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Supplementary Patients and Methods

Study population

aHUS was defined by the coexistence of mechanical hemolytic anemia (hemoglobin < 10 g/dl, lactate dehydrogenase level > upper limit of normal (ULN), presence of schizocytes on blood smear), thrombocytopenia (platelets count < 150 G/L) and renal failure (serum creatinine level > ULN for age or/and proteinuria > 0.5 g/day or nephrotic syndrome) and/or by TMA lesions at kidney biopsy (capillary and/or arteriolar thrombosis, "double contour"). aHUS remission was defined by normalization of the platelet and LDH levels, relapse was defined by recurrence of mechanical hemolytic anemia and/or thrombocytopenia and/or a 25% increase in serum creatinine after at least two weeks remission. Written informed consent for the genetic analysis was obtained from all patients. We arbitrary defined the age of 16 to discriminate between the pediatric and adult onset of aHUS. Three patients who developed the disease between 16 to 18 years of age were enrolled in the adults sub group.

Healthy individuals were recruited in the study through the Research clinic Unit of the Hopital Europeen Georges Pompidou, Paris, France and the study was approved by the Institutional Review Board (Programme Hospitalier de Recherche Clinique, AOM 08198).

Study design

Blood samples from the patients with aHUS were collected for complement investigation between 2000 and 2008 in voluntarily participating pediatric (n=24) and adult (n=36) nephrology centers in France**.** Patients were included regardless of the date of the first episode of aHUS. None of the patients had ADAMST13 deficiency (enzymatic activity <10%). The medical files of the patients were reviewed retrospectively, and the relevant data (age at onset; sex; triggering events; symptoms at onset; disease outcome, including the occurrence and timing of relapses, date of ESRD, date and cause of death) were collected. Patients with anti-factor H antibodies were taken into account only for the analysis of data concerning the whole cohort of patients. Comparison between the adults and children was not possible, as most patients were children. This group of patients has been described in a previous publication (1).

Complement investigations

The complement work-up was conducted in the department of Immunology in the Hopital Europeen Georges Pompidou, Paris, France, which is the reference center for the evaluation of complement disorders in human diseases that virtually receives all samples from French patients with aHUS. The plasma concentrations of CFH and CFI were measured by ELISA, C4, C3 and FB were measured by nephelometry, and MCP expression was analyzed on granulocytes using anti-MCP phycoerythrin (PE)-conjugated antibodies (Serotec, UK). Screening for anti-CFH ab was performed as previously described (2).

We used data from the NCBI SNP database (http://www.ncbi.nlm.nih.gov/snp) and the 1000 Genomes Project (http://www.1000genomes.org) to identified ultra rare SNPs found in less than 1/100 of normal individuals. If the sequence variant was not found in the normal French population (200 pairs of chromosomes from normal donors) or in the SNPs databases, it was classified as a disease-causing mutation. We arbitrarily included ultra rare SNPs that have been found in association with a second mutation or identified in more than one unrelated patient in the group of disease causing mutations.

Four SNPs in the *CFH* gene [rs 3753394 (-257 C>T); rs800292 (c.184G>A; p.Val62Ile); rs1061170 (c.1204T>C; p.Tyr402His); rs1065489 (c.2808G>T; p.Glu936Asp)], one SNP in the MCP gene [rs2796268 (P2-366 A>G)] and two variants in the *CFHR1* gene (deletion *CFHR1-CFHR3* and *CFHR1*B*) were selected for the association analysis.

For *CFH*, five SNPs (rs3753394, -331 C>T; rs800292 (c.184G>A; p.Val62Ile); rs1061170 (c.1204T>C; p.Tyr402His); rs3753396 (c.2016A>G; p.Gln672Gln) and rs1065489 (c.2808G>T; p.Glu936Asp) define one low-risk (protective) haplotype CFH cgcag and one at-risk haplotype CFH tgtgt (3). In MCP, five SNPs (P1–652 A>G (rs2796267), P2-366 A>G (rs2796268), P3IVS9-78 G>A (rs1962149), P4IVS12+638 G>A (rs859705) and P5 c.4070 T>C (rs7144).) define three low-risk (protective) haplotypes and one at-risk haplotype GGAAC (4). The CFH and MCP haplotypes were analyzed using SNPstats software at the Web site http:bioinfo.iconcologia.net/snpstats/start;htm.

