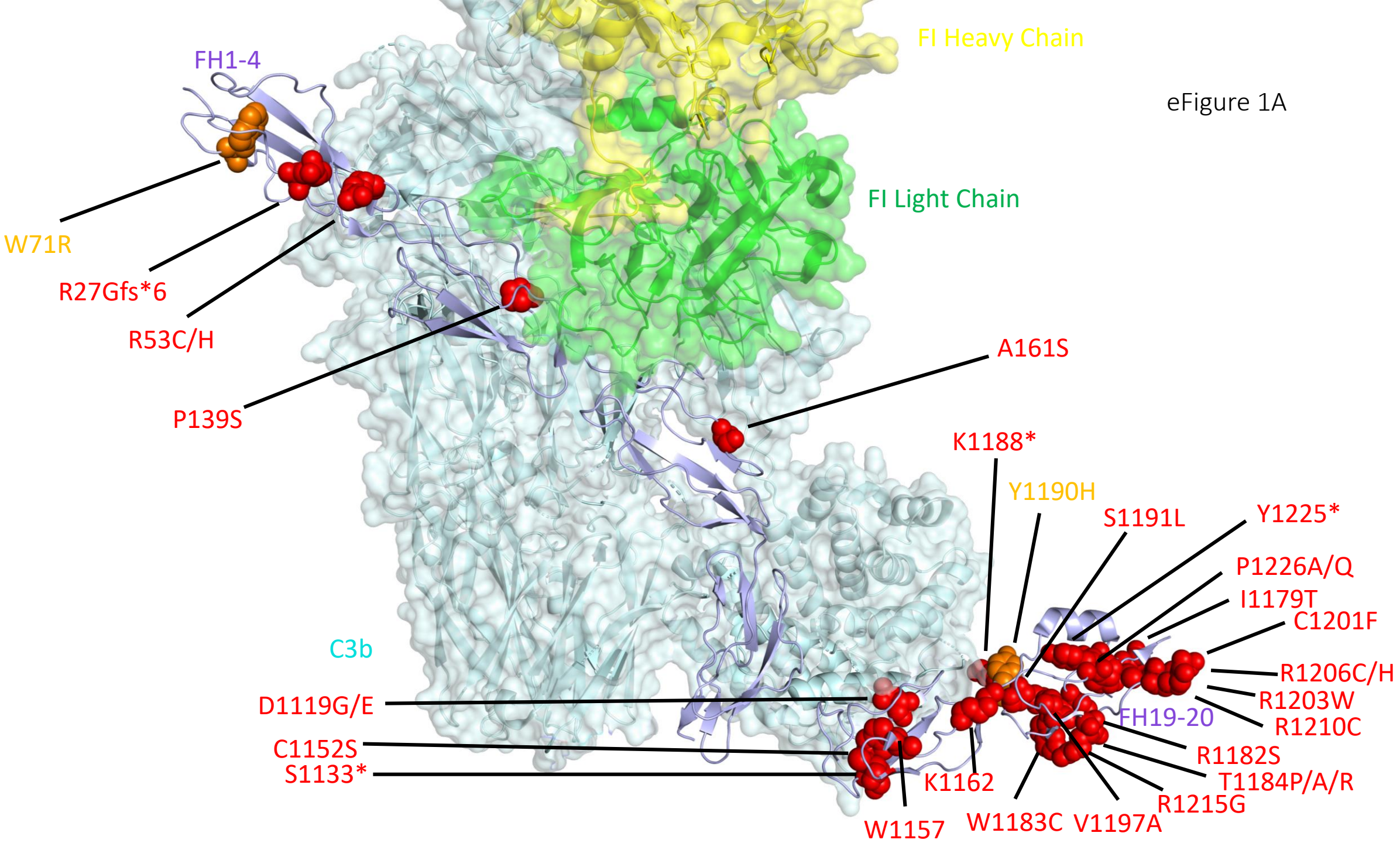
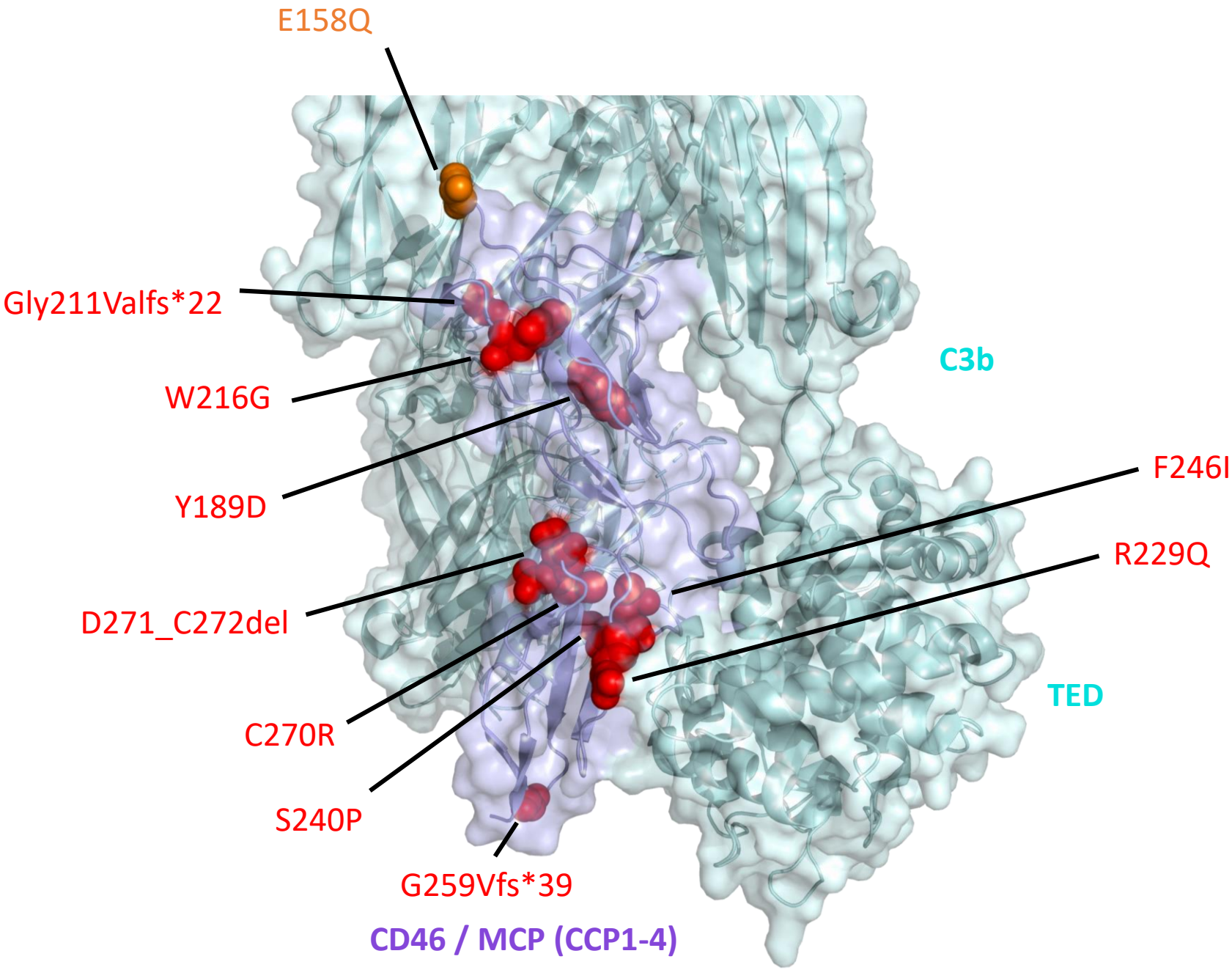
Supplemental Figures

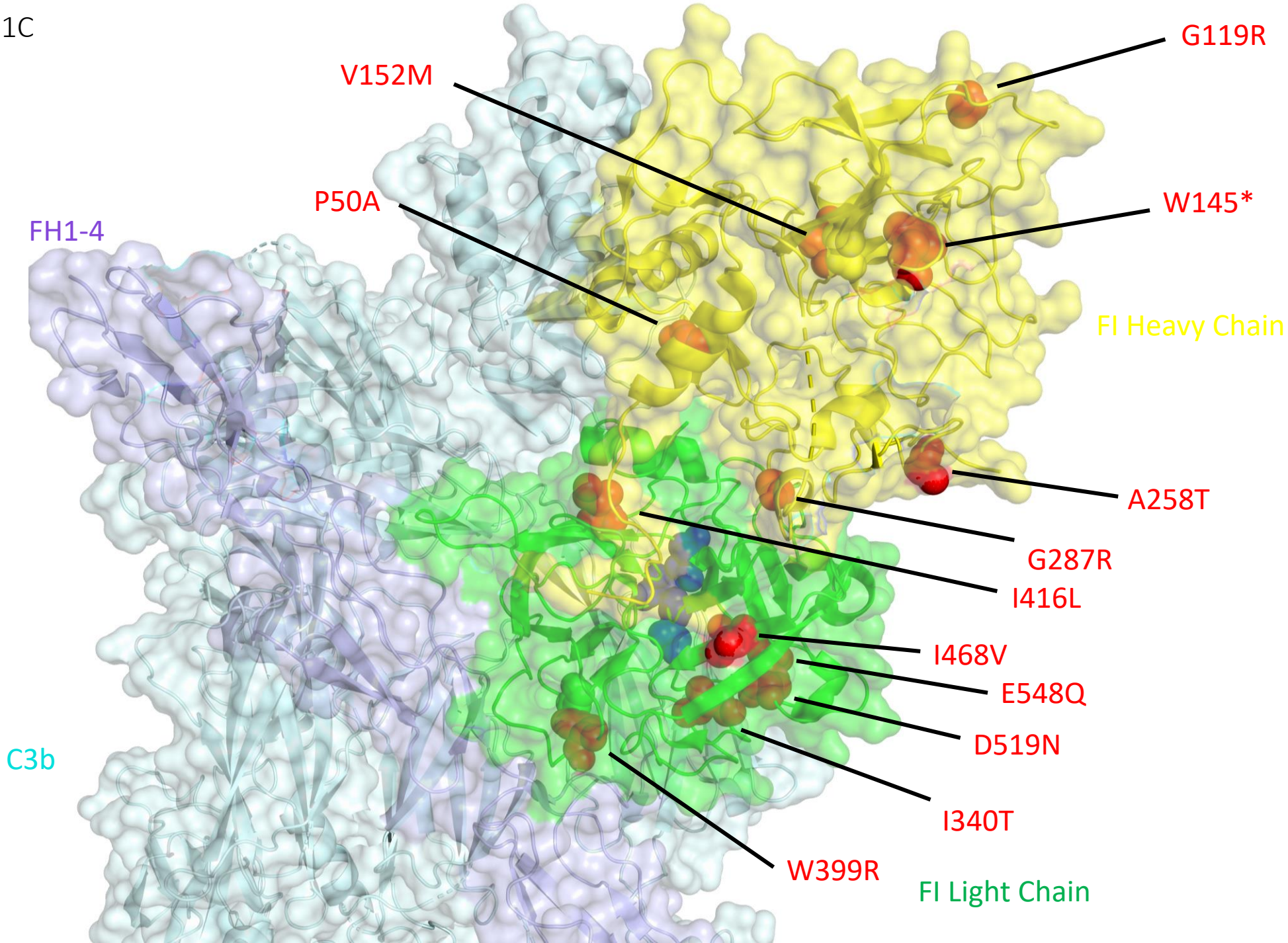

FH1-4
FI Heavy Chain
FI Light Chain
W71R
R27Gfs*6
R53C/H
P139S
A161S
K1188*
Y1190H
S1191L
Y1225*
P1226A/Q
I1179T
C1201F
C3b
R1206C/H
R1203W
R1210C
D1119G/E
FH19-20
C1152S
S1133*
R1182S
T1184P/A/R
K1162
R1215G
W1157
W1183C
V1197A

eFigure 1A

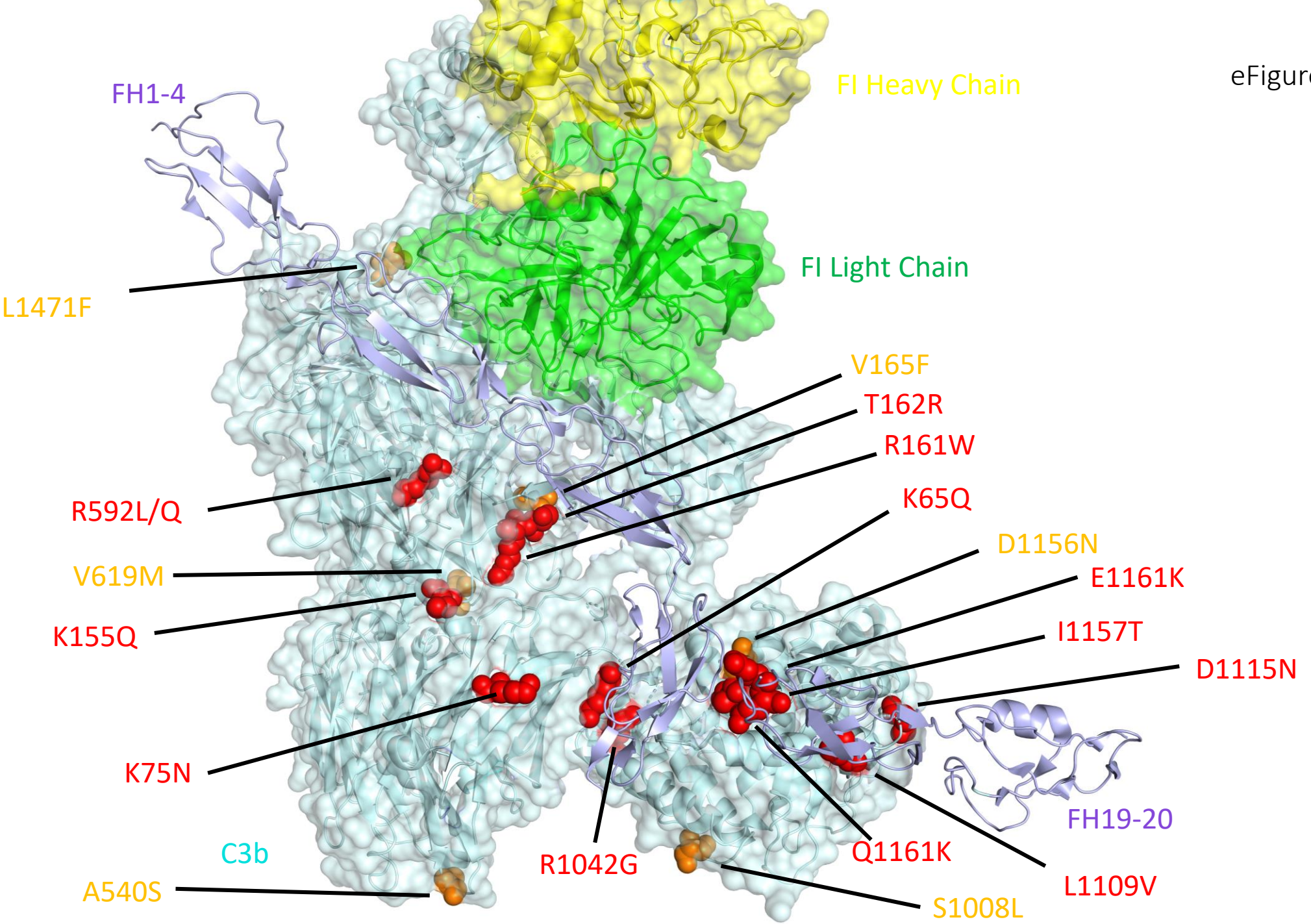
eFigure 1B


E158Q
Gly211Valfs*22
W216G
Y189D
D271_C272del
C270R
S240P
G259Vfs*39
C3b
F246I
R229Q
TED
CD46 / MCP (CCP1-4)

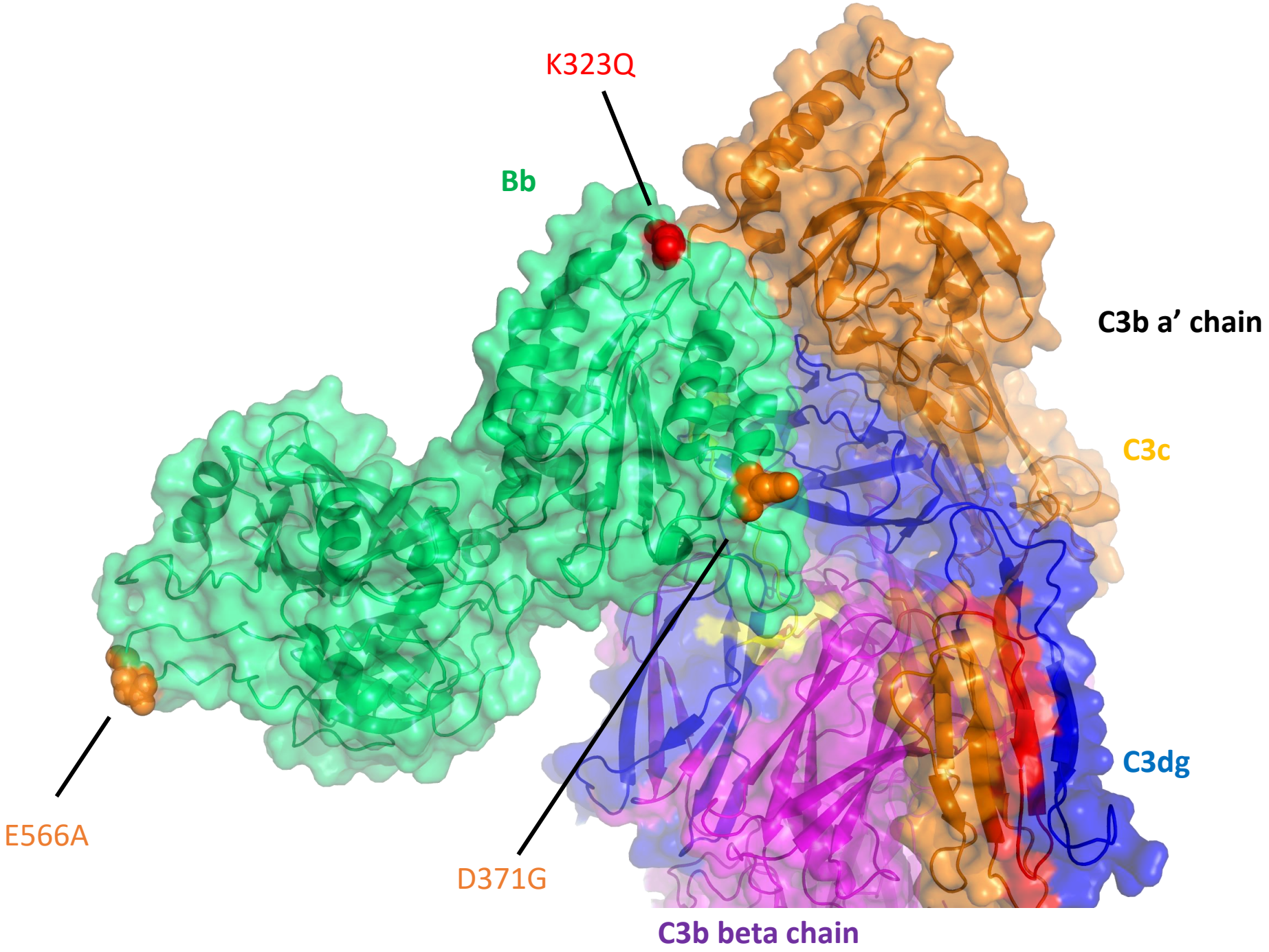
eFigure 1C


G119R
V152M
P50A
W145*
FH1-4
FI Heavy Chain
A258T
G287R
I416L
I468V
E548Q
D519N
C3b
I340T
W399R
FI Light Chain

eFigure 1D

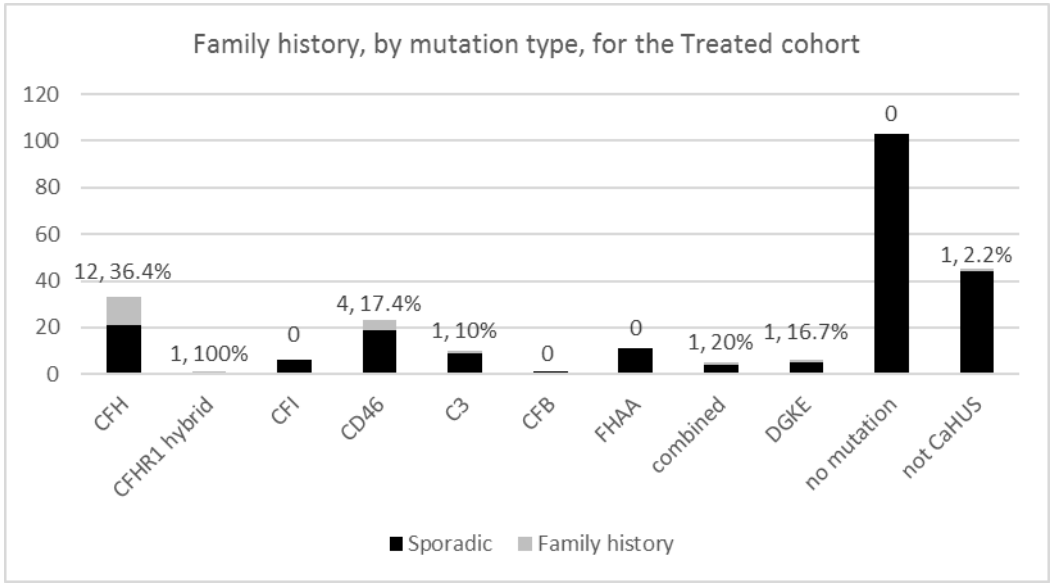

FH1-4
FI Heavy Chain
FI Light Chain
L1471F
V165F
T162R
R161W
R592L/Q
K65Q
D1156N
V619M
E1161K
K155Q
I1157T
D1115N
K75N
FH19-20
C3b
R1042G
Q1161K
L1109V
A540S
S1008L

eFigure 1E



eFigure 2

A



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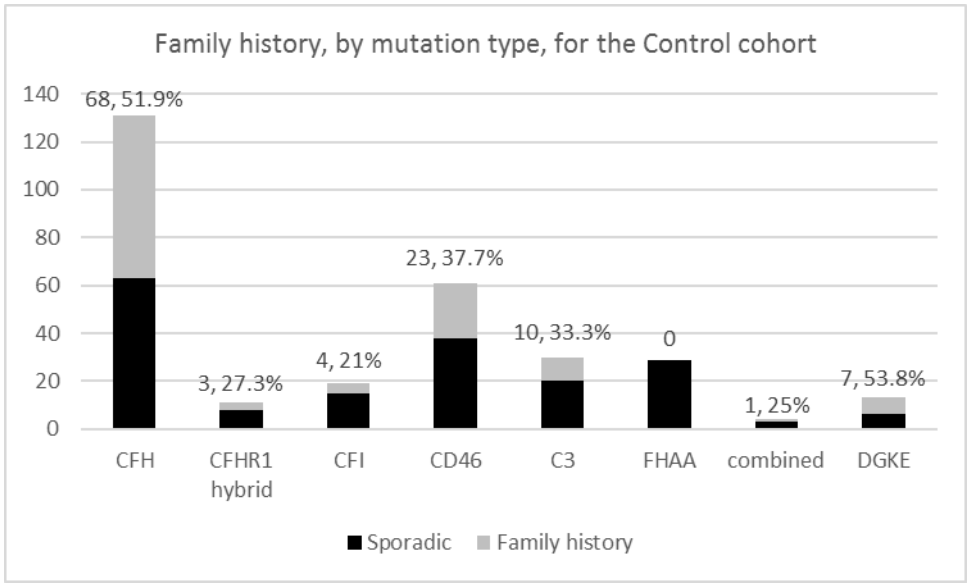

