d'activation de la voie alterne:

⇨Importante (C3 et Facteur B diminués)ou modérée: C3 diminué, Facteur B normal

Dosage du Facteur H, du Facteur I et étude de l'expression membranaire de MCP

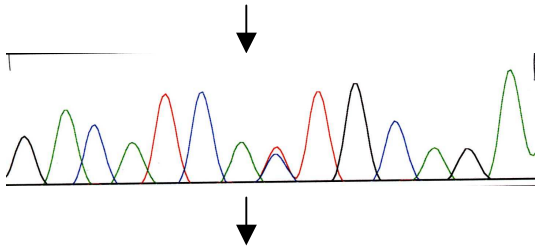
et

Etude des gènes de CFH, CFI et MCP

- diminué : déficit quantitatif

Déficit homozygote (<1%)

déficit hétérozygote (10% à 60%)



❖**Mutation ou Polymorphisme**
❖**Conséquences fonctionnelles**

A confirmer par la caractérisation moléculaire

Mutation associée à déficit fonctionnel

Anticorps anti FH + Recherche des gènes Hybride (MLPA)

Mutation in complement genes and other TMA etiology

	Number of patients	% of mutation in CFH, CFI or MCP gene	References
HELLP	11	23	Fakhouri et al, 2008; Blood
MAT "de novo"after renal Transplantation	24	29	Le quintrec M et al, 2008; Am J Transplant
Typical HUS with STEC	Case report (n=3) and 2 in the french cohort		Fang et al, Blood 2008; Edey et al, Am J Kidney dis, 2008; Fremeaux-Bacchi et al, J Am Soc Nephrol. 2006
Sd d' Upshaw-Schulman (Hereditary ADAMTS13 deficiency)	Case report (n=1) and 3 in the french cohort		Noris et al, J Am Soc Nephrol. 2005
PTT and acquired ADAMTS13 deficiency	Case report (1 French, 1 Italian)		in preparation

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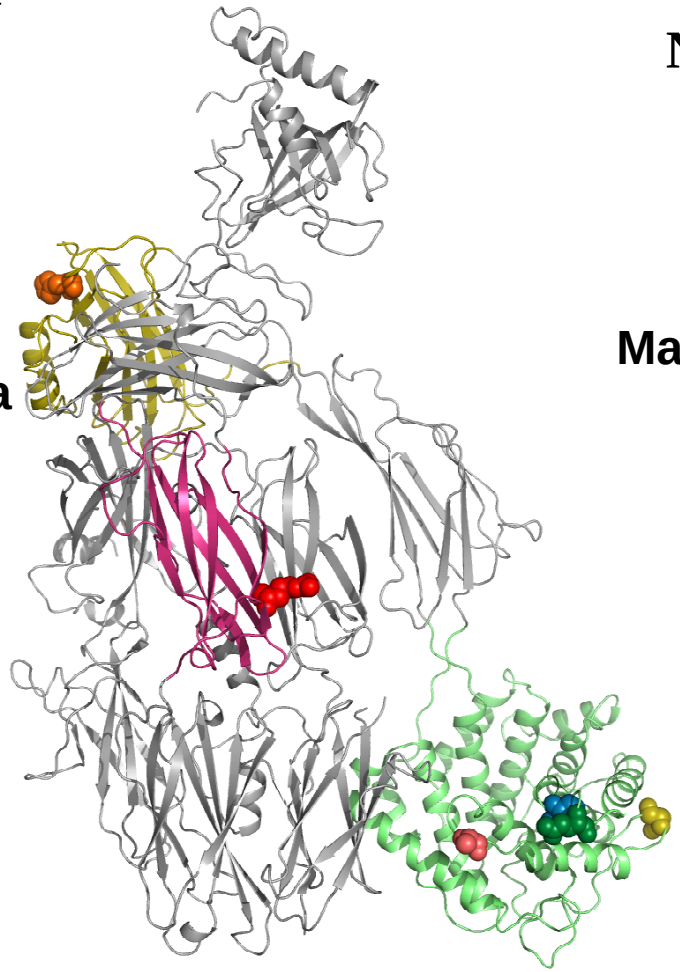

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