Supplementary Table 1: Distribution frequencies of rare and ultra- rare SNPs

1-Four rare SNPs in the CFH (p.Asn516Lys), MCP (p.A353V or A304V), CFI (IVS12+5) and C3 (p.Lys155Glu) genes were identified in healthy controls and patients and were not considered as mutations.

Rare variants	Heathly controls	aHUS patients (%)	p
MCP (p.A353V; A304V*)	1.1 (2/181)	1.4 (3/214)	0.8
CFH (p.Asn516Lys)	1.1 (2/181)	1.9 (4/214)	0.5
CFI (IVS12+5)	1.3 (5/181)	2.8 (6/214)	0.9
C3 (p.Lys155Glu;K133Q)	2.7(5/185)	1.4 3/214)	0.4

* The A304V mutation was identified in patient each with fatal Stx-HUS, the HELLP syndrome, and glomerulonephritis with C3 deposits (5) and has been previously reported as susceptibly factors in aHUS (6). A304V MCP mutant was deficient in its ability to control the alternative pathway of complement activation on a cell surface (5).

2-Seven SNPs (in CFI:G119R, H183R, G261D, I416L, P553S; in CFB: I242L; in C3: R735W) were not found in the French control group but are represented in SNP databases. Two SNPs have been excluded from the mutation list (CFB: I242L; C3: R735W). Five SNPs in the CFI gene (G119R, H183R, G261DI416L, P553S) have been identified in association with a disease-causing mutation or in more than one patient (as indicated in the legend of Table 1) and have been arbitrary considered as mutations.

Supplementary Table 2: Association analysis of 7 selected SNPs and haplotypes in CFH, MCP and CFHR1 with aHUS.

All (pediatric and adult onset), Children (age of first episode of aHUS less than 16 y), Adults (onset after the age of 16 y) from the French cohort versus controls.

			Controls		**aHUS (all)**		all vs Controls		**Children**		Children vs Controls		**Adults**		Adults vs Controls		Adults vs Chidren	
Genes	SNPs	Allele	n	freq	n	freq	p	OR (95% CI)	n	freq	p	OR (95% CI)	n	freq	p	OR (95% CI)	p	OR (95% CI)
CFH	?257C>T (rs3753394)	T	197	0.24	145	0.48	<0.0001	2.94 (2.13-4.1)	54	0.42	<0.0001	2.28 (1.4-3.6)	91	0.51	<0.0001	3.33 (2.3-4.8)	0.12	1.46 (0.9-2.37)
CFH	c.184G>A; p.Val62Ile (rs800292)	c.62Ile	232	0.24	154	0.17	0.016	0.64 (0.44-0.93)	54	0.19	0.3	0.76 (0.45-1.28)	100	0.16	0.01	0.58 (0.37-0.89)	0.44	0.79 (0.43-1.45)
CFH	c.1204T>C; p.Tyr402His (rs1061170)	c.402H	239	0.39	152	0.21	<0.0001	0.41 (0.3-0.57)	51	0.25	0.007	0.51 (0.31-0.83)	101	0.19	<0.0001	0.36 (0.24-0.54)	0.18	0.68 (0.38-1.20)
CFH	c.2808G>T; p.Glu936Asp (rs1065489)	c.936E	238	0.17	159	0.42	<0.0001	3.54 (2.56-4.91)	57	0.38	<0.0001	3 (1.91-4.69)	102	0.45	<0.0001	3.99 (2.76-5.75)	0.20	1.36 (0.85-2.17)
MCP	?366A>G (rs2796268)	G	112	0.38	136	0.6	<0.0001	2.41 (1.68-3.46)	54	0.59	0.0003	2.38 (1.5-3.8)	79	0.6	<0.0001	2.46 (1.6-3.74)	0.89	1.04 (0.63-1.71)
CFHR1		deletion CFHR1-R3	172	0.24	145	0.17	0.026	0.64 (0.43-0.95)	54	0.15	0.04	0.55 (0.30-0.98)	91	0.18	0.12	0.70 (0.44-1.09)	0.47	1.27 (0.66-2.44)
		CFHR1*B	172	0.31	145	0.54	<0.0001	2.61 (1.89-3.62)	54	0.56	<0.0001	2.77 (1.78-4.31)	91	0.53	<0.0001	2.47 (1.71-3.58)	0.64	0.89 (0.55-1.44)
	Haplotypes																	
CFH	***tgtgt***		275	0.13	166	0.38	<0.0001	4.05 (2.90-5.84)	59	0.32	<0.0001	3.15 (1.99-5)	107	0.41	<0.0001	4.64 (3.21-6.7)	0.11	1.47 (0.92-2.36)
MCP	***ggaac***		192	0.25	166	0.52	<0.0001	3.18 (2.32-4.36)	59	0.49	<0.0001	2.9 (1.89-4.45)	107	0.53	<0.0001	3.36 (2.36-4.78)	0.52	1.16 (0.74-1.81)