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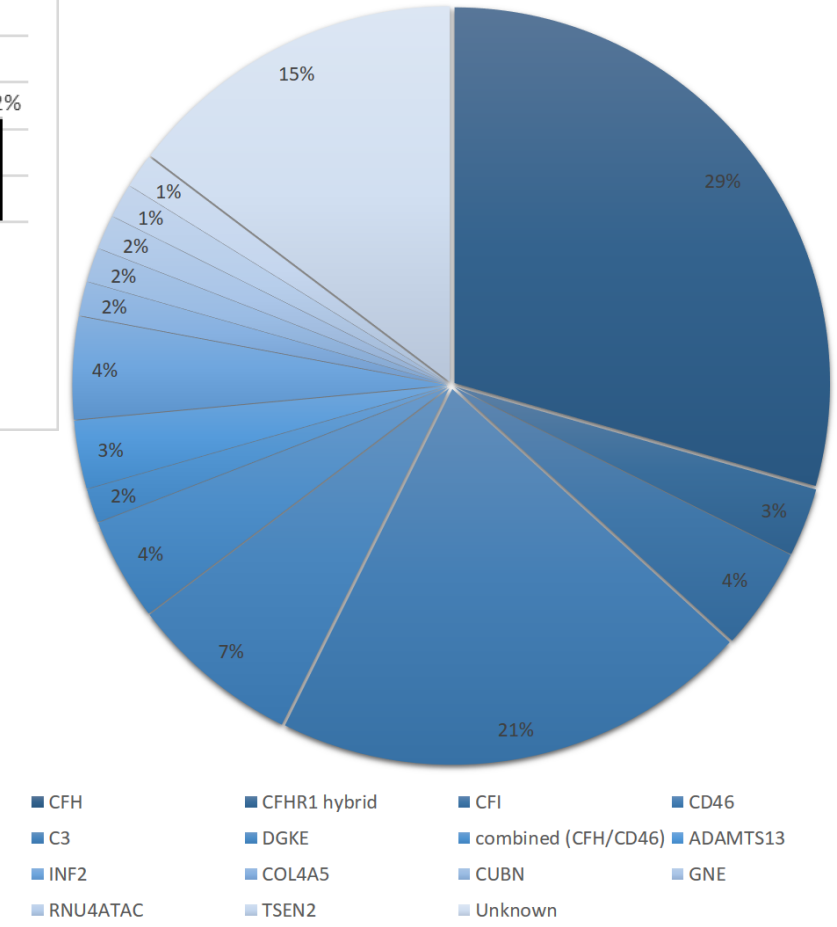
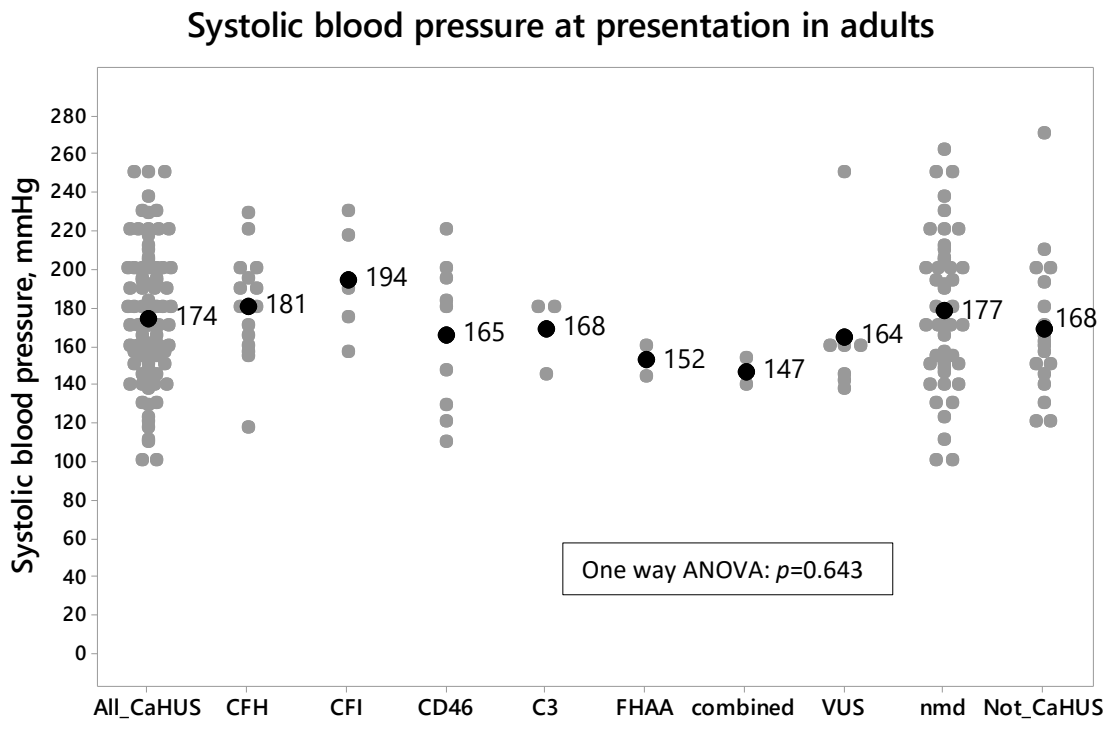


Complement Mediated aHUS	
CFH including *CFH* hybrids	29.9%
CD46	20.9%
C3	7.5%
CFI	4.5%
CFHR1 hybrid	3%
Combined *CD46/CFH*	1.5%
Other	
DGKE	4.5%
ADAMTS13	3%
TSEN2	1.5%
INF2	4.5%
COL4A5	1.5%
CUBN	1.5%
GNE	1.5%
NRU4ATAC	1.5%
No gene identified	15%

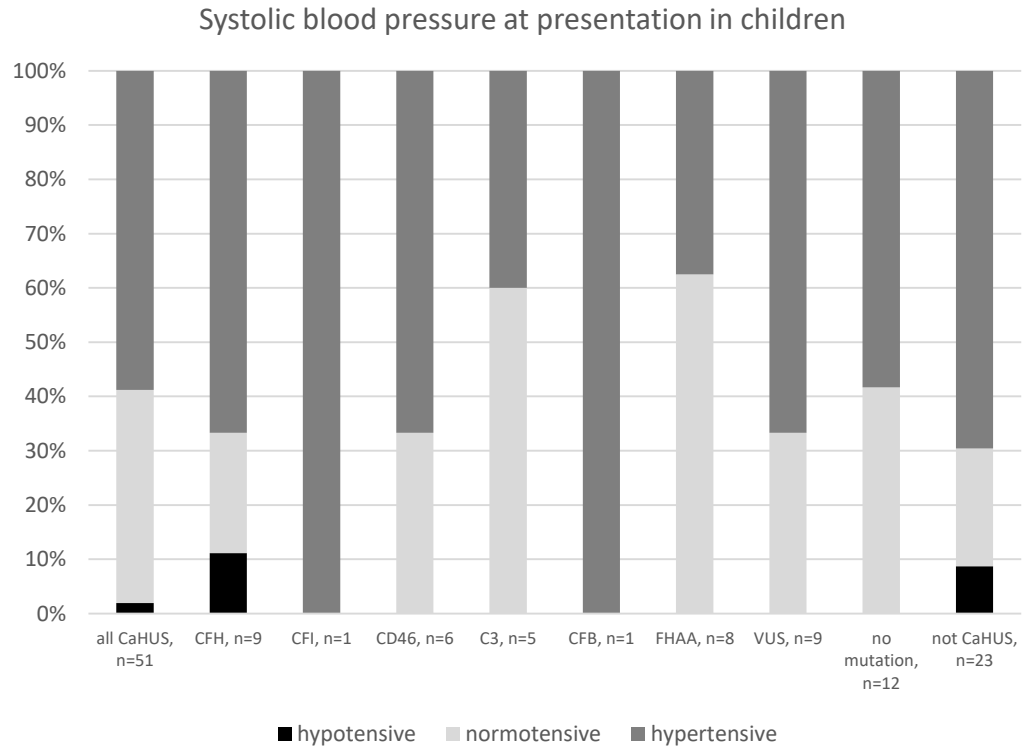
eFigure 3: Clinical characteristics at presentation

A. Blood pressure

i. Adults

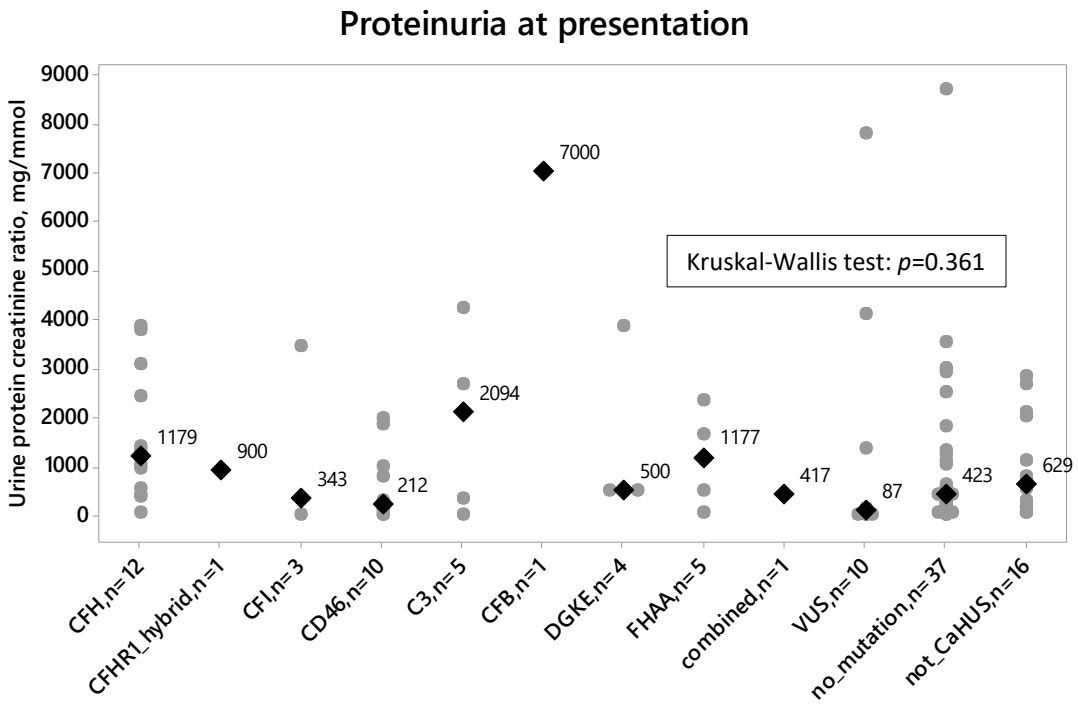


ii. Children

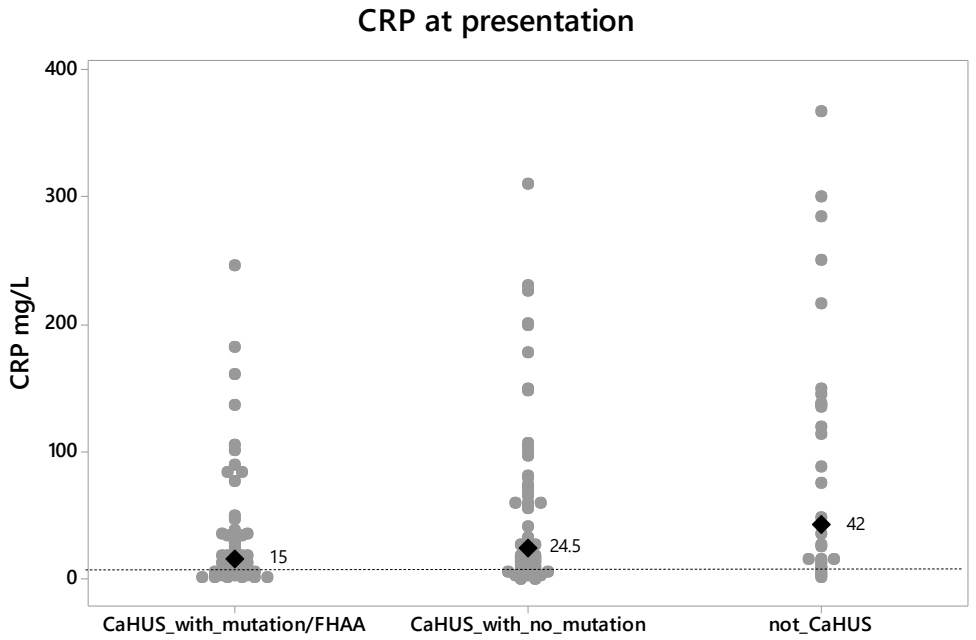


eFigure 3: Clinical characteristics at presentation

B. Proteinuria



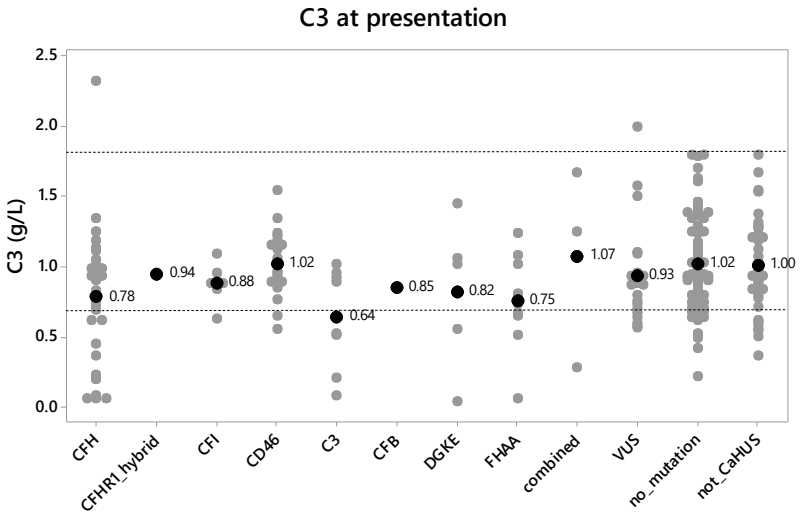
C. CRP



Kruskal-Wallis test:
CaHUS with mutation/FHAA-CaHUS with no mutation: p=0.1
CaHUS with mutation/FHAA-not CaHUS: p=0.009
CaHUS with no mutation-not CaHUS: p=0.643

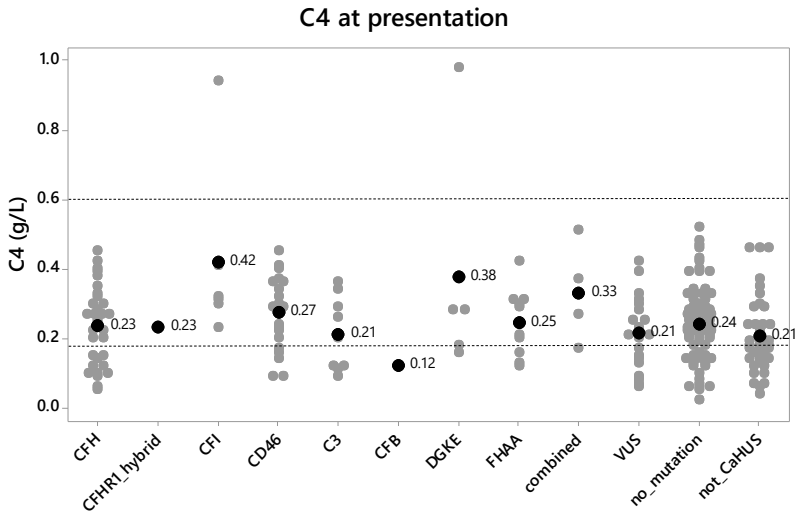
eFigure 3: Clinical characteristics at presentation
D. Complement profile

i.



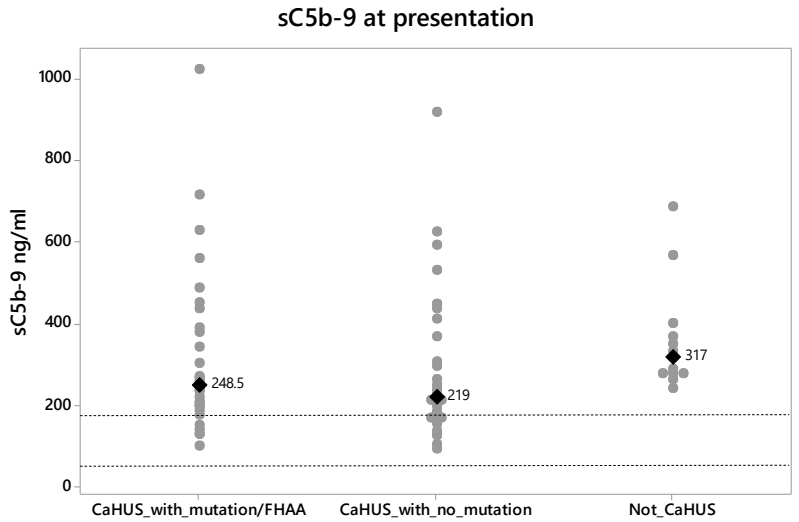
Applying the Gabriel multiple comparisons post hoc analysis to the one way ANOVA showed a statistically significant difference only between the C3 and no mutation groups, *p*=0.028

ii.



Applying the Gabriel multiple comparisons post hoc analysis to the one way ANOVA showed a statistically significant difference only between the CFI and no mutation groups, *p*=0.001

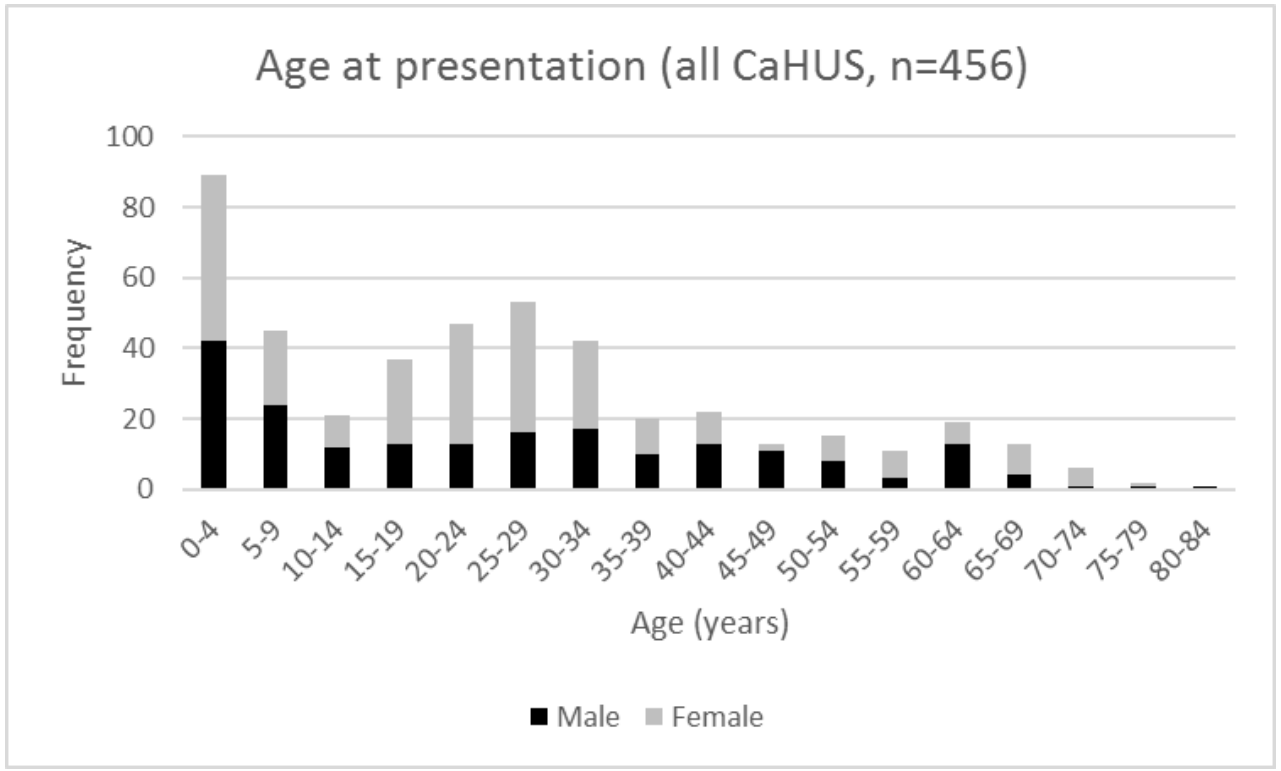
iii.