The at risk *tgtgt* CFH haplotype was tagged by detection of the genotypes rs3753394 in the promotor and rs800292 (c.184G>A; p.Val62Ile), rs1061170 (c.1204T>C; p.Tyr402His), rs3753396 (c.2016A>G; p.Gln672Gln) and rs1065489 (c.2808G>T; p.Glu936Asp). The at-risk *ggaac* MCP haplotype was tagged by genotyping the following SNPs: -652 A>G (rs2796267), -366 A>G (rs2796268), IVS9-78 G>A (rs1962149), IVS12+638 G>A (rs859705), c.4070 T>C (rs7144) (4,7-8). The frequency of each selected SNP and the haplotypes in the aHUS patients (all, children and adults) was compared with that in controls, and the p-values and ORs were calculated using a Pearson x2 test of association. Patients with anti-CFH antibodies were excluded for this association analysis. In total, 90% of patients with anti-CFH antibodies carry the homozygous CFHR1-R3 deletion.

Supplementary Table 3: Clinical course and outcome in the 214 patients with atypical HUS.

A comparison was performed only if the number of patients was higher than 5 in both age groups. Therefore, patients with anti-CFH antibodies (10 children, 4 adults) and CFB mutation (2 children, 2 adults) are included only in the total cohort ("All"). The outcome of patients with anti-CFH antibodies has been previously reported in (2). The child who died 14 years after onset had CFB mutation. M months; d day

3.1-Mortality rate

	All			**CFH**			**CFI**			**MCP**			**C3**			**No identified mutation**		
	C	*A*		*C*	*A*		*C*	*A*		*C*	*A*		*C*	*A*		*C*	*A*	
	(n=89)	*(n=125)*	*p*	*(n=19)*	*(n=40)*	*p*	*(n=6)*	*(n=12)*	*p*	*(n=12)*	*(n=8)*	*p*	*(n=7)*	*(n=11)*	*p*	*(n=30)*	*(n=41)*	*p*
Death	7 (7.8%)	2 (1.6%)	0.02	2 (11%)	1 (2.5%)	0.2	2 (33%)	0	0.02	0	0	**ND**	0	0	**ND**	2 (7%)	1 (2%)	0.4
Time after aHUS onset	7 d-12 m and 14 y	2 m,7y		4 m, 12 m	2 m		7d, 3 m	-		-	-		-	-		22 d; 2.5m	7 y	

3.2- Cumulative rate of ESRD or death according to time after atypical HUS onset

ESRD/Death	**All**			**CFH**			**CFI**			**MCP**			**C3**			**No identified mutation**		
	C	*A*		*C*	*A*		*C*	*A*		*C*	*A*		*C*	*A*		*C*	*A*	
	(n=89)	*(n=125)*	*p*	*(n=19)*	*(n=40)*	*p*	*(n=6)*	*(n=12)*	*p*	*(n=12)*	*(n=8)*	*p*	*(n=7)*	*(n=11)*	*p*	*(n=30)*	*(n=39)*	*p*
At 1 month	15 (17%)	57 (46%)	<0.001	6 (33%)	19 (48%)	0.25	2 (33%)	5 (42%)	0.8	0	2 (25%)	0.06	0	5 (45%)	0.04	5 (17%)	18 (46%)	0.01
At 1 year	26 (29%)	70 (56%)	<0.001	11 (56%)	24 (60%)	0.88	3 (50%)	5 (42%)	0.6	0	5 (63%)	0.001	3 (43%)	7 (63%)	0.5	7 (23%)	19 (49%)	0.03
At 5 years	32 (36%)	80 (64%)	<0.001	12 (63%)	27 (68%)	0.74	3 (50%)	10 (83%)	0.2	2 (17%)	5 (63%)	0.03	3 (43%)	7 (63%)	0.5	8 (27%)	22 (56%)	0.01
At last follow-up	35 (39%)	89 (71%)	<0.001	13 (68%)	27 (68%)	0.94	3 (50%)	11 (91%)	0.1	3 (25%)	5 (63%)	0.09	3 (43%)	8 (72%)	0.3	11 (37%)	27 (69%)	0.008
Median follow-up (months)	45 (1-493)	57 (1-353)	0.2	6 (1-163)	24 (1-353)	0.04	46 (1-75)	46 (1-250)	0.9	214 (13-444)	16 (4-177)	0.02	222 (90-398)	50 (17-213)	0.04	46 (1-220)	54 (2-150)	0.3