Kruskal-Wallis test:
CaHUS with mutation/FHAA-CaHUS with no mutation: *p*=1.0
CaHUS with mutation/FHAA-not CaHUS: *p*=0.152
CaHUS with no mutation-not CaHUS: *p*=0.041

eFigure 4

A



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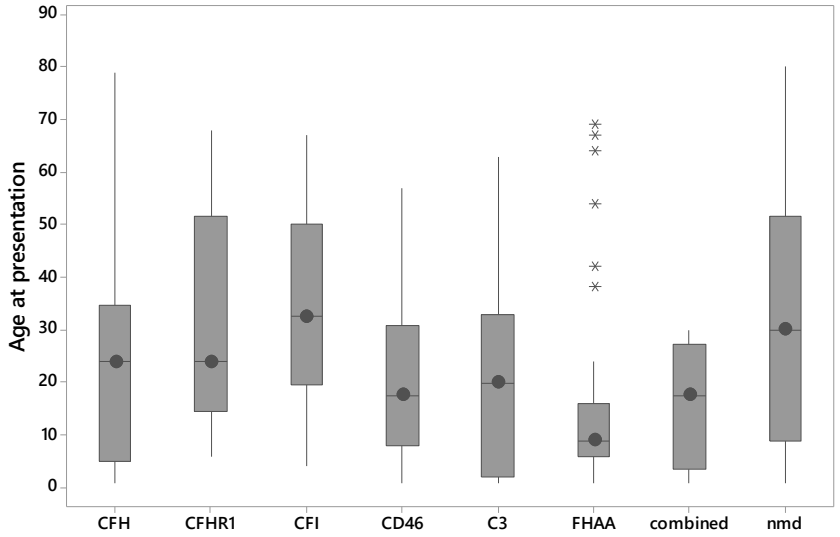
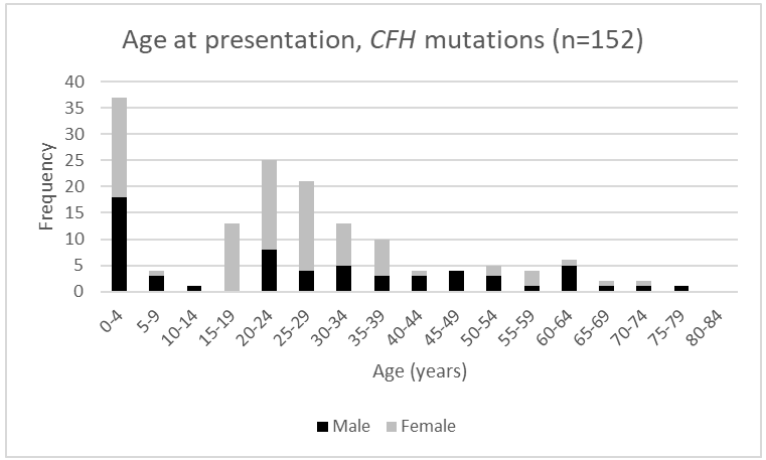


After applying the Bonferroni multiple comparisons there is a difference in age at presentation between the FHAA group and the no mutation group (p=0.001) and between the FHAA group and the *CFI* group (p=0.008) at the table-wide 0.05 level.

eFigure 4

C



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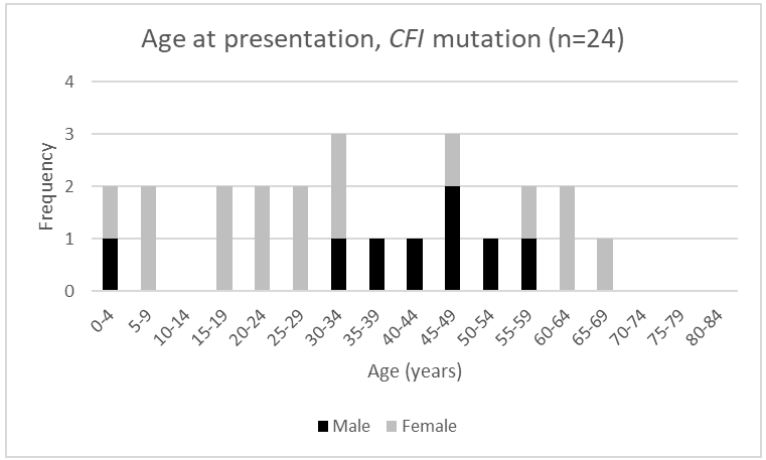

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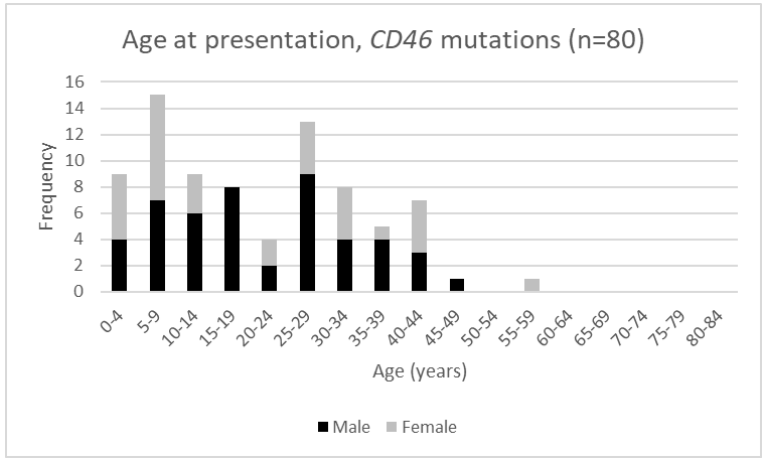

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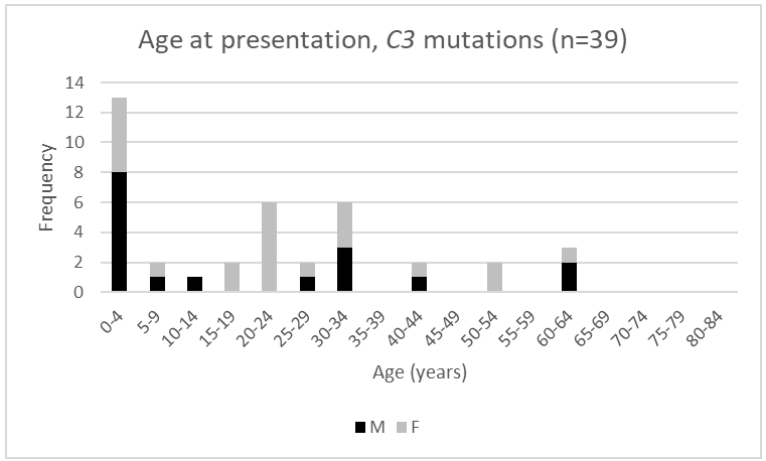

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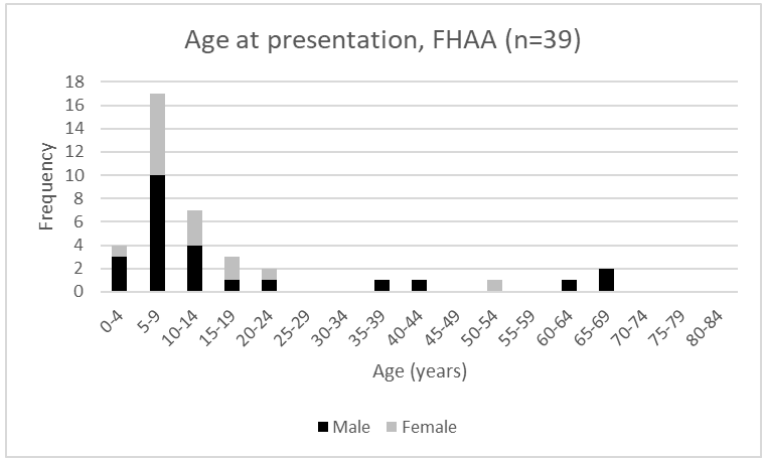

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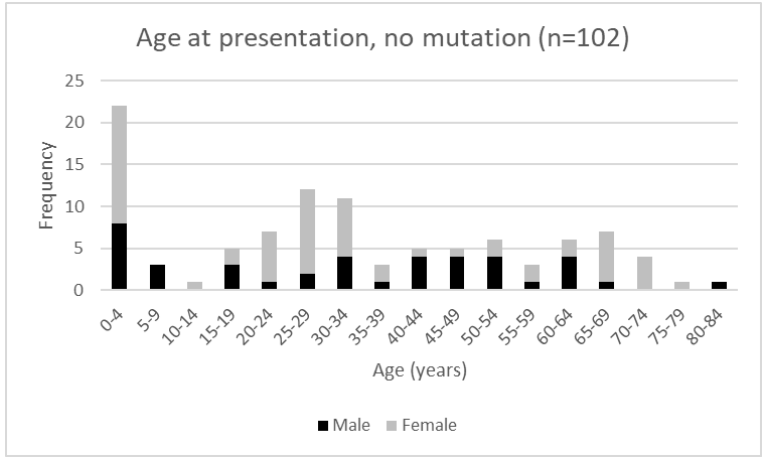

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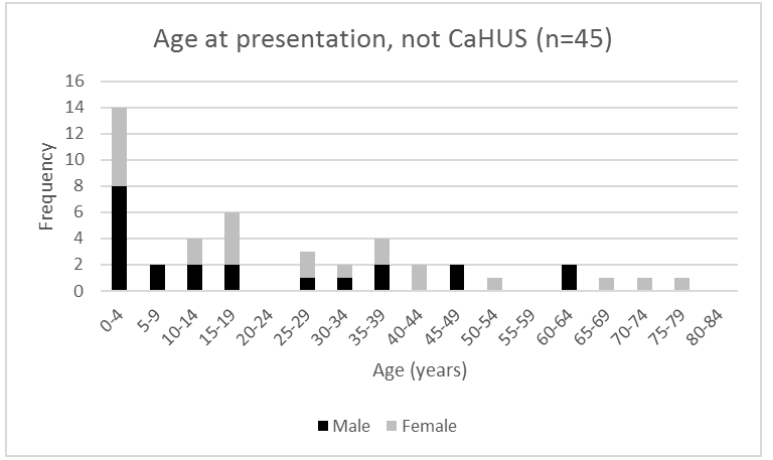
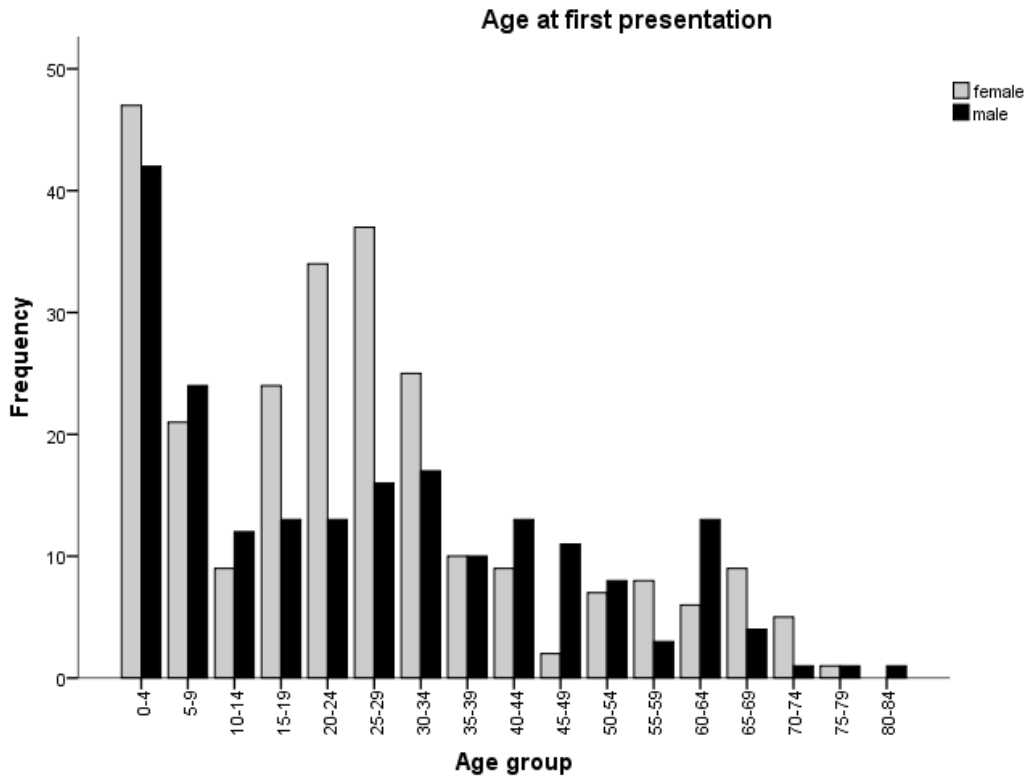


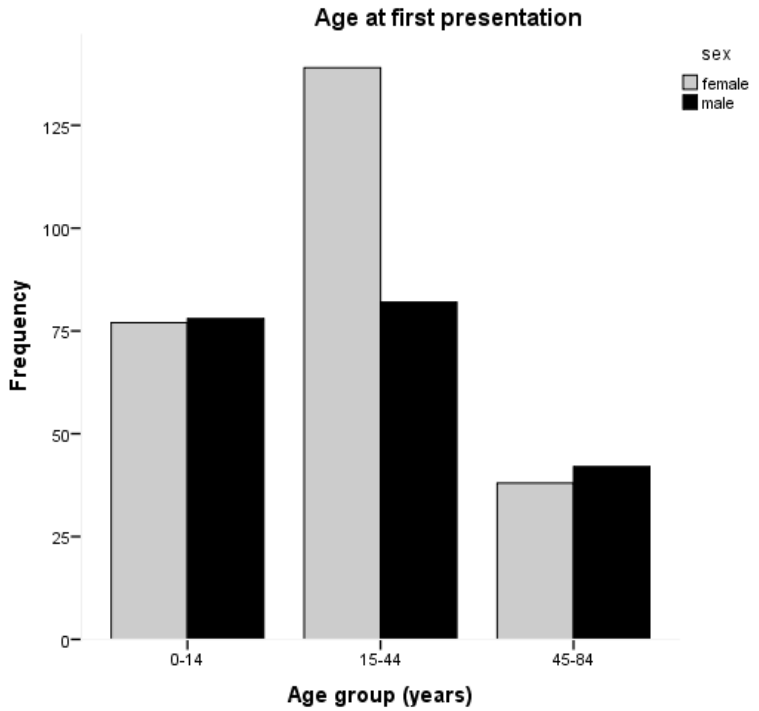
eFigure 4

J



Pearson Chi-Square p=0.003

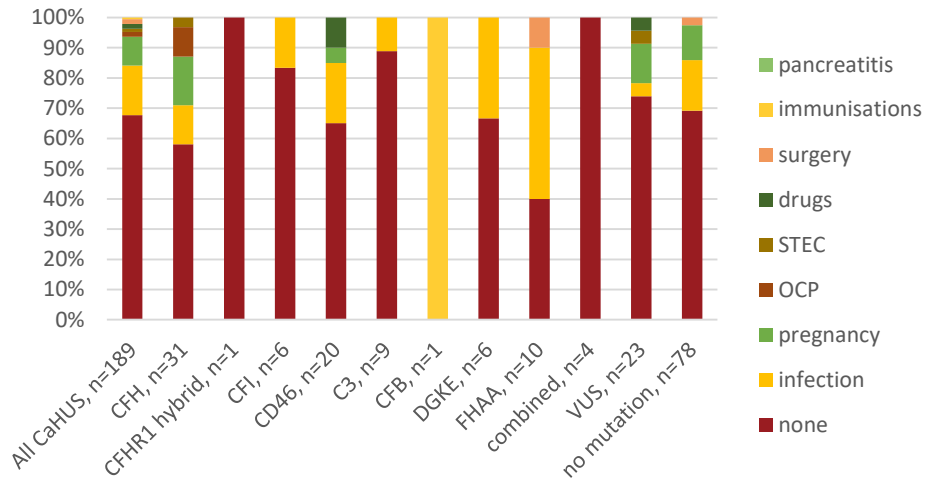
K



Pearson Chi-Square p=0.011

eFigure 5

A



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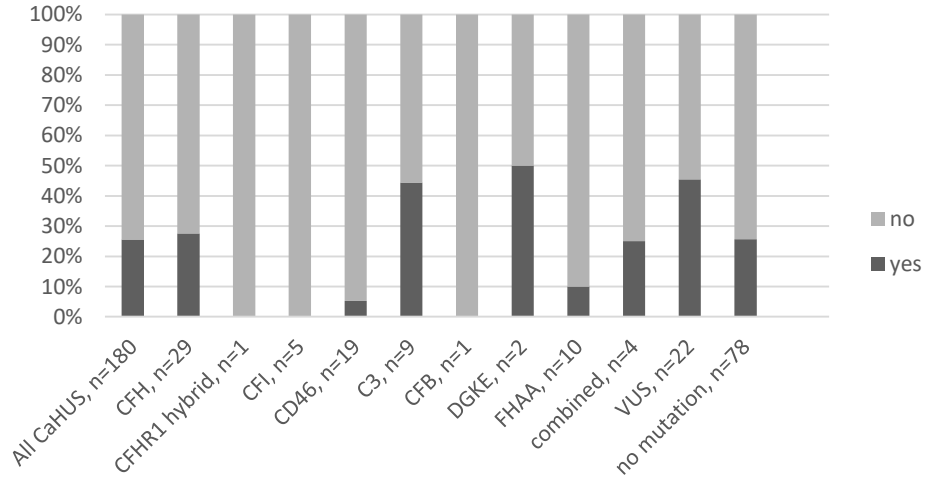

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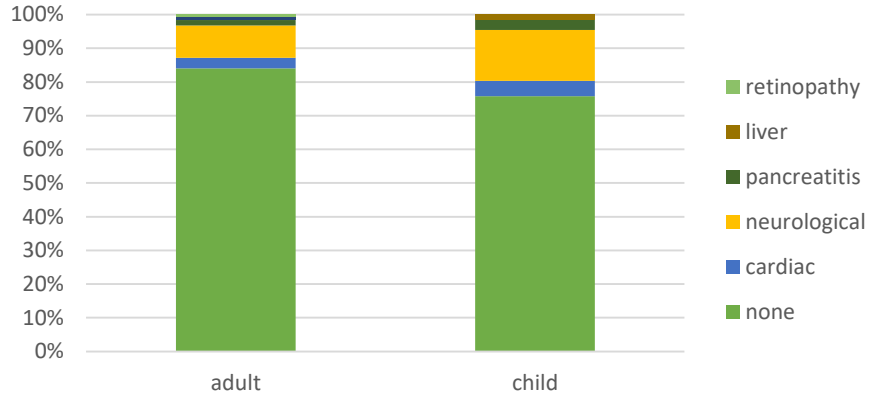

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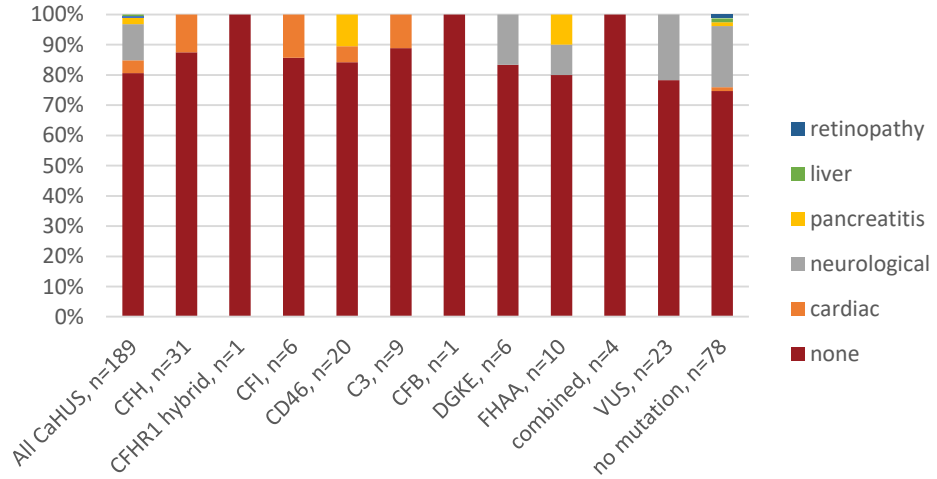
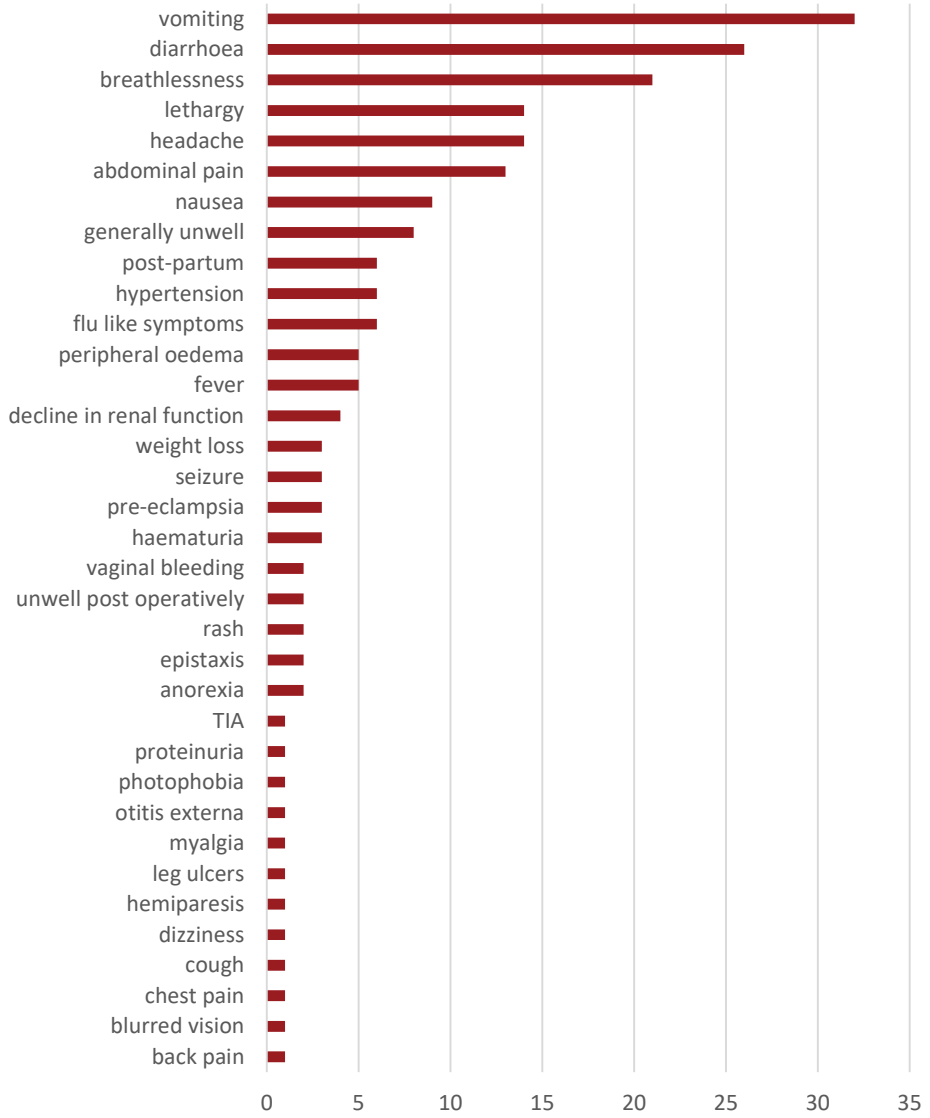
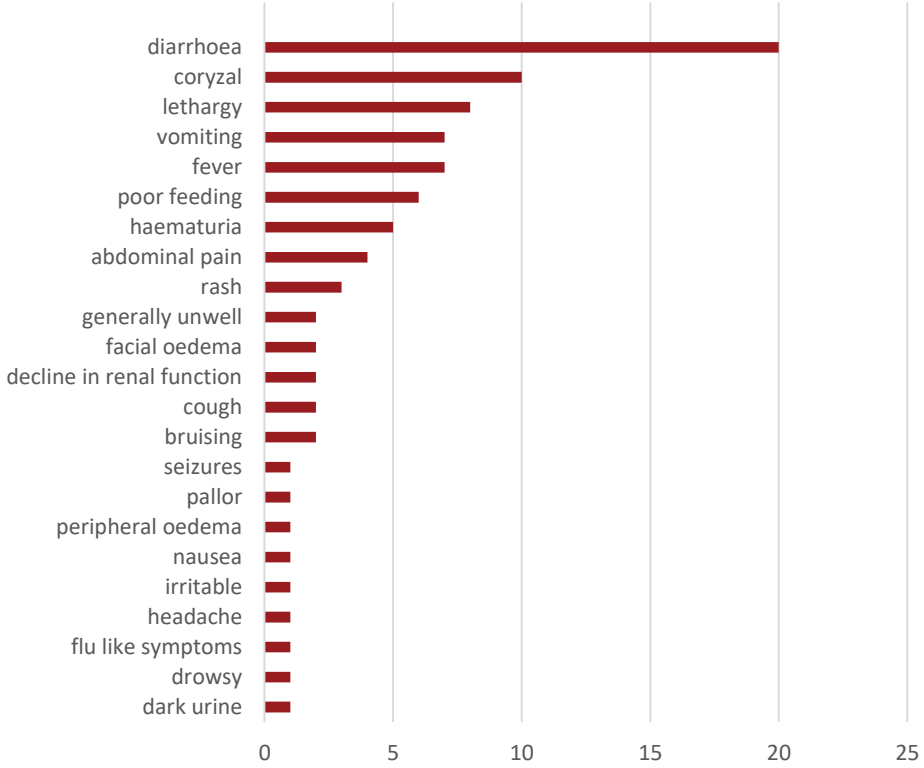


eFigure 5

E

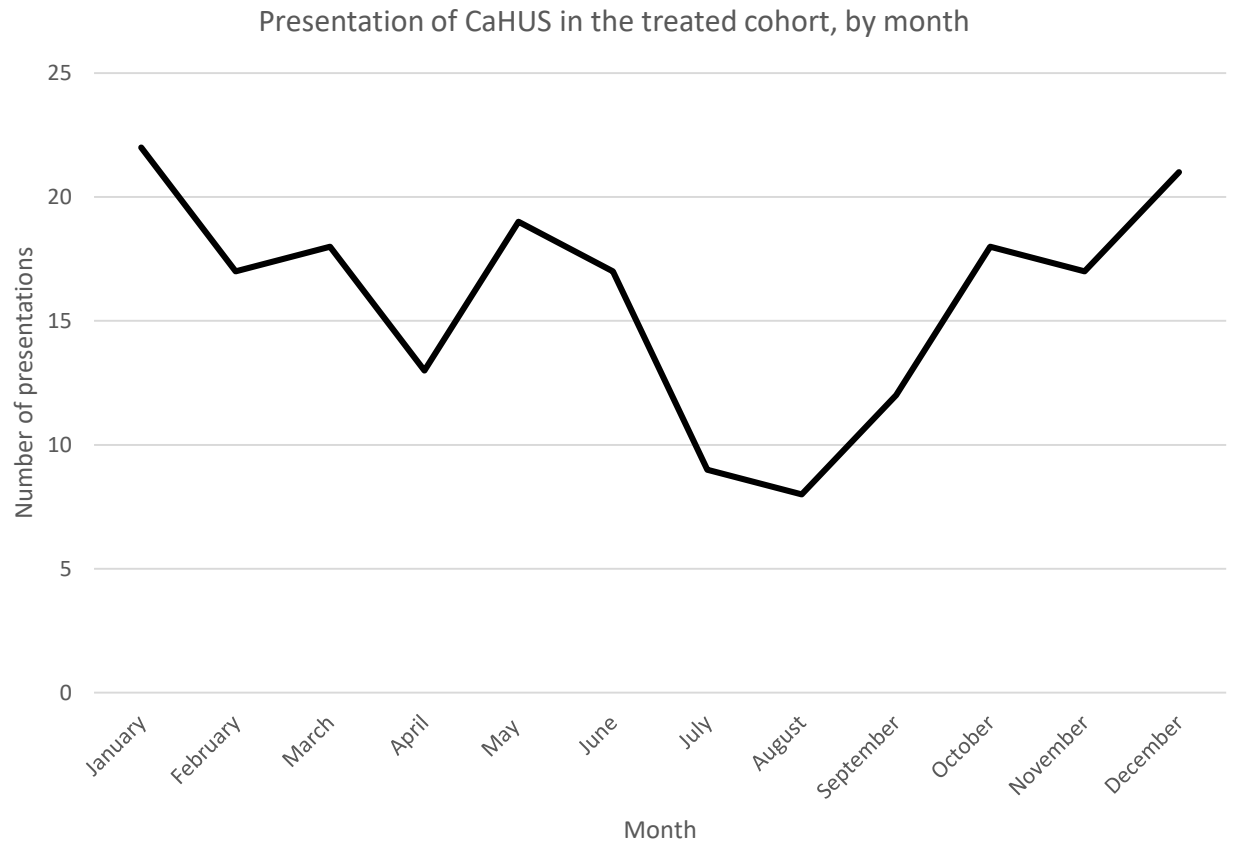

Prodromal symptoms or circumstances in adults
vomiting
diarrhoea
breathlessness
lethargy
headache
abdominal pain
nausea
generally unwell
post-partum
hypertension
flu like symptoms
peripheral oedema
fever
decline in renal function
weight loss
seizure
pre-eclampsia
haematuria
vaginal bleeding
unwell post operatively
rash
epistaxis
anorexia
TIA
proteinuria
photophobia
otitis externa
myalgia
leg ulcers
hemiparesis
dizziness
cough
chest pain
blurred vision
back pain
0
5
10
15
20
25
30
35