3.3-Relapse pattern in patients who had not reached ESRD or died at the first atypical HUS episode

In chidren and adults 57 % (16/28) and 82% (19/23) of relapses occurred during the first year respectively.

	All			**CFH**			**CFI**			**MCP**			**C3**			**No identified mutation**		
	C	*A*		*C*	*A*		*C*	*A*		*C*	*A*		*C*	*A*		*C*	*A*	
	(n=65)	*(n=66)*	*p*	*(n=13)*	*(n=20)*	*p*	*(n=5)*	*(n=8)*	*p*	*(n=12)*	*(n=6)*	*p*	*(n=7)*	*(n=7)*	*p*	*(n=25)*	*(n=21)*	*p*
Follow up (months)	68	52	0.06	12	55	0.03	73	58	0.05	214	11	0.01	222	50	0.03	50	42	0.2
	(2-444)	(2-298)		(2-163)	(2-261)		(3-75)	(25-250)		(20-493)	(4-65)		(90-398)	(13-213)		(3-243)	(2-298)	
First Relapse, n patients (%)	28/65 (43%)	23/66 (35%)	0.3	4/13 (31%)	6 /20 (30%)	0.9	1/5 (20%)	3/8 (38%)	0.5	10/12 (83%)	2/11 (33%)	0.03	3/7 (43%)	5/7 (71%)	0.2	7/25 (28%)	7/21 (33%)	0.7
(1^{st} relapse ≤ 1 y)	16/65 (25%)	19/65 (29%)	0.55	4/13 (31%)	6 /20 (30%)	0.9	1/5 (20%)	3/8 (38%)	0.5	3/12 (25%)	2/6 (33%)	0.7	0	3/7 (43%)	0.05	6 /25 (24%)	5/20 (25%)	0.9
*(1^{st} relapse > 1 y)**	12/65 (18%)	3/65 (5%)	0.01	0	0		0	0		7/12 (58%)	0	0.01	3/7 (43%)	2/7 (28%)	0.5	1 /25 (4%)	1/20 (5%)	0.8
Relapse > 1y*, n patients (%)**	25/53 (47%)	11/55 (20%)	0.002	2/8 (25%)	3/16 (19%)	0.7	0/3 (0%)	2/8 (25%)		11/12 (92%)	1/3 (33%)	0.08	2/4 (50%)	1/5 (20%)	0.5	7/22 (32%)	4/20 (20%)	0.4

- *patients who had not reached ESRD or died at the 1-year follow-up.
- ** including patients with the first relapse during the first year after onset

Children (C), Adults (A)

ESRD: end-stage renal disease

Supplementary Table 4: Causes and time of death in patients with aHUS.

Pediatric onset					
Patients	**Genetic abnormality**	**Familial aHUS**	**Age at onset (year)**	**Months (m) or days (d) after the onset**	**Cause of death**
1	CFH (Incomplete)	yes	0,01	12 m	Cardio-respiratory arrest (on automated peritoneal dialysis)
2	CFH	no	1,54	4 m	Pulmonary hemorrhage concomitant with hemolysis and thrombocytopenia
3	CFI	yes	0,08	7 d	Cardiac arrest (uncertain cause)
4	CFI (Incomplete)	yes	0,45	3.1 m	Staphylococcal aureus septic shock (from peritoneal catheter)
5	No identified	no	0,57	2.5 m	Multivisceral failure including central nervous system and heart during relapse of HUS
6	No identified	no	0,47	22 d	Multivisceral failure including central nervous system
7	CFB	no	0,10	162 m	Cerebral hemispheric infarction due to carotid artery dissection after attempt of carotid siphon angioplasty (9)
Adult onset					
8	No identified		39,00	92 m	Not documented
9	CFH		85,00	2,4 m	Not documented

Supplementary Table 5: Characteristics of adults and children with anti-CFH antibody-associated aHUS.