F


Prodromal symptoms or circumstances in children
diarrhoea
coryzal
lethargy
vomiting
fever
poor feeding
haematuria
abdominal pain
rash
generally unwell
facial oedema
decline in renal function
cough
bruising
seizures
pallor
peripheral oedema
nausea
irritable
headache
flu like symptoms
drowsy
dark urine
0
5
10
15
20
25

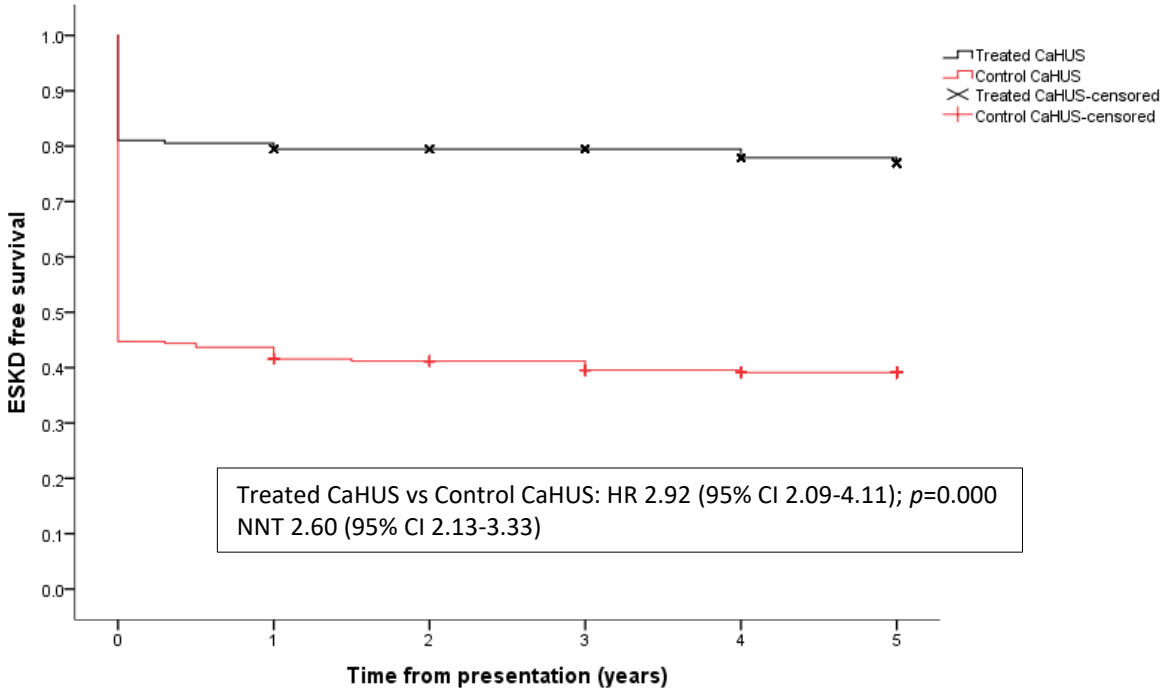
eFigure 5

G


Presentation of CaHUS in the treated cohort, by month
Number of presentations
25
20
15
10
5
0
January
February
March
April
May
June
July
August
September
October
November
December
Month

eFigure 6

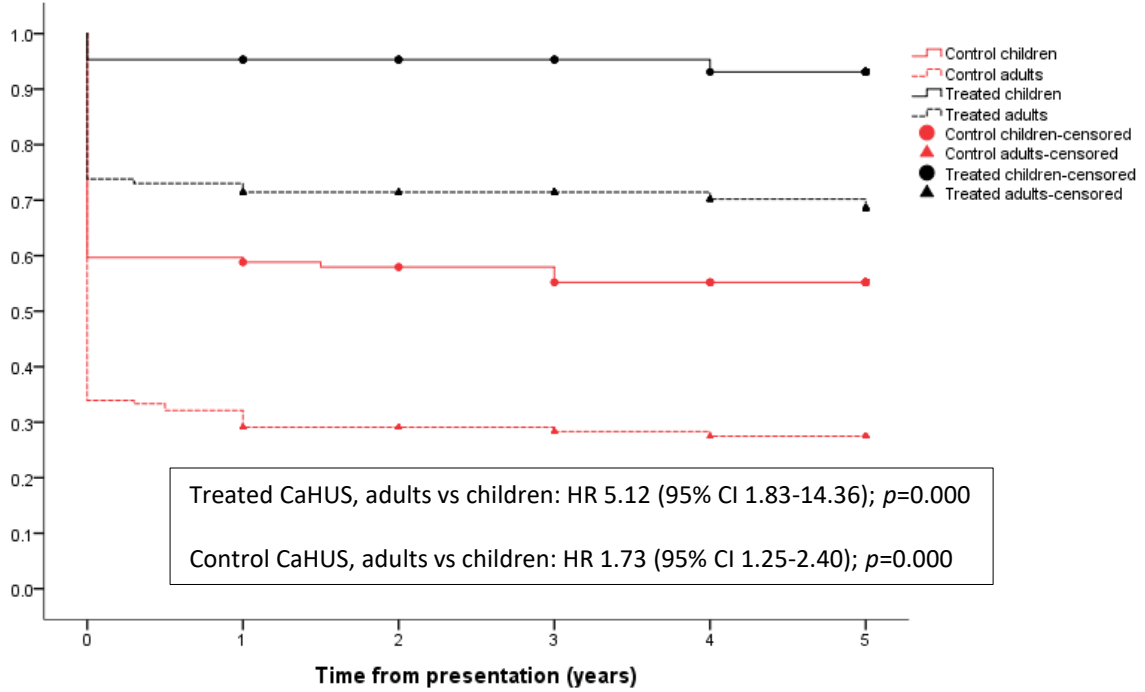
A. Treated group vs Control CaHUS



Treated CaHUS vs Control CaHUS: HR 2.92 (95% CI 2.09-4.11); *p*=0.000
NNT 2.60 (95% CI 2.13-3.33)

Number at risk						
Treated	190	153	137	123	101	83
Control	284	124	109	101	90	79

B. Treated group vs Control CaHUS Children vs Adults



Treated CaHUS, adults vs children: HR 5.12 (95% CI 1.83-14.36); *p*=0.000

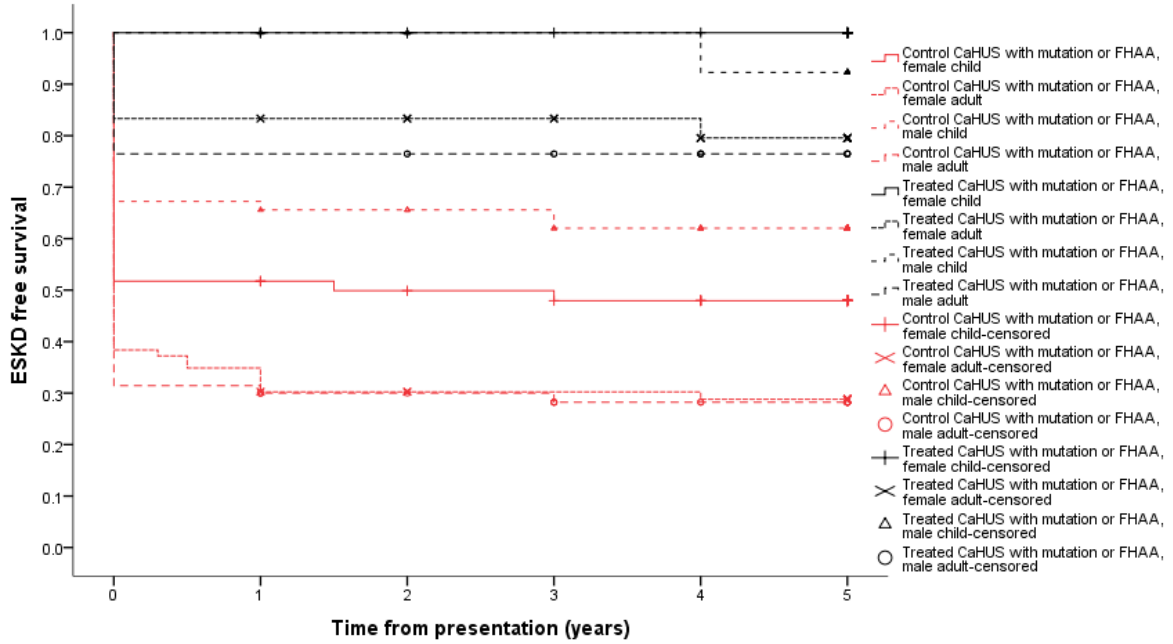
Control CaHUS, adults vs children: HR 1.73 (95% CI 1.25-2.40); *p*=0.000

Number at risk						
Treated children	64	61	55	49	43	40
Treated adults	126	92	82	74	58	43
Control children	119	71	66	63	57	49
Control adults	165	53	43	38	33	30

When comparing the control CaHUS cohort with the treated CaHUS cohort (including those without a mutation or FHAA) five-year cumulative estimate (Kaplan-Meier) of ESKD free survival was 39.5% vs 78%; HR 2.92 (95% CI 2.09-4.11), *p*=0.000, NNT 2.60 (95% CI 2.13-3.33) (eFigure 6A) ESKD free survival was worse in individuals presenting for the first time as adults than those presenting in childhood; in those with CaHUS with our without mutations or autoantibody for adults vs children in the control group HR was 1.73 (95% CI 1.25-2.40), *p*=0.000 and 5.12 (95% CI 1.83-14.36), *p*=0.013 in the treated group.

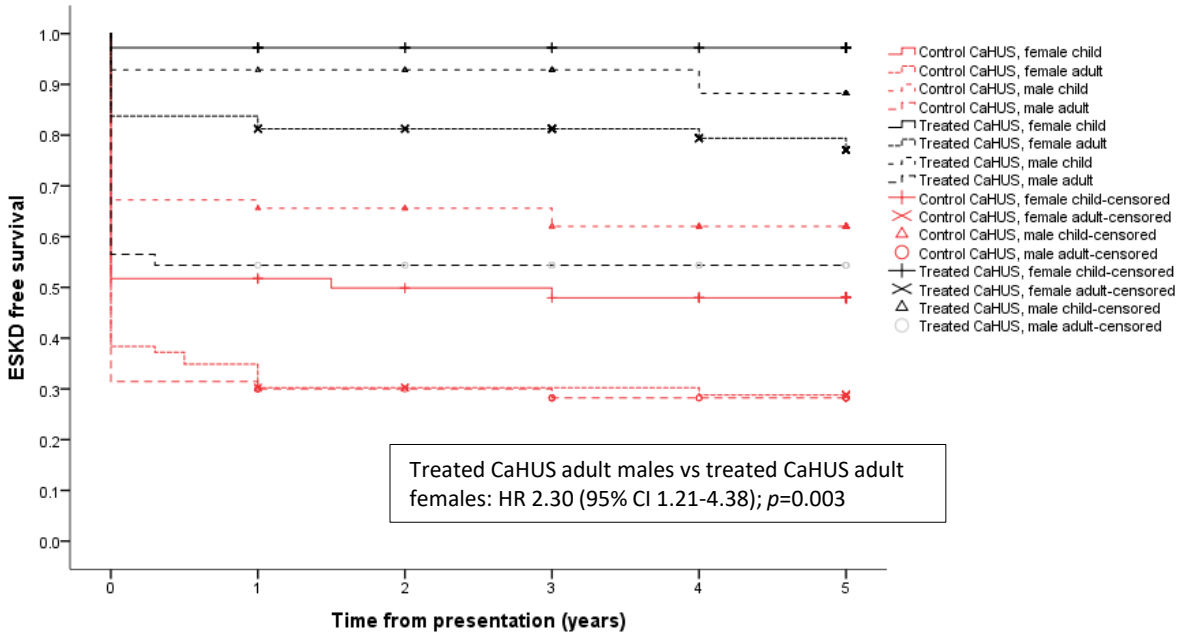
eFigure 6

C. Treated CaHUS with mutation or FHAA vs control CaHUS, by sex and age group



Number at risk						
Treated female child	20	20	17	14	13	12
Treated female adult	36	30	28	25	22	17
Treated male child	16	16	15	13	13	12
Treated male adult	17	13	13	11	9	5
Control female child	58	30	27	26	24	20
Control female adult	86	30	24	21	21	20
Control male child	61	41	39	37	33	29
Control male adult	70	22	18	17	12	10

D. Treated CaHUS vs Control CaHUS, by sex and age group

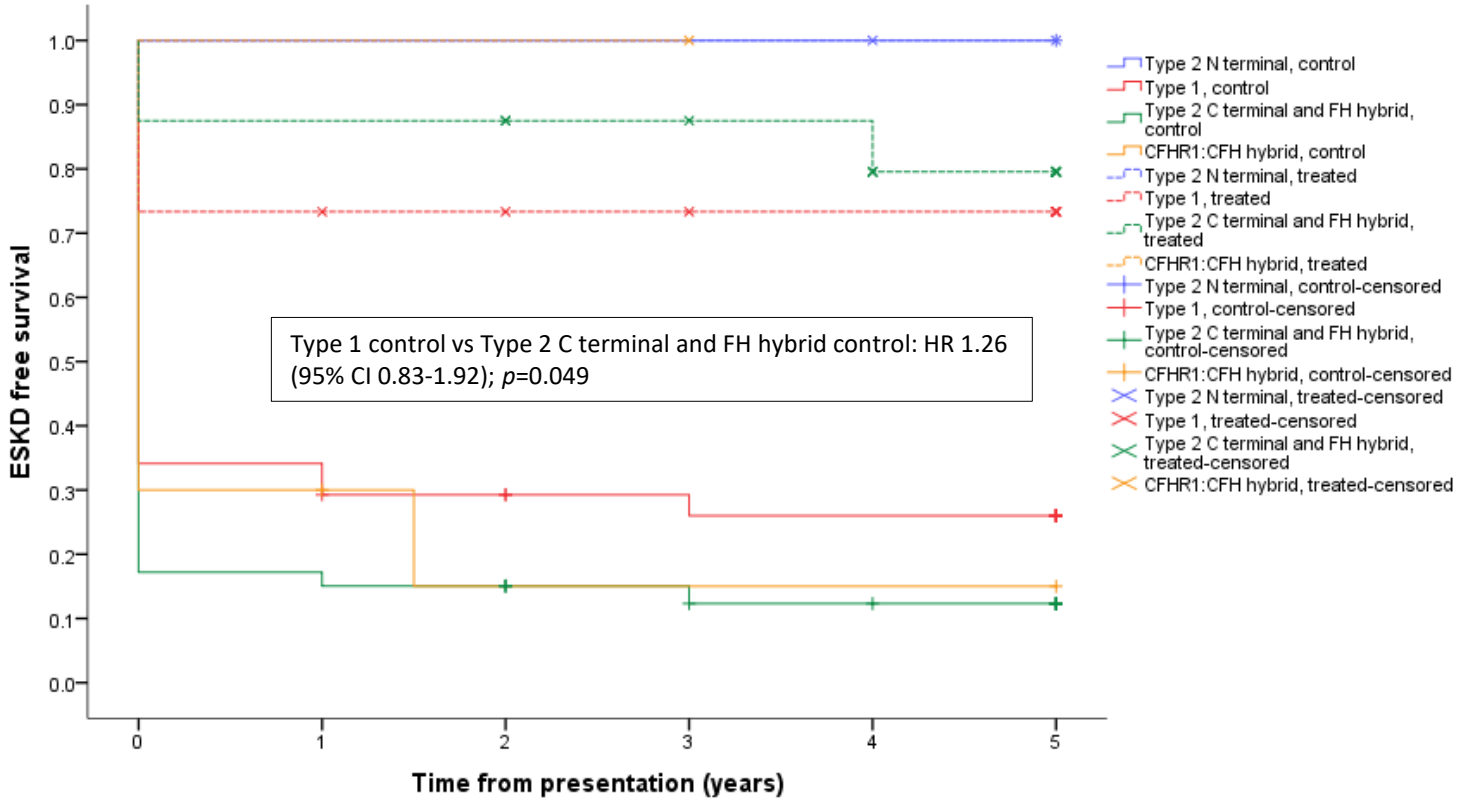


Number at risk						
Treated female child	36	35	30	26	23	21
Treated female adult	80	67	59	54	44	34
Treated male child	28	26	25	23	20	19
Treated male adult	46	25	23	20	14	9
Control female child	58	30	27	26	24	20
Control female adult	86	30	24	21	21	20
Control male child	61	41	39	37	33	29
Control male adult	70	22	18	17	12	10

The five-year cumulative estimate (Kaplan-Meier) of ESKD free survival also varied depending on sex and age, though the only significant difference was seen when the entire CaHUS cohort was analysed: treated adult males had a worse prognosis than treated adult females; HR 2.30 (95% CI 1.21-4.38); *p*=0.003

eFigure 6E

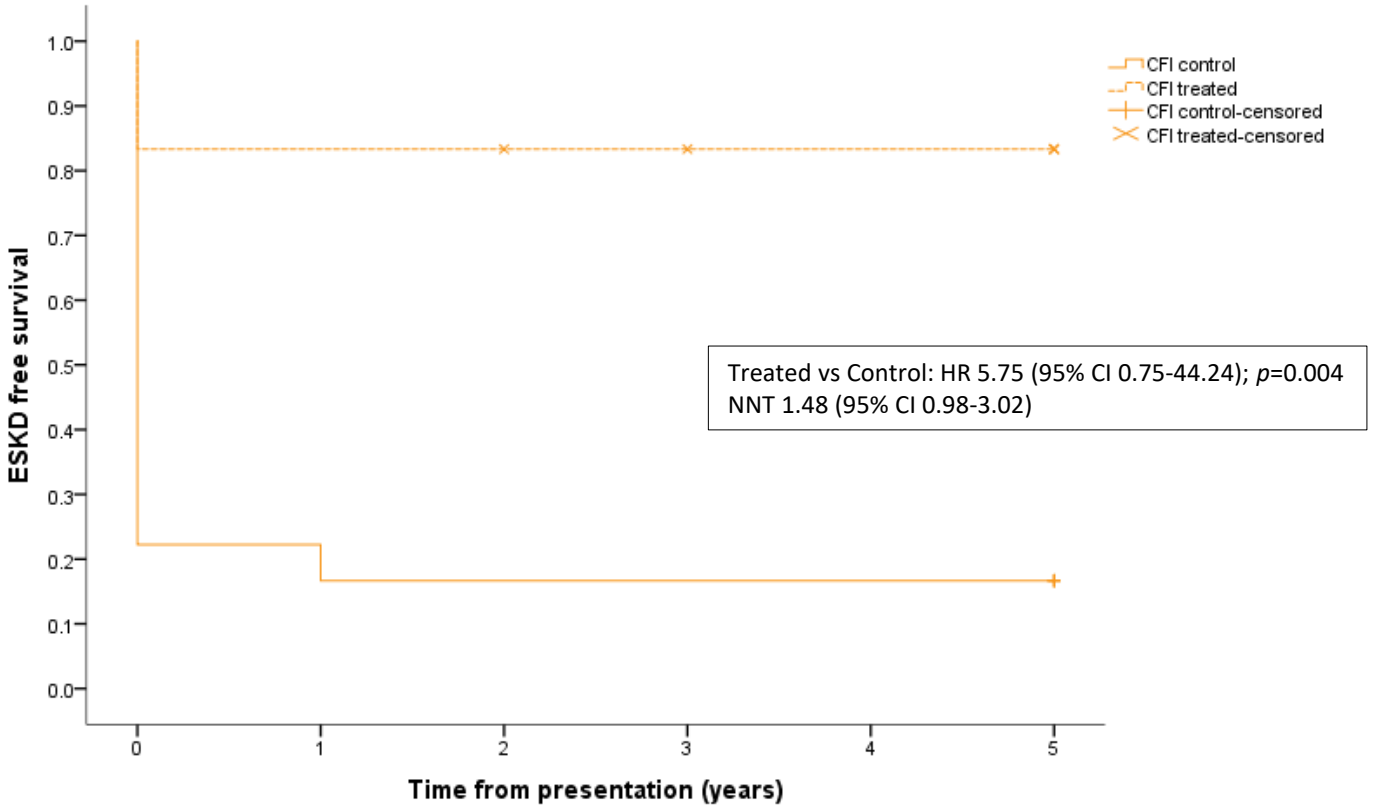
ESKD free survival: *CFH* mutations, by type, treated vs control