	Children (n= 10)	Adults (n= 4)
Age at onset	8.2 (0.7-11.4)	31.5 (21-45)
F/M	6/4	1/3
Mean SCr (µmol/l)	401 (246-1218)	1175 (758-1590)
Platelet count (G/L)	62 (19-213)	52 (30-74)
Plasma therapy	8 (80%)	3/4 (75%)
ESRD at 1 s^t aHUS episode	1/10	0
aHUS relapse	6/10 (60%)	0
ESRD at last follow-up	2/10	2/4
Complete CFHR1 deletion	9/10	4/4

Among the 4 adult patients, the presence of anti-FH IgG was diagnosed retrospectively in 3 of them. One was treated conservatively and developed ESRD, one was treated by PE and relapsed, and the last one was treated by PE and IS but developed CRI and cardiac insufficiency as sequelae. The last patient was diagnosed prospectively and was rapidly treated by PE and IS and had no sequelae.

Supplementary Table 6: Number of aHUS patients reaching ESRD at the first aHUS episode according to the age at onset, the type of complement gene abnormalities and the intensity of the plasma therapy.

Plasma exchange (PE) and/or fresh frozen plasma (FFP) infusions were administered in 61.5% (120/195) of the aHUS patients at the first episode (35/89, 39% in children; 85/106, 80% in adults). Only 146 patients for whom data regarding plasma therapy are available are included in the analysis. High –intensity plasma therapy was administered in 45% (66/146) of the aHUS patients at the first episode (19/74, 25.6% in children; 47/72, 65.2% in adults).

Adults*

	High-intensity treatment	Low-intensity treatment /no plasma	p
CFH (28)	11/21 (52%)	5 /7 (71%)	0.3
C3 (n=7)	2/4 (50%)	1/3 (33%)	1
CFB (n=2)	2/2 (100%)	0/0	-
CFI (n=10)	1/4 (25%)	3/6 (50%)	0.57
MCP (n=5)	1/5 (20%)	0/0	-
No identified mutation (n=20)	5/11 (45%)	4/9 (44%)	1

*Data regarding the intensity of treatment are available for only 72 adult patients.

Children**

	High-intensity treatment	Low-intensity treatment /no plasma	p
CFH (19)	1/6 (16%)	8 /13 (62%)	0.06
C3 (n=7)	1/1 (100%)	1/6 (16%)	0.28
FB (n=2)	0/0	1/2 (50%)	-
CFI (n=6)	1/3 (33%)	1/3 (33%)	1
MCP (n=12)	0/2	0/10	1
No identified mutation (n=28)	4/7 (57%)	4/21 (19%)	0.14

**Data regarding the intensity of treatment are available for only 74 children.

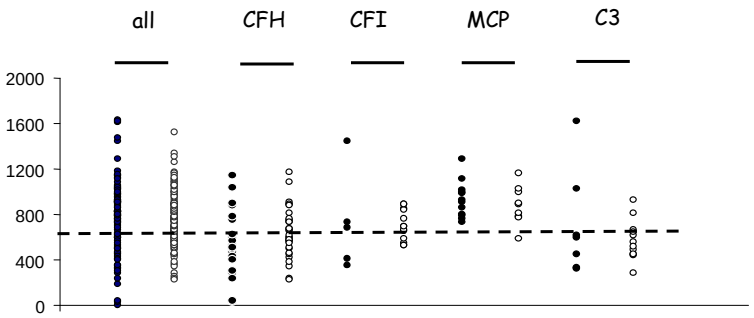
ESRD: end-stage renal disease; aHUS: atypical hemolytic uremic syndrome

Legends of supplementary figures

Supplementary Figure 1:

Distribution of the C3 plasma level in children and adults with atypical hemolytic uremic syndrome according to the mutations. The mean values are indicated

The dotted line shows the lower limit of normal values (-2SD of normal, 660 mg/L)