Number at risk						
Type 2 N terminal, control	1	1	1	1	1	1
Type 1, control	41	14	11	9	9	8
Type 2 C terminal and FH hybrid, control	93	16	14	11	8	7
CFHR1:CFH hybrid, control	10	3	1	1	1	1
Type 2 N terminal, treated	1	1	1	1	1	1
Type 1, treated	15	11	10	9	8	8
Type 2 C terminal and FH hybrid, treated	11	10	10	8	8	5
CFHR1:CFH hybrid, treated	1	1	1	1	0	0

eFigure 6F

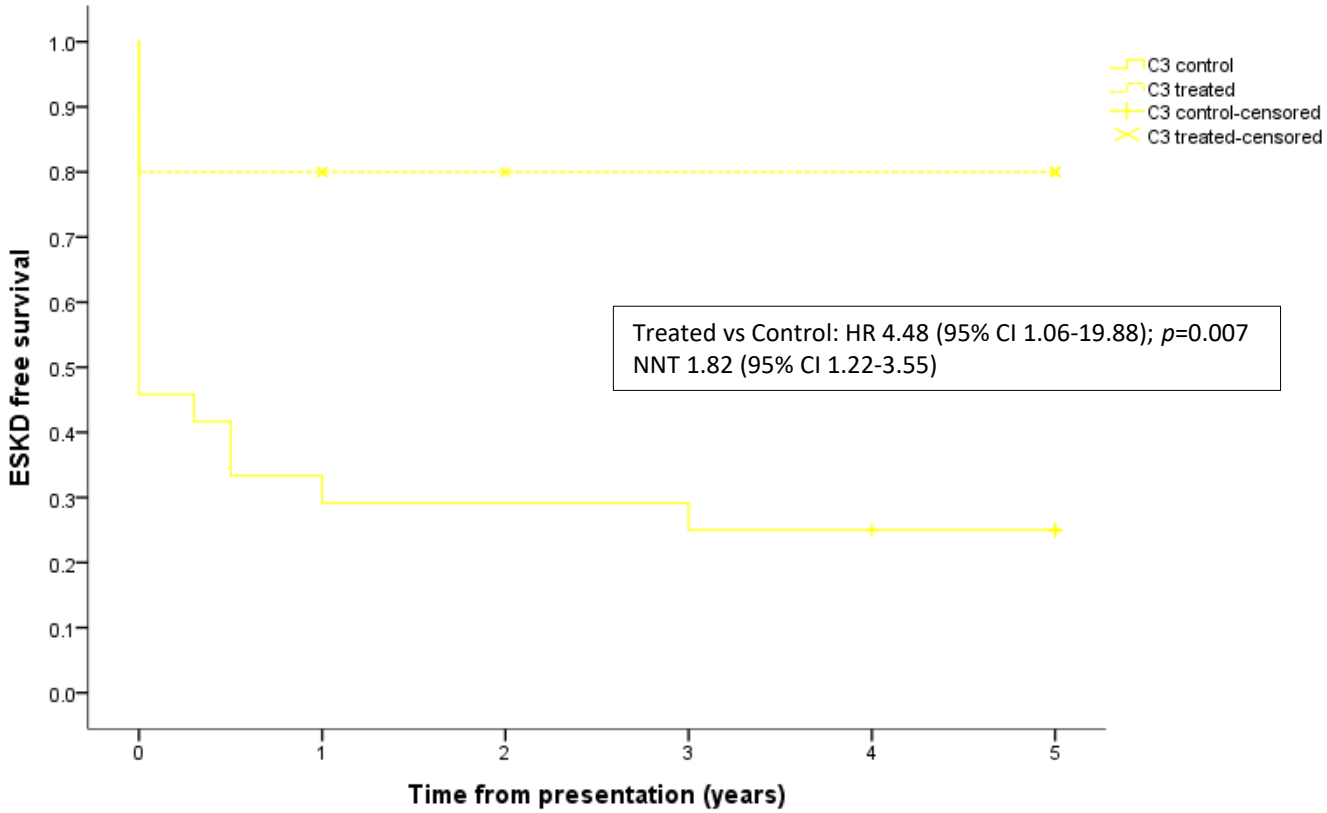
ESKD free survival: *CFI,* treated vs control



Number at risk						
Treated	6	5	5	4	3	3
Control	18	4	3	3	3	3

eFigure 6G

ESKD free survival: *C3,* treated vs control

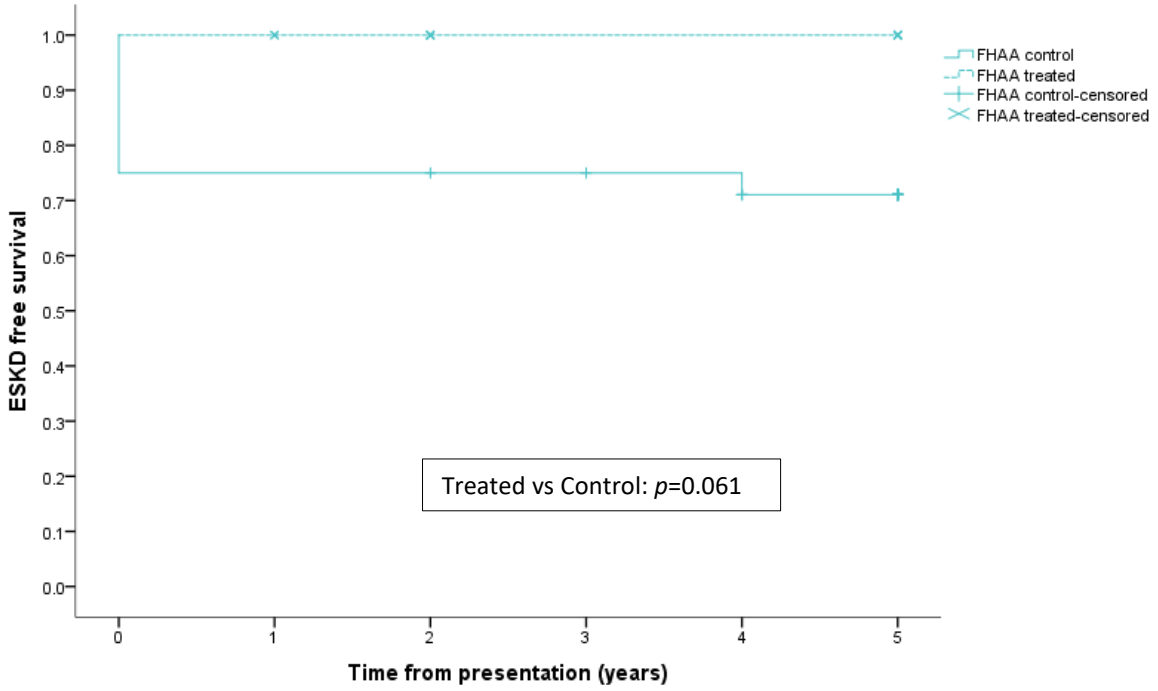


Number at risk						
Treated	10	8	6	5	5	5
Control	24	8	7	7	6	5

eFigure 6

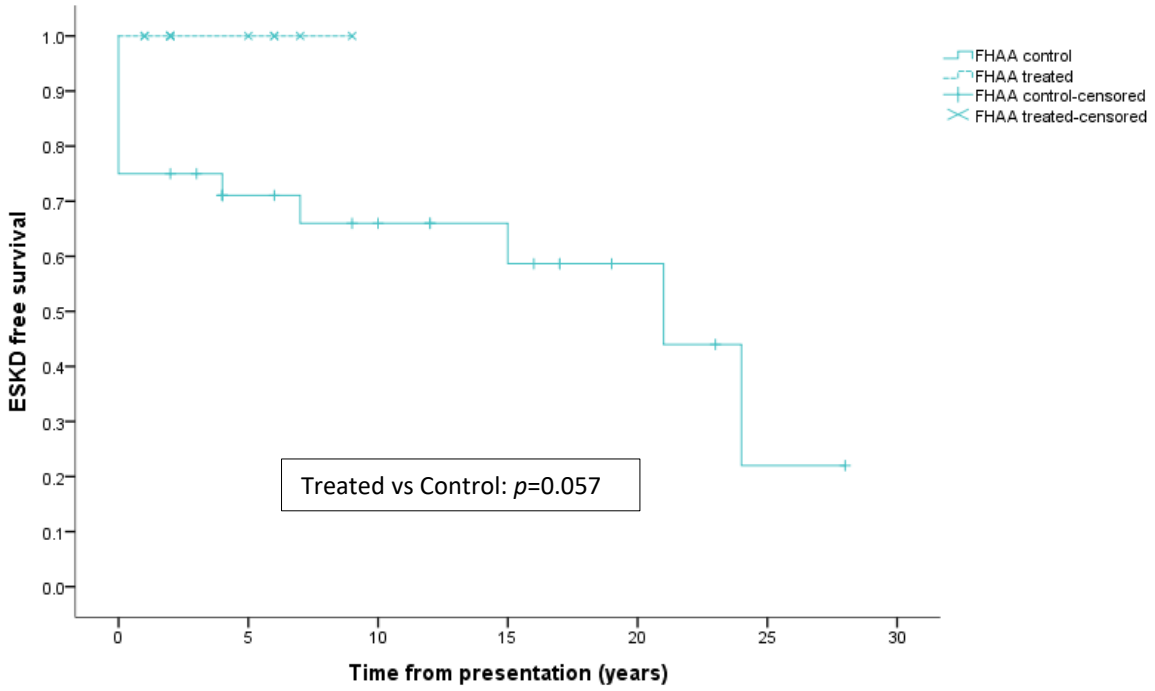
ESKD free survival: FHAA, treated vs control

H. 5-year



Number at risk						
Treated	10	10	8	4	4	4
Control	28	21	21	20	19	15

I. Uncensored

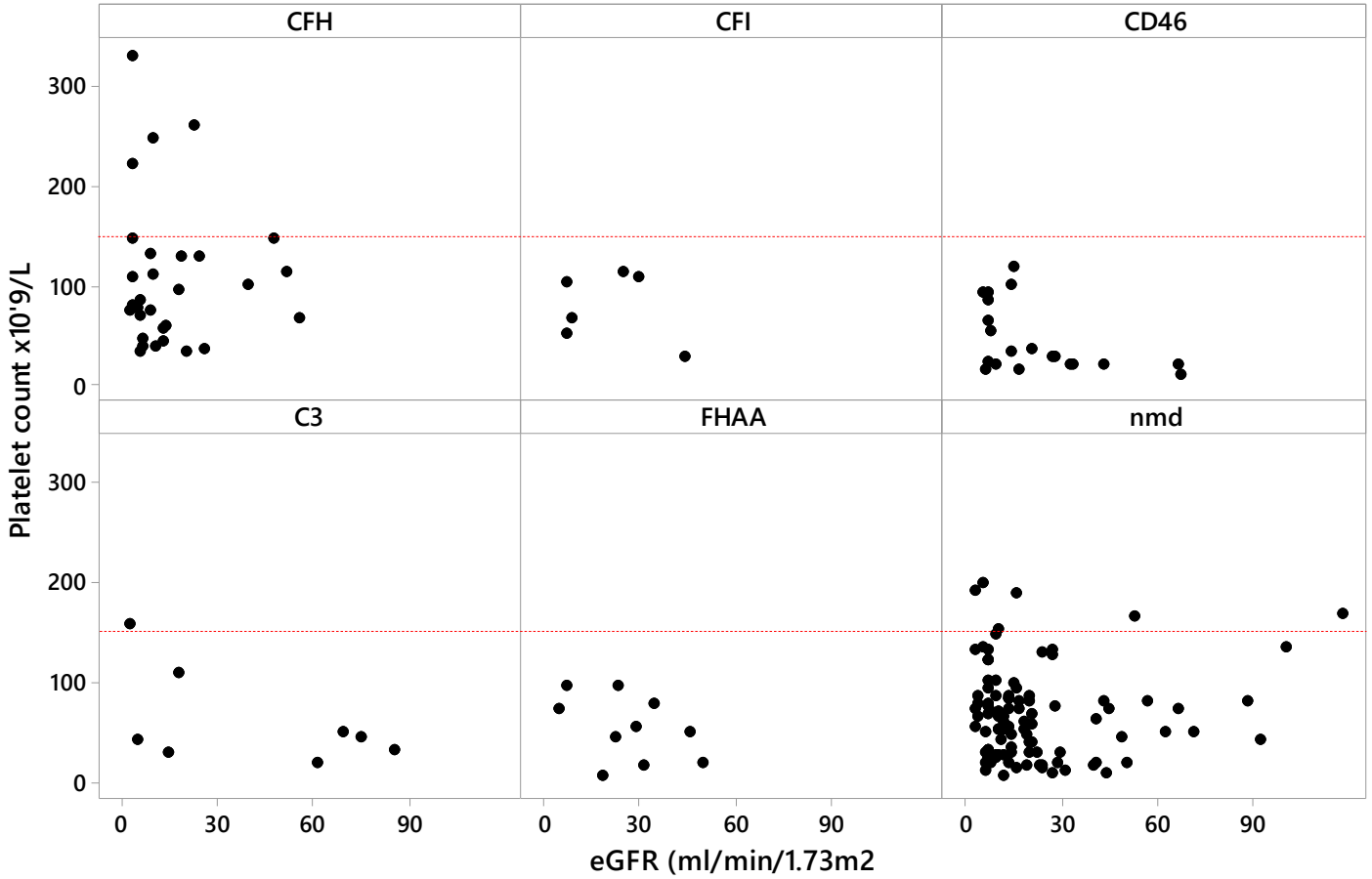


eFigure 7

			Albuminuria category, mg/mmol			
			A1	A2	A3	Unknown
			<3	3-30	>30	
eGFR categories (ml/min per 1.73m^2)	1	>90	23 (15%)	21 (14%)	5 (3%)	3 (2%)
	2	60-89	12 (8%)	6 (4%)	7 (5%)	5 (3%)
	3a	45-59	2 (1%)	4 (3%)	5 (3%)	3 (2%)
	3b	30-44	2 (1%)	4 (3%)	3 (2%)	0
	4	15-29	0	4 (3%)	4 (3%)	2 (1%)
	5	<15	0	0	2 (1%)	1 (0.5%)
	5D	On dialysis	n/a	n/a	n/a	23 (14%)
	5T	Transplanted	n/a	n/a	n/a	12 (8%)

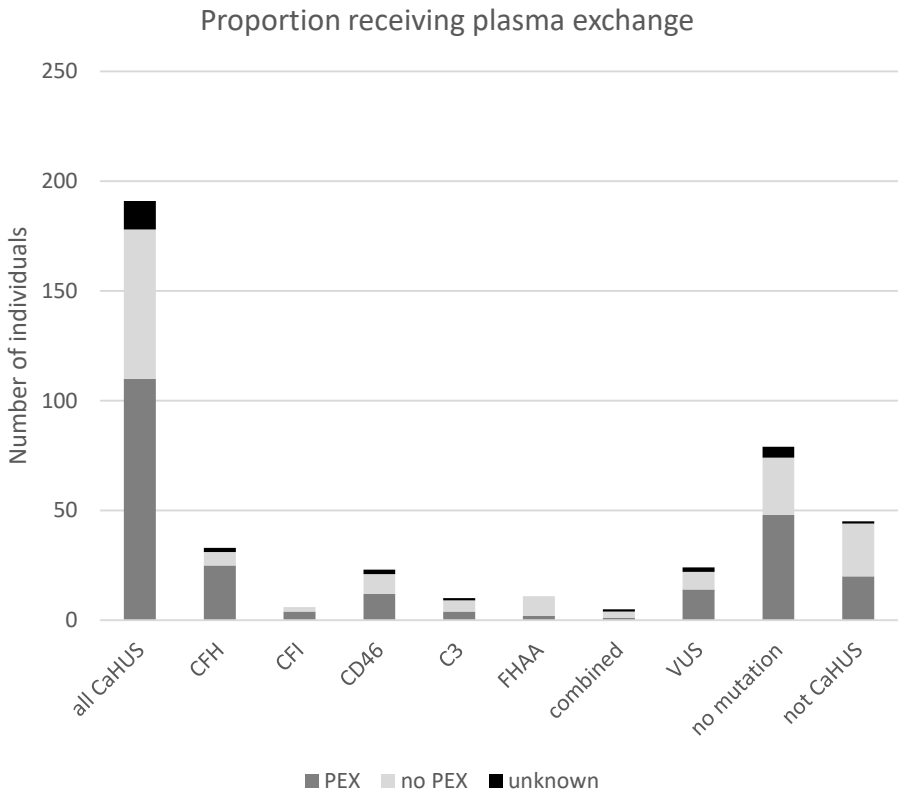
eFigure 8

A


CFH
CFI
CD46
C3
FHAA
nmd
Platelet count x10'9/L
300
200
100
0
0
30
60
90
eGFR (ml/min/1.73m2

eFigure 8

B



C

Haematological response to eculizumab in 71 individuals who did not receive plasma exchange prior to starting eculizumab

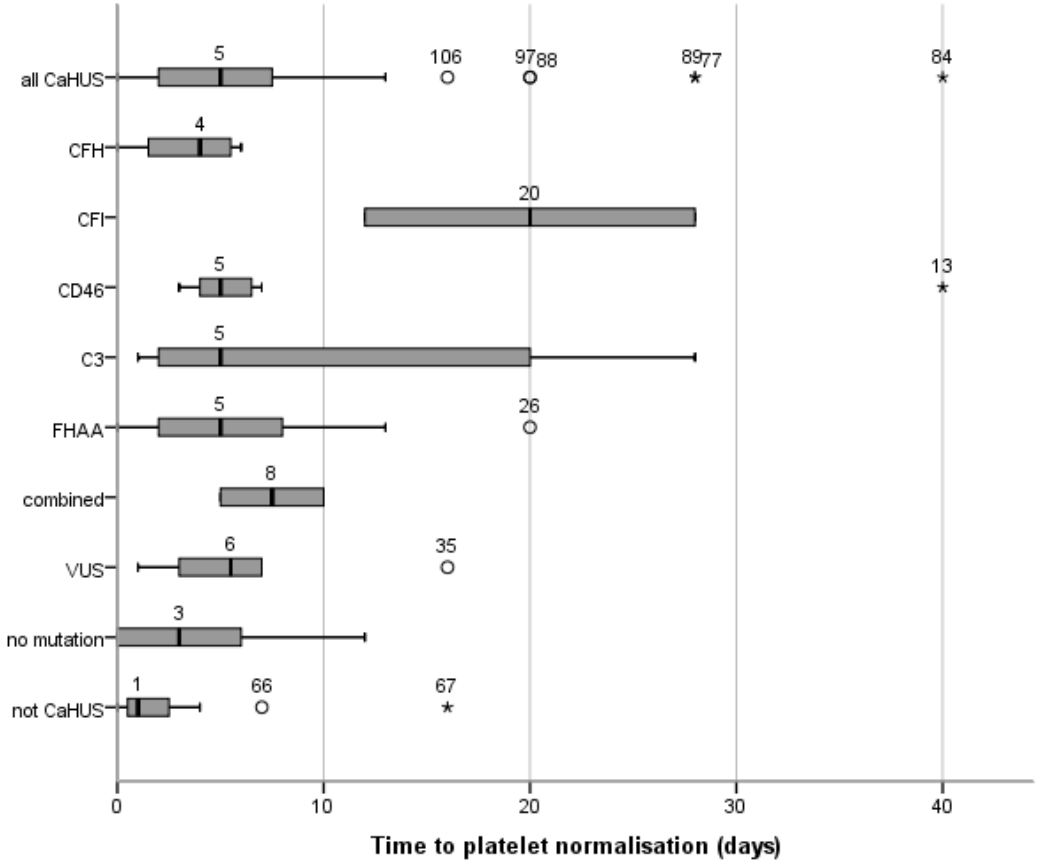


Figure 9: Multivariate analysis using logistic regression model

A. On dialysis at 6 months

	UNIVARIATE		MULTIPLE	
All individuals with treated CaHUS, n=173				
Risk Factor	Odds ratio	p value	Odds ratio	p value
Platelets	1.010 [1.003, 1.016]	0.004	1.010[1.002, 1.017]	0.001
Creatinine	1.001 [1.001, 1.002]	0.0004	1.001[1.00, 1.002]	0.07
Age at presentation	1.041 [1.022, 1.060]	<0.001	1.043[1.022, 1.064]	<0.001
Systolic BP sub-group, n=88				
Risk Factor	Odds ratio	p value	Odds ratio	p value
Systolic BP	1.016 [1.002, 1.029]	0.024	1.014[0.999, 1.028]	0.06
Platelets	1.012 [1.002, 1.021]	0.013	1.014 [1.004, 1.023]	0.007
Age at presentation	1.028 [1.002, 1.057]	0.034	1.036[1.005, 1.068]	0.02

An increase of one unit on each of the above variables lead to an increase in the odds ratio of being on dialysis at 6 months (either in the univariate or multiple analysis).