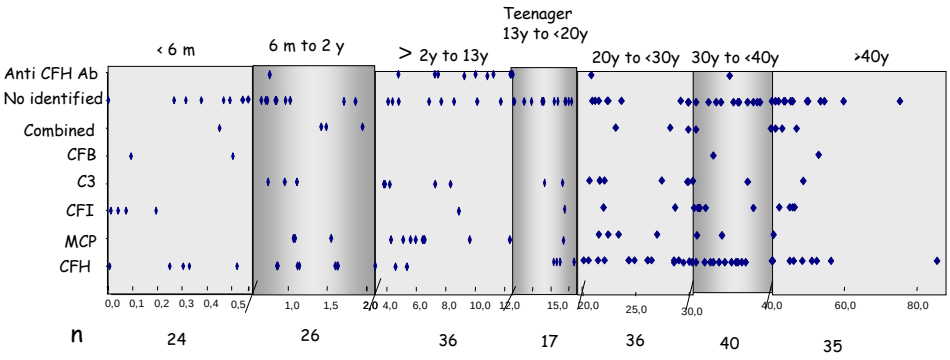
Pediatric onset	+		+		+		+		+	
Adult onset		+		+		+		+		+
Low C3 (%)	31	39	70	52	60	50	0	11	70	85

Supplementary Figure 2

Schematic representation of the age of patients at the onset of atypical hemolytic uremic syndrome.

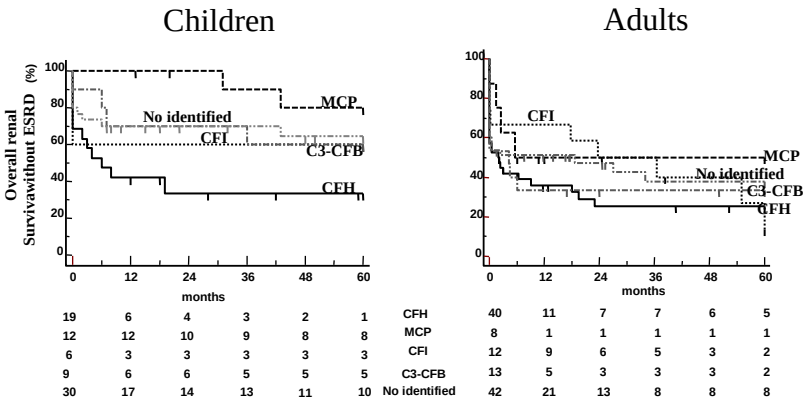
Each point represents one patient. Seven periods of life are indicated. Three patients in adults (2 CFH and one C3 mutations) developed the disease between 16 to 18 years of age.

m: month; y: year



Supplementary Figure 3: Cumulative Kaplan Meier estimates of the rates of survival without ESRD and death according to the genetic background in children and adults

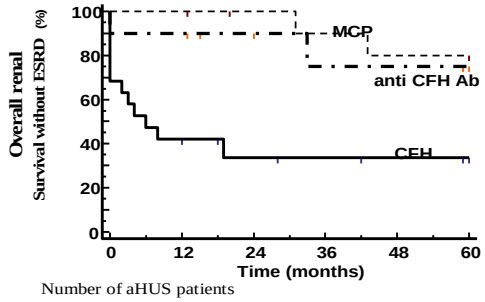
The proportion of patients without ESRD at any time point according to the presence of mutations in CFH (Homozygous and Heterozygous), CFI, C3, MCP, or with no identified mutation are shown. The most relevant comparisons are shown in the table.



		Children		Adults
		p	OR	p
No identified vs	CFH	0.039	0.3 [0.14-0.9]	0.23
	MCP	0.2		0.79
	CFI	0.7		0.69
	C3-CFB	0.9		0.5
MCP vs	CFH	0,002	0.17 [0.05-0.5]	0.3

Supplementary Figure 4: Kaplan Meier survival without ESRD and death estimates for pediatric patients with anti-CFH antibodies or CFH and MCP mutations

We identified 10 children with anti-CFH antibodies (anti–CFH Ab). At disease onset, 1 patient was managed conservatively, 9 received plasma therapy (1 fresh frozen plasma, 8 plasma exchanges, PE) and this was the only treatment for 3 of these patients. The other 6 patients also received immunosuppressive treatments (IS). None was treated by IS only. The Kaplan-Meier estimate of the 5-year survival without ESRD was significantly better in children with anti-CFH Ab or MCP mutations compared to children with CFH mutations. The most relevant comparisons are shown in the table.



Number of aHUS patients						
CFH	19	6	4	3	2	1
MCP	12	12	10	9	8	8
Anti CFH Ab	10	9	6	5	5	4

MCP vs anti CFH Ab (p=0.6);
CFH vs anti CFH Ab (p=0.02; OR : 3.7 [1.2 -11]);
CFH vs MCP (p=0.002; OR : 5.8 [1.8 -18])

Supplementary References

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