B. eGFR >60ml/min/1.73m^2 at 6 months

	UNIVARIATE		MULTIPLE	
All treated individuals with CaHUS, n=173				
Risk Factor	Odds ratio	p value	Odds ratio	p value
Presentation to ECU	1.00 [0.999, 1.001]	0.5	0.998 [0.997,1.00]	0.022
Platelets	0.984 [0.977, 0.992]	<0.0001	0.983[0.974, 0.993]	0.001
Creatinine	0.997 [0.996, 0.998]	<0.0001	0.998[0.996, 0.999]	0.002
Age at presentation	0.934 [0.914, 0.954]	<0.0001	0.934[0.912, 0.956]	<0.001
Systolic BP sub-group, n=88				
Risk Factor	Odds ratio	p value	Odds ratio	p value
Systolic BP	0.953 [0.930, 0.976]	<0.0001	0.945 [0.915,0.976]	0.001
Presentation to ECU	0.941 [0.891, 0.995]	0.031	0.934 [0.885,0.986]	0.013
Platelets	0.962 [0.944, 0.981]	<0.0001	0.955 [0.929, 0.981]	0.001
Age at presentation	0.940 [0.903, 0.978]	0.002	0.94[0.89, 0.993]	0.03

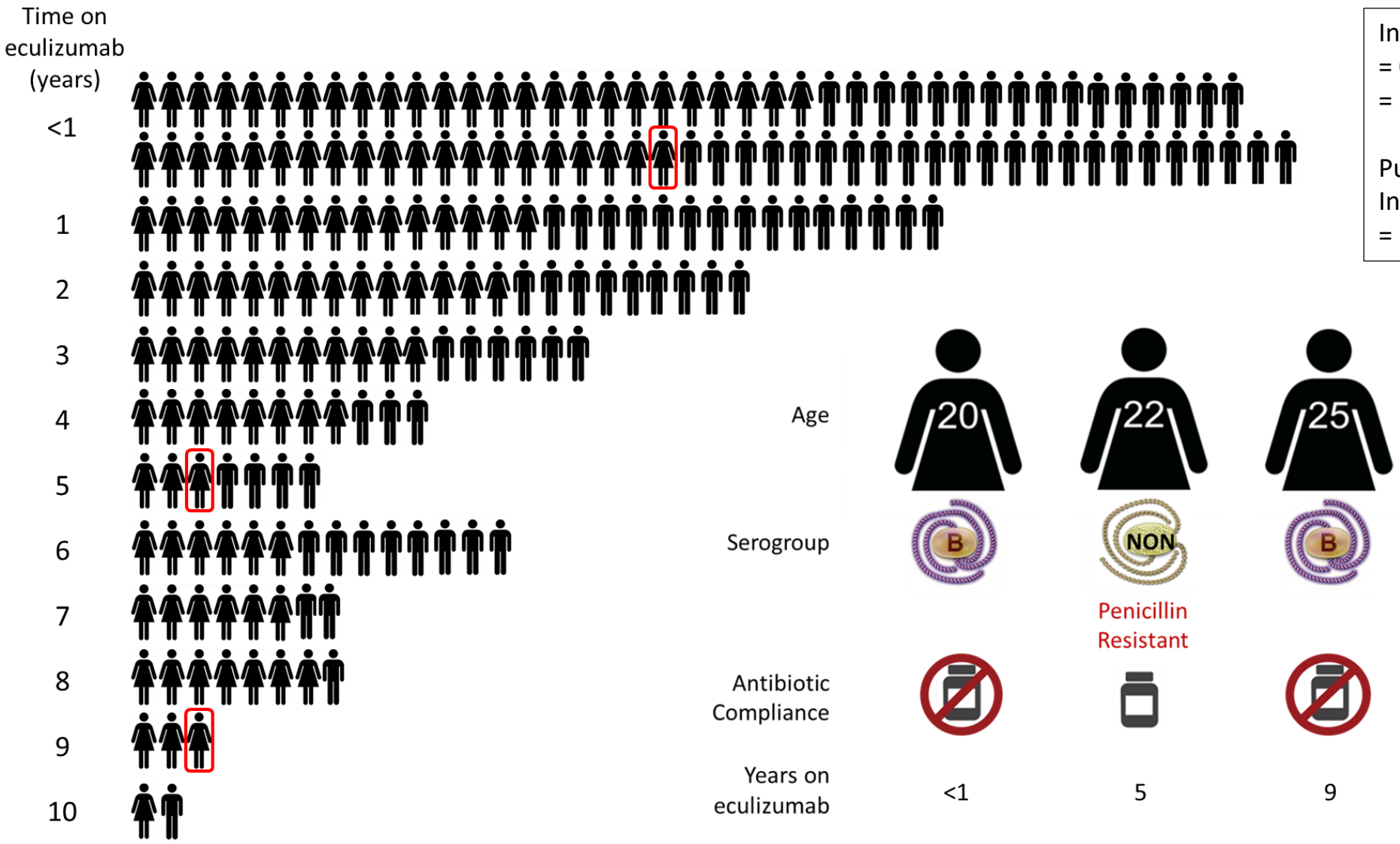
An increase of one unit on each of the above variables lead to a reduction in the odds of having eGFR>60ml/min/1.73m^2 at 6 months (either in the univariate or multiple analysis).

C. Renal response at 6 months

	UNIVARIATE		MULTIPLE	
All treated individuals with CaHUS, n=173				
Risk Factor	Odds ratio	P value	Odds ratio	P value
Platelets	0.987 [0.980, 0.994]	0.0002	0.985[0.978, 0.993]	<0.001
Age at presentation	0.968 [0.952, 0.984]	<0.0001	0.963[0.946, 0.980]	<0.001
Systolic BP sub-group, n=88				
Risk Factor	Odds ratio	P value	Odds ratio	P value
Systolic BP	0.984 [0.971, 0.997]	0.02	0.986 [0.972,1.00]	0.054
Platelets	0.989 [0.980, 0.998]	0.014	0.987 [0.978, 0.997]	0.001
Age at presentation	0.974 [0.949, 1.00]	0.054	0.97[0.942, 0.999]	0.001

An increase of one unit on each of the above variables lead to a reduction in the odds ratio of having a renal at 6 months (either in the univariate or multiple analysis).

eFigure 10



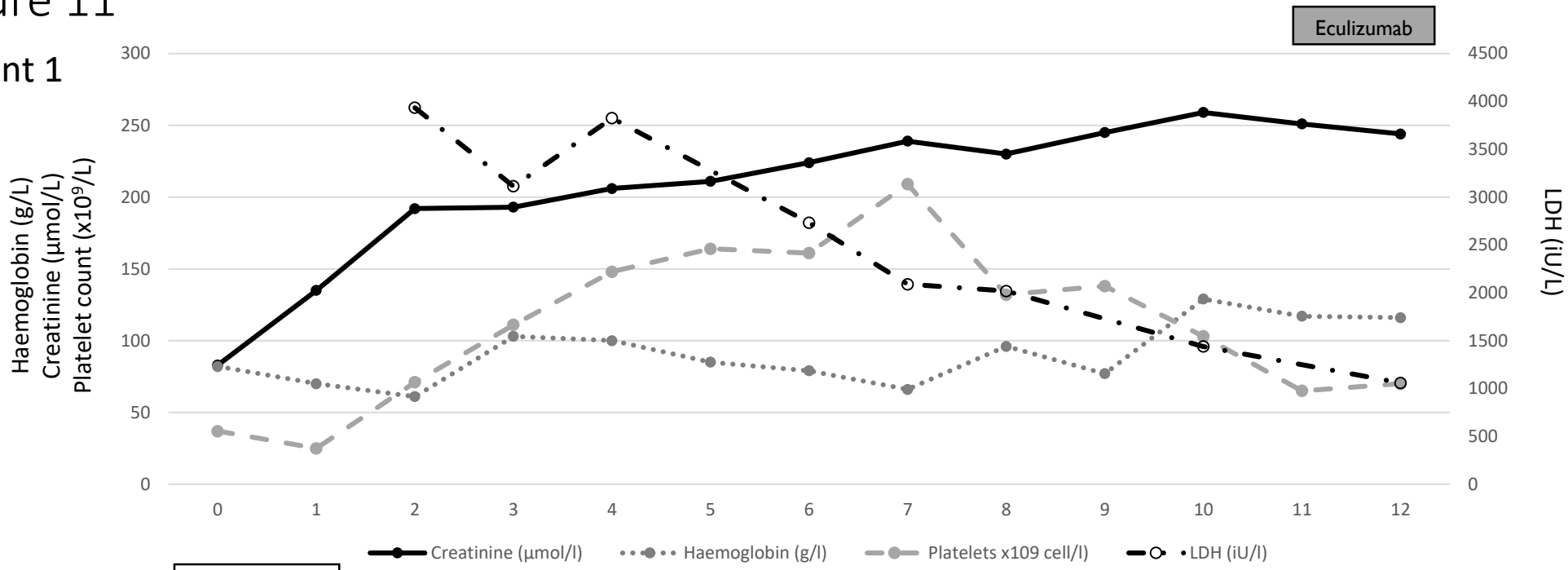
Incidence of meningococcal infection
= 0.0055 per person year
= 550 per 100,000

Public Health England data for 2018-2019:
Incidence of meningococcal infection
= 1 per 100,000

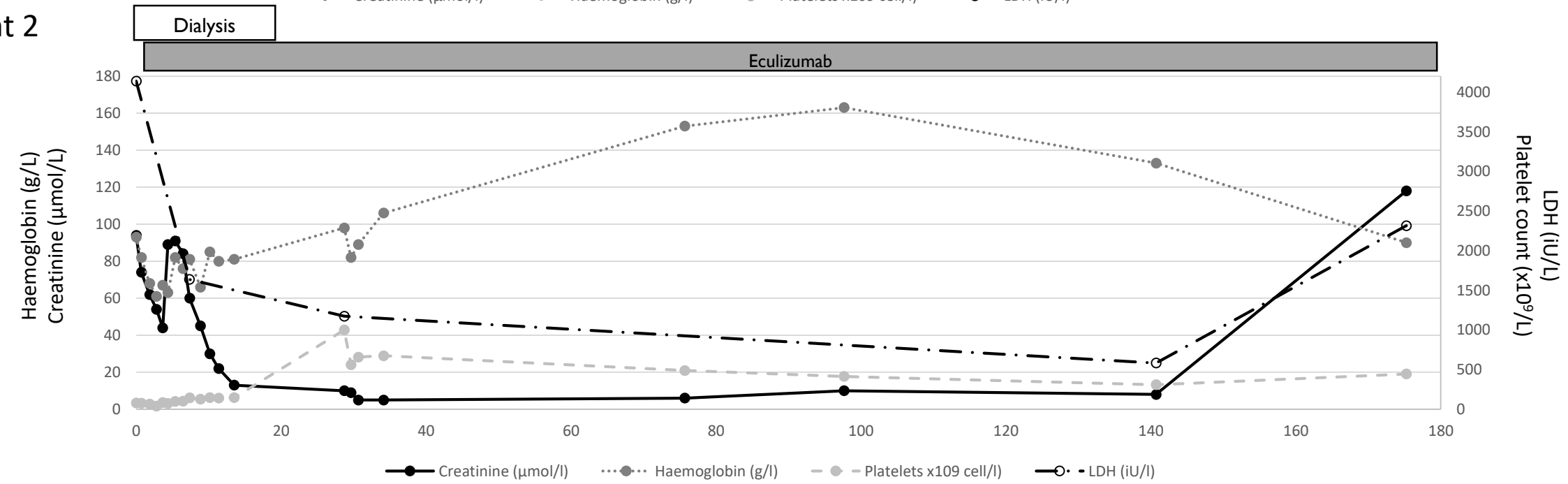
All vaccinated against ACWYB

eFigure 11

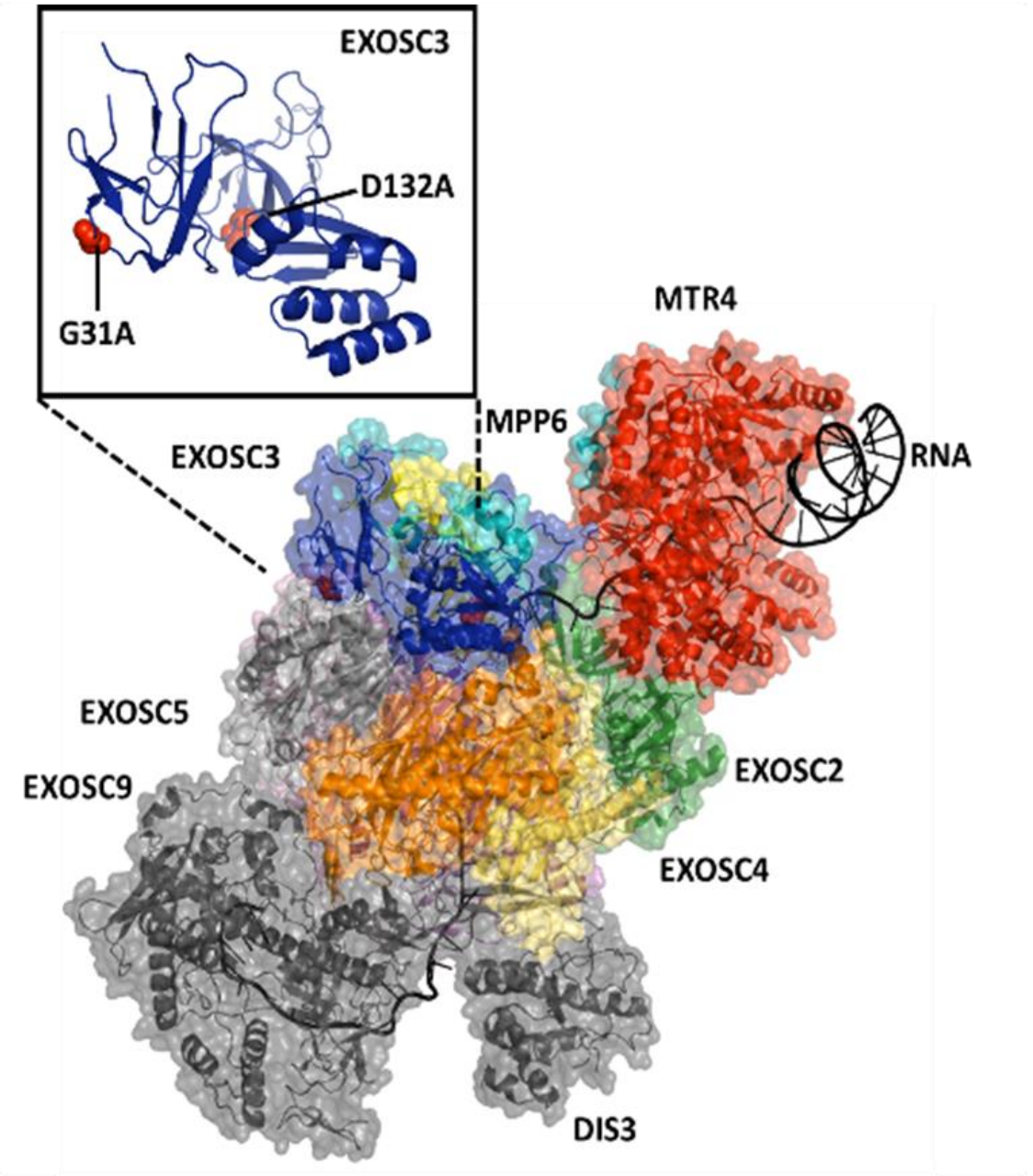
Patient 1



Patient 2



eFigure 12


EXOSC3
D132A
G31A
MTR4
MPP6
EXOSC3
RNA
EXOSC5
EXOSC9
EXOSC2
EXOSC4
DIS3

SUPPLEMENTAL FIGURE LEGENDS

eFigure 1: Modelling of variants

A. *CFH* Mutations and VUS in FH modelled within the alternative pathway (AP) regulatory tri-molecular complex (TMC) of C3b:FH:FI. Produced in Pymol V2.0 (Schrodinger LLC) using the PDB file 5o32 (Xue et al. 2017), this 3D model of FI (heavy chain: yellow; light chain: green) bound to C3b (pale cyan) and FH complement control protein modules (CCPs) 1-4 (purple) displays the putative sites of amino acid residues altered by mutations (red spheres) and VUS (orange spheres) identified in *CFH* coding for amino acids in CCPs1-4 and 19-20 in the aHUS cohorts interrogated by the present study.

B. *CD46* Mutations and VUS in CD46 CCP1-4 modelled within the C3b:CD46 CCP1-4 complex. Produced in Pymol V2.0 (Schrodinger LLC) using the PDB file 5fo8 (Forneris et al. 2016), this 3D model of CD46 (purple) bound to C3b (pale cyan) displays the putative sites of amino acid residues altered by mutations (red spheres) and VUS (orange spheres) identified in *CD46* in the aHUS cohorts interrogated by the present study.

C. *CFI* Mutations and VUS in FI modelled within the AP Regulatory TMC of C3b:FH:FI. Produced in Pymol V2.0 (Schrodinger LLC) using the PDB file 5o32 (Xue et al. 2017), this 3D model of FI (heavy chain: yellow; light chain: green) bound to C3b (pale cyan) and FH CCPs 1-4 (purple) displays the putative sites of amino acid residues altered by mutations (red spheres) and VUS (orange spheres) identified in *CFI* in the aHUS cohorts interrogated by the present study.

D. *C3* Mutations and VUS in C3 modelled within the AP Regulatory TMC of C3b:FH:FI. Produced in Pymol V2.0 (Schrodinger LLC) using the PDB file 5o32 (Xue et al. 2017), this 3D model of FI (heavy chain: yellow; light chain: green) bound to C3b (pale cyan) and FH CCPs 1-4 (purple) displays the putative sites of amino acid residues altered by mutations (red spheres) and VUS (orange spheres) identified in *C3* in the aHUS cohorts interrogated by the present study.

E. *CFB* Mutations and VUS in Bb modelled within the C3 convertase. Produced in Pymol V2.0 (Schrodinger LLC) using the PDB file 2win (Wu et al. 2009), this 3D model of Bb (green) bound to C3b (C3c: orange; C3dg: blue; beta chain: purple; C3f: red) displays the putative sites

of amino acid residues altered by mutations (red spheres) and VUS (orange spheres) identified in *CFB* in the aHUS cohorts interrogated by the present study.

eFigure 2: Family history.

A. Proportion of individuals with a family history of aHUS in the treated cohort. Number and percentage of individuals with a family history for each gene are labelled. This is more representative because all incident aHUS patients in England were referred. **B.** Proportion of individuals with a family history of aHUS in the control cohort. Number and percentage of individuals with a family history for each gene are labelled. This will not be representative because families were preferentially referred to our centre. **C.** Genetic causes in 67 pedigrees referred to the NRCTC with familial TMA. 29.5% had *CFH* mutations, 21% had *CD46* mutations, and 15% remain unsolved.

eFigure 3: Clinical characteristics at presentation in the treated cohort.

A. Blood pressure. **i.** Systolic blood pressure in adults at presentation, by mutation type. Solid circle = mean. There was no statistical difference between the groups (one way ANOVA). **ii.** Proportion of children with hypertension at presentation, by mutation type (hypertension defined as systolic blood pressure and/or diastolic blood pressure at or above the 95th percentile).[35]

B. Proteinuria at presentation, by mutation type. Data (urine PCR) was available for 104/243 (44%) of patients; many were anuric. Solid diamond = median. Two extreme outliers were not included on graph: 17,520 (*CD46*), 31,000 (not CaHUS).

C. CRP at presentation, by group: CaHUS with a mutation or FHAA, CaHUS with no mutation or FHAA, and not CaHUS. Solid diamond = median. The dashed line represents normal value (<5mg/L). There was a statistically significant difference between the CaHUS with mutation or FHAA and the not CaHUS groups: p=0.009.

D. Complement profile. **i.** C3 at presentation. Solid circle = mean. The dashed lines represent normal range (0.68-1.8 g/L). **ii.** C4 at presentation. Solid circle = mean. The dashed lines represent normal range (0.18-0.6g/L). **iii.** sC5b-9 at presentation. Solid diamond = median. The dashed lines represent normal range (53-173 ng/ml). An extreme outlier was excluded from figure: 4360 in a patient with FHAA and CaHUS/C3G cross over.

eFigure 4: Age at presentation.

Age at first presentation (data from both control and treated cohorts). **A.** All CaHUS. **B.** Box plot of age at presentation for the different CaHUS groups. **C.** *CFH* mutation. **D.** *CFI* mutations. **E.** *CD46* mutations. **F.** *C3* mutations. **G.** FHAA. **H.** no mutation. **I.** Not CaHUS. **J.** There is a significant difference in the age at presentation of CaHUS between males and female. **K.** When CaHUS age at presentation was analysed specifically looking at childhood, child bearing years and later adulthood there was a significant difference between males and females.

eFigure 5: Triggers, extra renal manifestations and prodrome.

A. Proportion with reported triggers of CaHUS in treated cohort, by mutation type. 31% with CaHUS had a reported trigger. **B.** Proportion with diarrhoeal prodrome in CaHUS treated cohort, by mutation type. 24% with CaHUS had a diarrhoeal prodrome. **C.** Proportion with extra-renal manifestations in presenting CaHUS episode in treated cohort, adults and children. Extra renal manifestations were reported in 19% with CaHUS. Neurological involvement was defined by the presence of seizures, stroke, focal neurological deficit or reduced conscious level. Cardiac involvement was defined by reduced left ventricular systolic function, with or without a rise in troponin. Pancreatitis was defined by a raised serum amylase. The reported liver involvement in one individual was acute liver failure. One individual had retinopathy which was described as hypertensive retinopathy. **D.** Proportion with extra-renal manifestations in presenting CaHUS episode in treated cohort, by mutation type. **E.** Prodromal symptoms or circumstances in adults with CaHUS in the treated cohort. **F.** Prodromal symptoms or circumstances in children with CaHUS in the treated cohort. **G**. Presentation of CaHUS in the treated cohort, by month.

eFigure 6: Five-year cumulative estimates (Kaplan-Meier) of end stage kidney disease free survival.

Hazard ratios (HR) and 95% confidence intervals calculated using the Cox proportional hazards regression model, p values calculated using the log-rank test, and number needed to treat (NNT) are shown where appropriate. **A.** Treated group (including those without a mutation or FHAA) vs control CaHUS**. B.** Treated group (including those without a mutation or FHAA) vs control CaHUS, children vs adults **C.** Treated CaHUS with mutation or FHAA vs

control CaHUS, by age and sex group. **D.** Treated CaHUS vs control CaHUS, by age and sex group. **E.** *CFH* mutation types, treated vs control. The only statistically significant difference between mutation types was for type 1 vs type 2 C terminal and FH hybrid mutations in the control group, HR 1.26 (95% CI 0.83-1.92); *p*=0.049. **F.** *CFI* mutations, treated vs control. **G.** *C3* mutations, treated vs control. **H.** FHAA, treated vs control. **I**. FHAA, treated vs control, uncensored.

eFigure 7: Long term outcomes.

Renal function at most recent follow up in the treated CaHUS cohort; follow up period 1 – 10 years; data available for 153/192 (80%).

eFigure 8: Haematological response to eculizumab

- **A.** Platelet count and eGFR (ml/min/1.73m^2) at presentation, by mutation type. 11 individuals had a platelet count above 150x109/L at presentation, but had evidence of TMA on kidney biopsy or evidence of haemolysis on the blood film. 46 individuals had a platelet count of <30.
- **B.** Proportion who received plasma exchange prior to the first dose of eculizumab, by mutation type. 58% of those with CaHUS received plasma exchange prior to the first dose of eculizumab.
- **C.** Haematological response to eculizumab, defined by number of days from first dose of eculizumab to platelet normalisation (>150x10^9/L), for 71 individuals who did not receive plasma exchange prior to starting eculizumab for whom data was available. Median, interquartile range, 1.5x interquartile range and outliers are shown. There was no statistical difference between the mutation types. The median for all CaHUS was 5 days, compared with 4 days for the analysis that included all individuals (Figure 3B).

eFigure 9: Multivariate analysis of factors associated with a response to eculizumab in the treated CaHUS cohort.

eFigure 10: Complications of eculizumab.

Time on treatment and incidence of meningococcal infection in the eculizumab treated cohort**.** All three individuals who had meningococcal infection survived with minimal

morbidity. In the UK monitoring of the serological response to the vaccine with annual testing of ACWY titres is recommended; we are not able to check B titres in patients receiving eculizumab because the assay is complement dependent. One individual stopped eculizumab because of headaches, but no other adverse effects of the drug were reported.

eFigure 11: Non- response to Eculizumab therapy in patients with EXOSC3 mediated aHUS. The two patients in the NRCTC cohort presented with aHUS after RSV infection and an unspecified respiratory virus.

eFigure 12: Mutations in EXOSC3 displayed on the crystal structure: Both patients had biallelic mutations in EXOSC3 patient 1: c.395A>C (p.D132A) and c.341_343del; patient 2 c.395A>C (p.D132A), c.92G>C (p.G31A); The Human RNA exosome with MTR4 delivering single stranded RNA bound,EXOSC3 highlighted in blue, with variants identified in this study highlighted on image inset. Generated on Pymol (PDB 6D6Q).

Supplemental Methods

Definition of complement mediated aHUS

Individuals referred to the NRCTC with suspected CaHUS undergo comprehensive diagnostic evaluation. Complement mediated aHUS is a diagnosis of exclusion.

Diagnostic criteria have been established in UK by the aHUS Rare Disease Group (http://rarerenal.org/rare-disease-groups/atypical-haemolytic-uraemic-syndrome-rdg/) for the diagnosis of aHUS[1]. Inclusion criteria are the triad of microangiopathic haemolytic anaemia (MAHA; evidence of erythrocyte fragmentation on peripheral blood film microscopy), thrombocytopenia and acute kidney injury (AKI), and/or a kidney biopsy showing thrombotic microangiopathy. Exclusion criteria are: thrombotic thrombocytopenic purpura (TTP) – ADAMTS13 <10%; shiga toxin HUS (STEC-HUS) – culture, serology and shiga toxin PCR; DGKE nephropathy – *DGKE* genetic analysis; disseminated intravascular coagulation (DIC) – abnormal coagulation; pneumococcal HUS – culture, urinary antigen, Coombs test positive, T-antigen; HIV; drug induced TMA – causative drug in relevant clinical context, including cisplatin, gemcitabine, mitomycin, interferon α,β, calcineurin inhibitors; cobalamin C deficiency TMA – serum homocysteine, methionine and methyl-malonic acid, and *MMACHC* genetic analysis; malignancy associated TMA; bone marrow transplant associated TMA; *de novo* TMA post solid organ transplant; glomerular disease associated TMA – kidney biopsy suggesting IgA nephropathy, ANCA associated vasculitis, focal segmental glomerulosclerosis, membranous nephropathy or C3 glomerulopathy; autoimmune disease associated TMA – systemic lupus erythematosus (ANA, anti-dsDNA antibodies), catastrophic anti-phospholipid syndrome (anti-phospholipid antibodies), scleroderma renal crisis (anti-Scl70 antibodies, RNA polymerase III); severe hypertension TMA.[2]

Study Population

Individuals with suspected CaHUS but no pathogenic mutation or autoantibody were not included in the control cohort because a comprehensive diagnostic evaluation to exclude other causes of thrombotic microangiopathy was not mandatory prior to the commencement of the national specialist service in 2013.

The treated cohort comprised individuals referred between 2013 and July 2019 with suspected CaHUS who received eculizumab for native kidney disease, and those in whom no alternative diagnosis was ultimately identified were included in the treated CaHUS cohort for analysis. Individuals referred prior to 2013 who were treated with eculizumab either as part of a clinical trial or on compassionate grounds were included in the treated cohort. Kidney transplant recipients were excluded.

In the survival analysis, individuals who were treated with eculizumab at the time of a relapse but not the first presentation of aHUS (n=17) were analysed in the control cohort up until the point at which they received eculizumab. The minimum follow up period was 12 months.

Incidence rates were calculated for the cohort presenting in England from 2013 – July 2019 using the estimated population of England according to the Office for National Statistics.[3]

Data Collection

For the control cohort outcome data (demographics, family history, death, renal outcome, genetic and autoantibody analysis) were obtained from the NRCTC database and communication with clinicians. For the control cohort data the only data point relating to management that was collected, if available, was whether or not plasma therapy was performed.

For the treated cohort, data were collected on demographics and family history, clinical presentation, laboratory characteristics, genetic and autoantibody analysis, response to eculizumab, and outcome (death and renal outcome). Individuals in England who receive eculizumab enter into a 'shared care agreement' between their local consultant and the NRCTC. Data were reported by local clinicians to the NRCTC and held in a central database. 27% of patients were registered with The National Registry of Rare Kidney Diseases (RaDaR) and this was used to retrieve laboratory test results. For individuals outside of England data were reported by local clinicians to the NRCTC. Patients with >75% complete datasets were included in the analysis.

The eculizumab treated cohort received the dosing schedule recommended by the manufacturer, Alexion Pharmaceuticals Inc (New Haven, CT) as well as meningococcal vaccination and prophylactic antibiotics (see **Supplemental data**).

Renal function and blood pressure

Renal function was classified by glomerular filtration rate (GFR) and albuminuria categories according to the Kidney Disease Improving Global Outcomes (KDIGO) recommendations.[4]

The estimated glomerular filtration rate (eGFR) was calculated as follows: for children (<18 years), the Schwartz formula was used, and for adults the CKD-EPI equation was used as previously described.[5]

Blood pressure in children was analysed with reference to the Fourth Report on Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, with hypertension defined as systolic blood pressure and/or diastolic blood pressure at or above the 95th percentile.[6]

Outcomes

The primary outcome in the comparison between the eculizumab treated CaHUS and control CaHUS cohorts was five-year end stage kidney disease (ESKD)-free survival.

In the analysis of the eculizumab treated CaHUS cohort the secondary outcomes were ESKD free survival at 6 months; estimated glomerular filtration rate (eGFR) of >60 ml/min at 6 months (chronic kidney disease stage (CKD) G1-212 or no CKD); and renal response to eculizumab at 6 months, a composite outcome of achieving dialysis independence if dialysis had been required, or >33% decrease in serum creatinine if dialysis had not been required (this represents the inverse of the ≥50% increase in serum creatinine within 7 days that prospectively defines KDIGO stage 1 acute kidney injury).

Other secondary outcomes in the analysis of the eculizumab treated cohort were haematological response to eculizumab (defined as normalisation of platelet count >150x109/L) and renal response to eculizumab (recovery from dialysis dependency or change in serum creatinine at 1 week, 2 weeks, 1 month, 3 months, 6 months and 12 months).

Statistical analysis

Patient characteristics were examined using descriptive statistics for continuous variables (mean, median) and categorical variables (number, %). Laboratory data are presented as mean (range). Renal survival was examined using Kaplan-Meier analysis and Cox Regression. Significance tests for continuous variables were the ANOVA for normally distributed data and the Kruskal-Wallis test for data that were not normally distributed. Serial creatinine measurements were analysed using the Friedman test.

In the multivariate analysis the association of factors of interest (genetics, age at initial presentation, ethnicity, serum creatinine, haemoglobin, platelet count, time from presentation to treatment, C3, C4; systolic blood pressure was not available for all patients so analyses were performed without (n=173) and with (n=88) systolic blood pressure) with the secondary outcomes in the analysis of the eculizumab treated cohort was assessed using logistic regression model. Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) and R.[7]

Complement assays

C3 and C4 levels were measured by rate nephelometry (Beckman Coulter Array 360, Beckman Coulter; High Wycombe, United Kingdom). The normal ranges were C3 (0.68–1.38 g/l), C4 (0.18–0.60 g/l). The FH autoantibody (FHAA) consensus assay was performed as previously described.[8]

Variant modelling

Variants were modelled using Pymol V2.0 (Schrodinger LLC)

Limitations of study

This study is limited by its observational nature, however CaHUS is an ultra-orphan disease and as such a randomised genotype matched controlled trial is not feasible. We acknowledge that the treated cohort presented from 2013 onwards, but individuals in the control cohort were referred in the 1990s through to 2012. The magnitude of this selection bias cannot be determined, but one-year unadjusted survival of incident adult renal replacement therapy patients in the United Kingdom was 87.0% in 1999 and 92.9% in 2018 for those <65 years and 67.9% in 1999 and 79.3% in 2018 for those ≥65 years[9]. Additionally there is selection bias relating to treatment inconsistency: some individuals who presented after 2013 were managed locally and not treated with eculizumab, and were included in the control cohort. In the control CaHUS group we felt that it was not possible to include individuals with no complement mutation due to variable diagnostic evaluation pre-2013 and as such Kaplan-Meier survival analysis was performed on a genotype matched subgroup.

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eTable 1: ¤Figure 1 additional data – individuals who presented after 2013 who were not treated with eculizumab, but were found to have a pathogenic variant and were included in the control cohort

Patient number	Gene	Reason not treated	Outcome
47	*CFH*	Managed locally without eculizumab, referred for transplant work up.	ESKD
67	*CFH*	Managed locally without eculizumab, referred for transplant work up.	ESKD
84	*CFH*	Managed locally without eculizumab, referred for transplant work up.	Recovered renal function
85	*CFH*	Managed locally without eculizumab, referred for transplant work up.	ESKD
162	*CFH*	Managed locally without eculizumab, referred for transplant work up.	ESKD
171	*CFH*	Managed locally without eculizumab. Thought to be hypertension associated TMA	Recovered renal function
178	*CFHR1* hybrid	Managed locally without eculizumab, spontaneous recovery	Recovered renal function
184	*CFI*	Managed locally without eculizumab, referred for transplant work up. Thought to be macrophage activation syndrome	Recovered renal function
185	*CFI*	Managed locally without eculizumab, referred for transplant work up.	ESKD
186	*CFI*	Managed locally without eculizumab, referred for transplant work up.	ESKD
190	*CFI*	Managed locally without eculizumab, referred for transplant work up.	ESKD
198	*CFI*	No TMA on biopsy	ESKD
199	*CFI*	Thought to be hypertension/CKD associated TMA	ESKD
200	*CFI*	Thought to be hypertension/CKD associated TMA	ESKD
201	*CFI*	Thought to be hypertension/CKD associated TMA	ESKD
230	*CD46*	Managed locally without eculizumab, thought to be hypertension related TMA, referred for transplant work up	ESKD
231	*CD46*	Spontaneous recovery	Recovered renal function
232	*CD46*	Spontaneous recovery	Recovered renal function
234	*CD46*	Spontaneous recovery	Recovered renal function
235	*CD46*	Spontaneous recovery	Recovered renal function
236	*CD46*	Not in UK, eculizumab not available	Recovered renal function
237	*CD46*	Spontaneous recovery	Recovered renal function
238	*CD46*	Spontaneous recovery	Recovered renal function
239	*CD46*	Spontaneous recovery	Recovered renal function
254	*CD46*	Spontaneous recovery	Recovered renal function
255	*CD46*	Spontaneous recovery	Recovered renal function
256	*CD46*	Spontaneous recovery	Recovered renal function
257	*CD46*	Not in UK, eculizumab not available	Recovered renal function
258	*CD46*	Spontaneous recovery	Recovered renal function
259	*CD46*	Spontaneous recovery	Recovered renal function
274	*C3*	Chronic TMA on biopsy	ESKD
292	*C3*	MPGN and TMA on biopsy	ESKD
23	FHAA	Spontaneous recovery	Recovered renal function

302	FHAA	Spontaneous recovery	Recovered renal function
305	FHAA	Diagnostic uncertainty	Recovered renal function
307	FHAA	Diagnostic uncertainty	Recovered renal function
310	FHAA	Not acute presentation, TMA on biopsy	Recovered renal function
311	FHAA	Managed locally without eculizumab, spontaneous recovery	Recovered renal function
315	Combined	Not in UK, eculizumab not available	Died
317	Combined	Managed locally without eculizumab, referred for transplant work up.	ESKD

eTable 2: Genetic and clinical data for the control cohort.

Patient Number	C' Gene	Mutation	Pathogenicity*	Function Refs	#Population frequency %	Family history	Sex	Age at onset	PEX	ESKD
41	*CFH*	c.1672T>G p.(Trp558Gly)	Type 1	-	NA	No	M	44	Y	yes
42	*CFH*	c.1705T>A p.(Cys569Ser)	Type 1	-	NA	No	F	36	U	yes
43	*CFH*	c.1873G>T p.(Glu625*)	Type 1	-	0.0014	Yes	F	20	U	yes
44	*CFH*	c.1873G>T p.(Glu625*)	Type 1	-	0.0014	Yes	F	26	U	yes
45	*CFH*	c.1975T>C; p.(Cys659Arg)	Type 1	-	0.0004	No	F	24	Y	no
46	*CFH*	c.2114C>T p.(Ser705Phe)	Type 1	-	0.0057	No	F	71	U	no
47	*CFH*	c.2409C>A, p.(Cys803*)	Type 1	-	NA	No	F	57	Y	yes
48	*CFH*	c.2596+1G>A	Type 1	-	NA	No	F	18	Y	no
49	*CFH*	c.2596+1G>C	Type 1	-	0.004	No	F	39	U	yes
50	*CFH*	c.2636G>A p.(Gly879Glu)	Type 2 (C-terminal)	-	NA	No	M	73	Y	yes
51	*CFH*	c.2880delT p.(Phe960Leufs*15) Homozygous	Type 1	-	NA	No	M	1	FFP	no
52	*CFH*	c.2918G>A p.(Cys973Tyr)	Type 1	[3]	NA	Yes	F	30	U	yes
53	*CFH*	c.3229T>C p.(Cys1077Arg)	Type 1	-	NA	No	M	32	Y	yes
54	*CFH*	c.3590T>C, p.(Val1197Ala)	Type 2 (C-terminal)	[4, 5]	0.00071	No	F	1	Y	no
55	*CFH*	c.3398C>G p.(Ser1133*)	Type 1		NA	No	F	16	Y	no
56	*CFH*	c.3468dupA p.(Trp1157Metfs*22)	Type 1	-	NA	No	F	26	Y	yes
57	*CFH*	c.3471G>C p.(Trp1157Cys)	Type 1	-	NA	No	F	69	Y	yes
58	*CFH*	c.3549G>T p.(Trp1183Cys)	Type 2 (C-terminal)	[8]	NA	No	F	20	U	no
59	*CFH*	c.3550A>C p.(Thr1184Pro)	Type 2 (C-terminal)	-	NA	No	M	56	U	yes
60	*CFH*	c.3550A>G p.(Thr1184Ala)	Type 2 (C-terminal)	[9]	NA	No	F	34	Y	yes
61	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	No	F	21	N	yes
62	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[10, 11]	NA	Yes	M	24	N	yes
63	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[10, 11]	NA	Yes	F	25	U	no
64	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	No	F	35	Y	yes
65	*CFH*	c.3590T>C, p.(Val1197Ala)	Type 2 (C-terminal)	[4, 5]	0.00071	No	M			
66	*CFH*	c.3590T>C, p.(Val1197Ala)	Type 2 (C-terminal)	[4, 5]	0.00071	No	F	32	Y	yes
67	*CFH*	c.3607C>T p.(Arg1203Trp)	Type 2 (C-terminal)	[13, 14]	0.0046	No	F	28	U	yes

68	*CFH*	c.3616C>T p.(Arg1206Cys)	Type 2 (C-terminal)	[13]	NA	No	F	30	U	yes
69	*CFH*	c.3628C>T p.(Arg1210Cys)	Type 2 (C-terminal)	[10]	0.015	No	M	22	U	yes
70	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	No	F	22	Y	yes
71	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	No	F	22	U	yes
72	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	26	N	yes
73	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	47	N	no
74	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	17	U	yes
75	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	25	Y	no
76	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	29	U	yes
77	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	No	M	64	U	yes
78	*CFH*	c.3643C>T p.(Arg1215*)	Type 1	-	0.0004	No	F	35	Y	no
79	*CFH*	c.3643C>T p.(Arg1215*)	Type 1	-	0.0004	No	M	62	U	yes
80	*CFH*	c.3644G>A p.(Arg1215Gln)	Type 2 (C-terminal)	[16]	0.000008*	No	M	51	Y	yes
81	*CFH*	c.3644G>A p.(Arg1215Gln)	Type 2 (C-terminal)	[16]	0.000008*	No	M	1	Y	no
82	*CFH*	c.3676C>G p.(Pro1226Ala)	Type 2 (C-terminal)	-	NA	No	F	39	N	no
83	*CFH*	c.3677C>A p.(Pro1226Gln) Homozygous	Type 2 (C-terminal)	-	NA	No	M		U	
84	*CFH*	c.481G>T p.(Ala161Ser)	Type 2 (N-terminal)	[18]	0.0092	No	F	1	N	no
85	*CFH*	CFH:CFHR1 hybrid	FH hybrid	[19]	NA	No	M	39	N	yes
86	*CFH*	CFH:CFHR1 hybrid	FH hybrid	[19]	NA	No	M	22	U	yes
87	*CFH*	c.2671T>G, p.(Tyr891Asp)	Type 1	-	NA	Yes	M	1	Y	yes
88	*CFH*	c.2671T>G, p.(Tyr891Asp)	Type 1	-	NA	Yes	M	1	N	no
89	*CFH*	c.3546_3581dup36 p.(Trp1183_Gly1194dup)	Type 1	-	NA	Yes	F	1	FFP	no
90	*CFH*	c.3546_3581dup36 p.(Trp1183_Gly1194dup)	Type 1	-	NA	Yes	M		U	
91	*CFH*	c.79_82del p.(Arg27Glufs*6)	Type 1	-	NA	No	M	37	U	yes
92	*CFH*	c.3550A>G p.(Thr1184Ala)	Type 2 (C-terminal)	[10]	NA	No	M	60	N	yes
93	*CFH*	c.3562_3564 del p.(Lys1188del)	Type 2 (C-terminal)	-	NA	No	M	42	Y	yes
94	*CFH*	c.3546G>T; p.(Arg1182Ser)	Type 2 (C-terminal)	[10]	NA	No	F	1	Y	yes
95	*CFH*	c.2018G>A p.(Cys673Tyr)	Type 1	-	NA	No	F	5	Y	yes
96	*CFH*	CFH:CFHR1 hybrid	FH hybrid	[19]	NA	No	M	23	N	yes
97	*CFH*	CFH::CFHR3 hybrid	FH hybrid	[19]	NA	Yes	F	25	N	yes
98	*CFH*	CFH::CFHR3 hybrid	FH hybrid	[19]	NA	Yes	M	44	Y	yes

99	*CFH*	0.59Mb deletion hg19 chr 1:g.196,711,285-196,770,525del	Type 1	-	NA	No	F	17	Y	yes
100	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	F	15	Y	yes
101	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[11]	NA	No	F	1	U	yes
102	*CFH*	c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	10]	0.00071	No	M	1	N	yes
103	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[11]	NA	No	F	1	Y	no
104	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	Yes	F		U	
105	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	Yes	M		U	
106	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	No	M	10	U	yes
107	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	Yes	F	1	N	yes
108	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	Yes	M	30	Y	yes
109	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	Yes	F	4	Y	yes
110	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	Yes	F	3	N	yes
111	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	Yes	F	4	Y	no
112	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Al)a	Type 2 (C-terminal)	[19]	NA	No	F	35	U	yes
113	*CFH*	CFH:CFHR1 hybrid	FH hybrid	[19]	NA	No	F	29	Y	yes
114	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	No	F	1	N	yes
115	*CFH*	c.3356A>G p.(Asp1119Gly)	Type 2 (C-terminal)	[10]	0.0004	Yes	F		U	yes
116	*CFH*	c.3356A>G p.(Asp1119Gly)	Type 2 (C-terminal)	[10]	0.0004	Yes	F	20	U	yes
117	*CFH*	c.3454T>A p.(Cys1152Ser)	Type 1	-	0.0004	No	F	32	Y	no
118	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	26	Y	yes
119	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	17	U	yes
120	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	60	U	yes
121	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	26	U	yes
122	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	23	U	yes
123	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	1	U	yes
124	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	1	U	yes
125	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	3	U	yes
126	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	15	U	yes
127	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	19	U	yes
128	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	20	U	yes
129	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	22	U	yes
130	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	24	U	yes

131	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	25	U	yes
132	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	27	U	yes
133	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	54	U	yes
134	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	68	U	yes
135	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	79	U	yes
136	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	50	U	yes
137	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	63	U	yes
138	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	M	28	N	yes
139	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	F	57	U	no
140	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	F	60	U	no
141	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	M	45	U	yes
142	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	M	46	U	yes
143	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	M		U	no
144	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	M	45	U	no
145	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	F	19	U	no
146	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	M	5	U	no
147	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	M	7	U	no
148	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	M	7	Y	yes
149	*CFH*	c.3674A>T, c.3675_3699del p.(Tyr1225*)	Type 1	-	NA	Yes	M	1	U	no
150	*CFH*	c.3674A>T, c.3675_3699del p.(Tyr1225*)	Type 1	-	NA	Yes	M	1	U	no
151	*CFH*	c.3674A>T, c.3675_3699del p.(Tyr1225*)	Type 1	-	NA	Yes	M	1	U	no
152	*CFH*	c.3674A>T, c.3675_3699del p.(Tyr1225*)	Type 1	-	NA	Yes	M	1	U	no
153	*CFH*	c.3674A>T, c.3675_3699del p.(Tyr1225*)	Type 1	-	NA	Yes	F	1	U	no

154	*CFH*	c.3674A>T, c.3675_3699del p.(Tyr1225*)	Type 1	-	NA	Yes	F	1	U	no
155	*CFH*	c.3674A>T, c.3675_3699del p.(Tyr1225*)	Type 1	-	NA	Yes	F	1	U	no
156	*CFH*	c.3674A>T, c.3675_3699del p.(Tyr1225*)	Type 1	-	NA	Yes	M	1	U	no
157	*CFH*	c.3486del p.(Lys1162Asnfs*7)	Type 1	-	NA	Yes	F		N	yes
158	*CFH*	c.3486del p.(Lys1162Asnfs*7)	Type 1	-	NA	Yes	F		N	yes
159	*CFH*	c.3628C>T p.(Arg1210Cys)	Type 2 (C-terminal)	[10]	0.015	No	F		N	yes
160	*CFH*	c.2425C>T p.(Gln809*)	Type 1	-	NA	No	F	24	N	yes
161	*CFH*	c.3551C>G p.(Thr1184Arg)	Type 2 (C-terminal)	-	NA	No	M	1	Y	no
162	*CFH*	CFH:CFHR1 hybrid	FH hybrid	[19]	NA	No	F	52	Y	yes
163	*CFH*	c.1160-2A>G	Type 1	-	NA	No	F	15	U	yes
164	*CFH*	c.3676C>G p.(Pro1226Ala)	Type 2 (C-terminal)	-	NA	No	F	26	N	yes
165	*CFH*	c.3628C>T p.(Arg1210Cys)	Type 2 (C-terminal)	[10]	0.015	No	F	1	N	yes
166	*CFH*	c.1107G>A; p.(Trp369*)	Type 1	-	NA	No	F	27	U	yes
167	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	No	F	59	U	yes
168	*CFH*	c.3536T>C p.(Ile1179Thr)	Type 1		NA	Yes	F	27	U	yes
169	*CFH*	CFH:CFHR1 hybrid	FH hybrid	[19]	NA	No	F		N	yes
170	*CFH*	CFH:CFHR1 hybrid	FH hybrid	[19]	NA	No	M	21	Y	yes
171	*CFH*	CFH:CFHR1 hybrid	FH hybrid	-	NA	No	F		N	no
172	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	No	M	19	Y	
173	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	No	F	14	U	yes
174	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	No	F	6	Y	yes
175	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	Yes	F	42	U	no
176	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	No	F	41	U	yes
177	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	No	F	55	Y	yes
178	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	No	M	68	Y	no

179	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	No	F	16	Y	yes
180	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	Yes	M	23	U	yes
181	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	Yes	F	14	U	no
182	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	No	M	62	Y	yes
183	*CFI*	c.434G>A p.(Trp145*)	Type 1	-	NA	No	F	32	Y	yes
184	*CFI*	c.859G>A p.(Gly287Arg)	Type 1	[8]	0.0046	No	F	4	N	no
185	*CFI*	c.355G>A p.(Gly119Arg)	Type 1	[41]	0.042	No	F	55	Y	yes
186	*CFI*	CFI gene deletion	Type 1	-	NA	No	M	36	N	yes
187	*CFI*	c.859G>A p.(Gly287Arg)	Type 1	[8]	0.0046	No	F	22	N	yes
188	*CFI*	c.1555G>A p.(Asp519Asn)	Type 2	[42]	NA	No	F	30	U	yes
189	*CFI*	c.1246A>C; p.(Ile416Leu)	Type 1	[8, 43, 44]	0.12	No	F	29	Y	no
190	*CFI*	c.1246A>C; p.(Ile416Leu) Homozygous	Type 1	[8, 43, 44]	0.12	No	M	47	Y	yes
191	*CFI*	c.355G>A p.(Gly119Arg)	Type 1	[41]	0.042	No	F	28	N	no
192	*CFI*	c.1019T>C p.(Ile340Thr)	Type 2	[45]	0.0072	No	F		U	
193	*CFI*	c.893del p.(His298Leufs*18)	Type 1	-	NA	Yes	M	33	Y	yes
194	*CFI*	c.893del p.(His298Leufs*18)	Type 1	-	NA	Yes	F	9	U	yes
195	*CFI*	c.1246A>C; p.(Ile416Leu)	Type 1	[8, 43, 44]	0.12	Yes	F	16	U	no
196	*CFI*	c.1246A>C; p.(Ile416Leu)	Type 1	[8, 43, 44]	0.12	Yes	F	19	U	no
197	*CFI*	c.355G>A p.(Gly119Arg)	Type 1	[41]	0.042	No	F	6	Y	no
198	*CFI*	c.1019C>T p.(Ile340Thr)	Type 2	[45]	0.0072	No	F	61	Y	yes
199	*CFI*	c.1195T>C p.(Trp399Arg)	Type 2	[10]	0.0018	No	M	57	N	yes
200	*CFI*	c.772G>A p.(Ala258Thr)	Type 1	-	0.012	No	M	51	Y	yes
201	*CFI*	c.1246A>C p.(Ile416Leu)	Type 1	[10]	0.12	No	M	41	N	yes
202	*CD46*	c.565T>G p.(Tyr189Asp)	Pathogenic Type 1	[46]	0.0018	No	M	42	U	yes
203	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	M	12	N	no
204	*CD46*	c.470G>A p.(Cys157Tyr)	Pathogenic Type 1	-	NA	Yes	M	3	Y	no
205	*CD46*	c.470G>A p.(Cys157Tyr)	Pathogenic Type 1	-	NA	Yes	M	15	Y	no
206	*CD46*	c.475+1G>A	Pathogenic Type 1	-	0.0004	No	M		U	
207	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	F	26	U	no
208	*CD46*	c.565T>G p.(Tyr189Asp)	Pathogenic Type 1	[46]	0.0018	No	F	8	U	no

209	*CD46*	c.130A>C p.(Met44Leu)	Pathogenic Type 1	-	0.037	No	F	32	U	no
210	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	F	8	Y	no
211	*CD46*	c.287-2A>G	Pathogenic Type 1	[8, 46]	0.0025	No	M	24	Y	no
212	*CD46*	c.175C>T p.(Arg59*)	Pathogenic Type 1	[47]	0.0012	No	M	21	Y	no
213	*CD46*	c.286+2T>G, and c.1007_1015delinsTTTGGA (p.Glu336_Leu339delinsValTrpIle)	Pathogenic Type 1	[46]	0.0052 and NA	No	F	34	N	no
214	*CD46*	c.686G>A p.(Arg229Gln)	Pathogenic Type 1	-	0.0046	No	M	13	U	yes
215	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	F	38	N	no
216	*CD46*	c.191G>T p.(Cys64Phe)	Pathogenic Type 1	[48]	NA	No	M	44	Y	no
217	*CD46*	c.191G>T p.(Cys64Phe)	Pathogenic Type 1	[48]	NA	No	M	16	Y	no
218	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	Yes	M	5	Y	no
219	*CD46*	c.565T>G p.(Tyr189Asp)	Pathogenic Type 1	[46]	0.0018	No	F	8	N	no
220	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	Yes	F	25	Y	no
221	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	Yes	M	25	U	no
222	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	Yes	M	30	Y	yes
223	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	Yes	M	28	U	no
224	*CD46*	c.565T>G p.(Tyr189Asp)	Pathogenic Type 1	[46]	0.0018	Yes	M		U	
225	*CD46*	c.565T>G p.(Tyr189Asp)	Pathogenic Type 1	[46]	0.0018	Yes	M		U	
226	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	F	57	N	yes
227	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	M	37	U	no
228	*CD46*	c.175C>T p.(Arg59*)	Pathogenic Type 1	[47]	0.0012	No	F		Y	
229	*CD46*	c.350A>G p.(Tyr117Cys)	Pathogenic Type 1	-	NA	No	M	27	N	yes
230	*CD46*	c.857-2A>C	Pathogenic Type 1	-	0.00071	No	F	42	N	yes
231	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	M	7	N	no
232	*CD46*	deletion exons 2-3	Pathogenic Type 1	-	NA	No	F	33	Y	no
233	*CD46*	c.351C>G p.(Tyr117*)	Pathogenic Type 1	-	NA	No	F	1	Y	no
234	*CD46*	c.565T>G p.(Tyr189Asp)	Pathogenic Type 1	[46]	0.0018	No	M	15	N	no
235	*CD46*	c.191G>T p.(Cys64Phe)	Pathogenic Type 1	[48]	NA	No	F	6	N	no
236	*CD46*	c.476-1G>A	Pathogenic Type 1	-	NA	No	F	5	FFP	no
237	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	M	13	Y	no
238	*CD46*	c.175C>T p.(Arg59*)	Pathogenic Type 1	[47]	0.0012	No	M	17	N	no
239	*CD46*	c.191G>T p.(Cys64Phe)	Pathogenic Type 1	[48]	NA	Yes	M	25	Y	no
240	*CD46*	c.718T>C p.(Ser240Pro)	Pathogenic Type 2	[50]	0.00071	Yes	M	8	N	no

241	*CD46*	c.718T>C p.(Ser240Pro)	Pathogenic Type 2	[50]	0.00071	Yes	M	15	Y	no
242	*CD46*	c.718T>C p.(Ser240Pro) Homozygous	Pathogenic Type 2	[50]	0.00071	Yes	M	17	FFP	no
243	*CD46*	c.718T>C p.(Ser240Pro) Homozygous	Pathogenic Type 2	[50]	0.00071	Yes	F	9	Y	no
244	*CD46*	c.811_816del p.(Asp271_Ser272del)	Pathogenic Type 1	-	NA	Yes	M	31	U	yes
245	*CD46*	c.811_816del p.(Asp271_Ser272del)	Pathogenic Type 1	-	NA	Yes	M	27	U	yes
246	*CD46*	c.811_816del p.(Asp271_Ser272del)	Pathogenic Type 1	-	NA	Yes	M	35	U	Yes
247	*CD46*	c.287-2A>G	Pathogenic Type 1	[47]	0.0025	No	M	3	Y	no
248	*CD46*	c.475+1G>A Homozygous	Pathogenic Type 1	-	0.0004	No	M	8	N	no
249	*CD46*	c.198del p.(Gly67Aspfs*40)	Pathogenic Type 1	-	NA	No	M	3	Y	no
250	*CD46*	c.736T>A p.(Phe246Ile) Homozygous	Pathogenic Type 1	-	NA	Yes	M	12	U	no
251	*CD46*	c.736T>A p.(Phe246Ile) Homozygous	Pathogenic Type 1	-	NA	Yes	M	15	U	no
252	*CD46*	c.736T>A p.(Phe246Ile) Homozygous	Pathogenic Type 1	-	NA	Yes	M	14	U	no
253	*CD46*	c.736T>A p.(Phe246Ile) Homozygous	Pathogenic Type 1	-	NA	Yes	M	10	U	no
254	*CD46*	c.191G>T p.(Cys64Phe)	Pathogenic Type 1	[48]	NA	No	M	41	Y	no
255	*CD46*	c.191G>T p.(Cys64Phe)	Pathogenic Type 1	[48]	NA	No	F	33	Y	no
256	*CD46*	c.565T>G p.(Tyr189Asp)	Pathogenic Type 1	[46]	0.0018	No	M	26	Y	no
257	*CD46*	c.388G>A p.(Gly130Ser)	Pathogenic Type 1	-	NA	No	F	1	N	no
258	*CD46*	c.191G>T p.(Cys64Phe)	Pathogenic Type 1	-	NA	No	F	11	N	no
259	*CD46*	c.946+24T>G	Pathogenic Type 1	-	0.003	No	F	44	Y	no
260	*CD46*	c.175C>T p.(Arg59*)	Pathogenic Type 1	-	0.0012	No	M	6	U	no
261	*CD46*	c.191G>T p.(Cys64Phe)	Pathogenic Type 1	[48]	NA	Yes	M	26	N	no
262	*CD46*	c.632delG p.(Gly211Valfs*22)	Pathogenic Type 1	-	0.0004	Yes	F	44	N	no
263	*C3*	c.1775G>A p.(Arg592Gln)	Pathogenic	[54]	0.00004[$]	No	F	2	FFP	yes
264	*C3*	c.1775G>T p.(Arg592Leu)	Pathogenic	[54]	NA	No	M	33	Y	yes
265	*C3*	c.193A>C p.(Lys65Gln)	Pathogenic	[55]	0.0048	No	F	24	Y	yes
266	*C3*	c.193A>C p.(Lys65Gln)	Pathogenic	[55]	0.0048	No	M	5	Y	yes
267	*C3*	c.193A>C p.(Lys65Gln)	Pathogenic	[55]	0.0048	No	F	30	Y	yes
268	*C3*	c.193A>C p.(Lys65Gln)	Pathogenic	[55]	0.0048	No	M	62	Y	yes
269	*C3*	c.193A>C p.(Lys65Gln)	Pathogenic	[55]	0.0048	No	F	43	Y	yes

272	*C3*	c.3124C>G p.(Arg1042Gly)	Pathogenic	[56]	NA	No	M	1	U	yes
273	*C3*	c.3343G>A p.(Asp1115Asn)	Pathogenic	[54, 57]	NA	Yes	F	20	Y	yes
274	*C3*	c.3343G>A p.(Asp1115Asn)	Pathogenic	[54, 57]	NA	Yes	F	53	N	yes
276	*C3*	c.463A>C p.(Lys155Gln)	Pathogenic	[58]	0.27	No	M		U	
278	*C3*	c.481C>T p.(Arg161Trp)	Pathogenic	[59]	0.0004	No	M	33	N	yes
279	*C3*	c.485C>G p.(Thr162Arg)	Pathogenic	-	NA	Yes	M	3	FFP	yes
280	*C3*	c.1774C>T p.(Arg592Trp)	Pathogenic	[54]	0.0004	Yes	M	40	U	yes
281	*C3*	c.1774C>T p.(Arg592Trp)	Pathogenic	[54]	0.0004	Yes	F	21	U	yes
282	*C3*	c.1774C>T p.(Arg592Trp)	Pathogenic	[54]	0.0004	Yes	M	1	U	yes
283	*C3*	c.3481C>A p.(Gln1161Lys)	Pathogenic	[54]	NA	No	M	1	N	no
285	*C3*	c.193A>C p.(Lys65Gln)	Pathogenic	[55]	0.0048	No	F	31	U	yes
286	*C3*	c.1775G>A p.(Arg592Gln)	Pathogenic	[54, 60]	0.00004[$]	Yes	F	28	Y	no
287	*C3*	c.1775G>A p.(Arg592Gln)	Pathogenic	[54, 60]	0.00004[$]	Yes	F	3	U	no
289	*C3*	c.1774C>T p.(Arg592Trp)	Pathogenic	[54]	0.0004	No	M	33	N	no
290	*C3*	c.1774C>T p.(Arg592Trp)	Pathogenic	[54]	0.0004	Yes	F	21	U	yes
291	*C3*	c.1774C>T p.(Arg592Trp)	Pathogenic	[54]	0.0004	Yes	F	24	U	yes
292	*C3*	c.193A>C p.(Lys65Gln)	Pathogenic	[55]	0.0048	No	F	60	N	yes
25	*DGKE*	c.463A>G p.(Arg155Gly) and c.1427T>C p.(Leu476Pro) Compound heterozygous	*In silico* analysis	-	0.00041 and NA	Yes	F	2	U	no
293	*DGKE*	c.463A>G p.(Arg155Gly) and c.1427T>C p.(Leu476Pro) Compound heterozygous	*In silico* analysis	-	0.00041 and NA	Yes	F	1	U	no
26	*DGKE*	c.826del p.(Val276Phefs*8) Homozygous	*In silico* analysis	-	NA	Yes	F	1	Y	no
294	*DGKE*	c.826del p.(Val276Phefs*8) Homozygous	*In silico* analysis	-	NA	Yes	M	U	U	no
295	*DGKE*	c.826del p.(Val276Phefs*8) Homozygous	*In silico* analysis	-	NA	Yes	F	U	U	no
296	*DGKE*	c.826del p.(Val276Phefs*8) Homozygous	*In silico* analysis	-	NA	Yes	F	U	U	no
27	*DGKE*	c.1597A>C p.(Thr533Pro) Homozygous	*In silico* analysis	-	0.0012	Yes	M	1	N	yes
28	*DGKE*	c.1A>T p.(Met1Leu) Homozygous	*In silico* analysis	-	NA	No	F	U	U	U
30	*DGKE*	c.393C>G p.(Asn131Lys) and c.465-2A>G Compound heterozygous	*In silico* analysis and RNA studies[β]	[61]	NA	no	F	1	N	no
33	*DGKE*	c.966G>A p.(Trp322*)	*In silico* analysis	[62]	0.0099	No	F	1	N	no

		Homozygous									
34	*DGKE*	c.1647_1650del p.(Thr550Metfs*13) Homozygous		*In silico* analysis	-	NA	No	M	8	N	no
38	*DGKE*	c.966G>A p.(Trp322*) Homozygous		*In silico* analysis	[62]	0.0099	No	M	1	Y	no
39	*DGKE*	c.966G>A p.(Trp322*) and c.465-2A>G Compound heterozygous		*In silico* analysis and RNA studies[β]	[61, 62]	0.0099 and NA	No	F	2	N	no
FHAA		**Copy number**		**FHAA titre at presentation[¤]**	**Refs**	**[#]Population frequency %**	**Family history**	**Sex**	**Age at onset**	**PEX**	**ESRD**
		CFHR1	**CFHR3**								
2	FHAA	0	0	1010	-	-	No	M	11	Y	no
4	FHAA	0	1	1249	-	-	No	F	4	Y	yes
5	FHAA	0	0	573	-	-	No	F	11	Y	yes
6	FHAA	2	2	2017	-	-	No	M	8	Y	yes
10	FHAA	0	1	3432	-	-	No	M	7	Y	no
12	FHAA	0	0	812	-	-	No	F	10	Y	yes
17	FHAA	0	0	2194	-	-	No	M	9	Y	no
18	FHAA	0	0	2130	-	-	No	M	5	Y	no
19	FHAA	2	2	2319	-	-	No	M	10	N	yes
21	FHAA	0	0	971	-	-	No	M	16	Y	no
22	FHAA	2	2	277	-	-	No	F	8	N	yes
23	FHAA	0	0	1350	-	-	No	M	6	Y	no
297	FHAA	0	0	>4000	-	-	No	M	38	N	yes
298	FHAA	0	0	1100	-	-	No	F	7	Y	no
299	FHAA	0	1	664	-	-	No	F	8	N	yes
300	FHAA	0	0	2491	-	-	No	F	22	N	yes
301	FHAA	1	1	470	-	-	No	F	17	Y	no
302	FHAA	1	1	1752	-	-	No	M	42	N	no
303	FHAA	0	0	804	-	-	No	F	14	Y	no
304	FHAA	0	0	465	-	-	No	M	10	U	yes
305	FHAA	1	2	572	-	-	No	M	67	Y	no
306	FHAA	0	0	2109	-	-	No	M	5	Y	no
307	FHAA	1	1	>4000	-	-	No	F	6	N	no
308	FHAA	2	2	3+	-	-	No	M	6	U	yes
309	FHAA	0	0	645	-	-	No	M		N	

310		FHAA	1	1	449	-	-	No	M	64	N	no
311		FHAA	2	2	162	-	-	No	M	24	Y	no
312		FHAA	2	2	600-1199	-	-	No	M	1	Y	yes
313		FHAA	0	0	Low titre	-	-	No	F	16	Y	no
5	314	*CFH*	c.2596+1G>C		Type 1	-	0.0004	No	F	30	Y	yes
		CFI	c.355G>A p.(Gly119Arg)		Type 1	[41]	0.042					
	315	*CFH*	c.3511C>T p.(Arg1171*)		Type 1	-	NA	No	F	1	Y	no
		CD46	c.286+2T>G		Pathogenic Type 1	[46]	0.0052					
	316	*CFH*	CFH:CFHR1 hybrid		FH hybrid	-	NA	Yes	F	U	U	yes
		CD46	c.133dupG p.(Glu45fs)		Pathogenic Type 1	-	NA					
	317	*CFI*	c.772G>A p.(Ala258Thr)		Type 1	[14]	0.012	No	F	17	Y	yes
		FHAA	CFHR1: 2	CFHR3: 2	Titre 622	-	-					

eTable 3: Genetic and clinical data for the eculizumab treated cohort.

Patient Number	C' Gene	Mutation	Pathogenicity	Function Refs	#Population frequency %	Family history	Sex	Age at onset	PEX	ESRD
318	*CFH*	c.3572C>T p.(Ser1191Leu) and c.3590T>C p.(Val1197Ala)	Type 2 (C-terminal)	[19]	NA	Yes	M	31	Y	yes
319	*CFH*	c.2836dupT p.(Ser946fs)	Type 1	-	NA	No	F	23	Y	no
320	*CFH*	c.213G>A p.(Trp71*)	Type 1	-	0.0004	No	F	24	Y	yes
321§	*CFH*	CFH:CFHR3 hybrid	FH Hybrid	[19]	NA	No	M	1	Y	yes
322§	*CFH*	CFH:CFHR1 hybrid	FH hybrid	[19]	NA	No	M	1	Y	no
323	*CFH*	c.1106G>A p.(Trp369*)	Type 1	-	NA	No	F	41	Y	yes
324	*CFH*	c.157C>T p.(Arg53Cys)	Type 2 (N-terminal)	[64]	0.0021	No	F	25	Y	no
325	*CFH*	c.158G>A p.(Arg53His)	Type 2 (N-terminal)	[65]	0.000032α	No	F	37	N	no
326§	*CFH*	c.1933del p.(Thr645Argfs*20)	Type 1	-	NA	No	F	34	Y	no
327	*CFH*	c.2383G>A p.(Gly795Arg) and c.965-1G>A	Type 1	-	NA	No	F	22	Y	yes
328	*CFH*	c.2918G>A p.(Cys973Tyr). Homozygous	Type 1	[3]	NA	Yes	F	1	N	no
329	*CFH*	c.3357C>G p.(Asp1119Glu) and c.3643C>T p.(Arg1215*)	Type 1	-	0.0011 and 0.0004	No	F	2	Y	no
330	*CFH*	c.3570T>G p.(Tyr1190*)	Type 1	-	NA	No	M	34	Y	no
331	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	Yes	F	18	Y	no
332	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	Yes	F	30	Y	no
333§	*CFH*	c.3602G>T p.(Cys1201Phe)	Type 1	-	NA	No	M	33	Y	yes
334	*CFH*	c.3616C>T p.(Arg1206Cys)	Type 2 (C-terminal)	[13]	NA	No	F	25	Y	no
335§	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	M	2	Y	no
336	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	20	Y	no
337	*CFH*	c.3643C>G p.(Arg1215Gly)	Type 2 (C-terminal)	[10]	0.000008*	Yes	F	22	N	no
338§	*CFH*	c.3644G>A p.(Arg1215Gln)	Type 2 (C-terminal)	[10]	0.000008*	No	F	19	Y	no
339	*CFH*	c.619+1G>A	Type 1	-	NA	No	F	25	Y	no
340§	*CFH*	c.942G>A p.(Trp314*)	Type 1	-	NA	No	F	28	U	no
341	*CFH*	CFH::CFHR3 hybrid	FH Hybrid	[19]	NA	Yes	F	20	Y	no
342	*CFH*	c.3628C>T p.(Arg1210Cys)	Type 2 (C-terminal)	[10]	0.015	No	M	24	N	yes
343§	*CFH*	CFH::CFHR3 hybrid	FH Hybrid	[19]	NA	Yes	F	1	Y	no
344¶	*CFH*	c.3691del p.(Arg1231Aspfs*40)	Type 1	-	NA	Yes	M	38	Y	yes
345	*CFH*	c.3691del p.(Arg1231Aspfs*40)	Type 1	-	NA	Yes	F	1	N	no
346	*CFH*	c.415C>T p.(Pro139Ser)	Type 1	-	NA	No	F	30	U	no
347	*CFH*	c.3572C>T p.(Ser1191Leu)	Type 2 (C-terminal)	[10]	NA	No	F	16	Y	no

348	*CFH*	c.3644G>A, p.(Arg1215Gln)	Type 2 (C-terminal)	-	0.000008*	No	F	50	Y	no
349	*CFH*	c.3617G>A p.(Arg1206His)	Type 2 (C-terminal)	[13]	NA	No	M	20	Y	no
350	*CFH*	c.2918G>A p.(Cys973Tyr). Homozygous	Type 1	[3]	NA	Yes	M	2	N	no
351	*CFHR1*	c.869T>C p.(Leu290Ser) and c.887C>T p.(Ala296Val)	CFHR1:CFH hybrid	[39]	NA	Yes	F	25	Y	no
352	*CFI*	c.651del p.(Ala219Glnfs*12)	Type 1	-	NA	No	F	67	Y	no
353	*CFI*	c.1402A>G p.(Ile468Val) and c.1642G>C p.(Glu548Gln)	Type 1	-	0.0032 and 0.082	No	M	4	N	no
354	*CFI*	c.148C>G p.(Pro50Ala)	Type 1	[10]	0.0096	No	F	64	Y	no
355	*CFI*	c.355G>A p.(Gly119Arg) and c.859G>A p.(Gly287Arg)	Type 1	-	0.042 and 0.0046	No	M	48	N	no
356	*CFI*	c.454G>A p.(Val152Met)	Type 1	-	0.0042	No	F	45	Y	no
357	*CFI*	c.1246A>C; p.(Ile416Leu)	Type 1	[8, 43, 44]	0.12	No	F	21	Y	no
358	*CD46*	c.718T>C p.(Ser240Pro)	Pathogenic Type 2	[50]	0.00071	No	M	39	N	yes
359	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	M	18	Y	no
360	*CD46*	c.646T>G p.(Trp216Gly)	Pathogenic Type 1	-	0.0004	Yes	M	27	Y	no
361	*CD46*	c.97+2_97+12del	Pathogenic Type 1	-	NA	No	F	8	N	no
362	*CD46*	c.808T>C p.(Cys270Arg)	Pathogenic Type 1	-	NA	No	F	4	N	no
363	*CD46*	c.97+2_97+12del	Pathogenic Type 1	-	NA	No	M	34	Y	no
364	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	F	20	Y	no
365	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	M	47	Y	no
366§	*CD46*	c.175C>T p.(Arg59*)	Pathogenic Type 1	[47]	0.0012	No	M	31	N	no
367	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	M	26	Y	no
368	*CD46*	c.389+5G>A	Pathogenic Type 1 β	-	NA	No	F	40	Y	no
369	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	M	36	Y	no
370§	*CD46*	c.286+2T>G and 286+2T>C	Pathogenic Type 1	[46]	0.0052	No	F	1	U	no
371§	*CD46*	c.104G>A p.(Cys35Tyr)	Pathogenic Type 1	-	0.0012	No	M	1	N	no
372§	*CD46*	c.390-2A>G	Pathogenic Type 1	-	NA	No	F	27	Y	no
373§	*CD46*	c.646T>G p.(Trp216Gly)	Pathogenic Type 1	-	0.0004	Yes	F	14	N	no
374	*CD46*	c.632delG p.(Gly211Valfs*22)	Pathogenic Type 1	-	0.0004	Yes	F	22	Y	no
375	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	Yes	M	5	Y	no
376§	*CD46*	c.286+2T>G	Pathogenic Type 1	[46]	0.0052	No	F	8	N	no
377	*CD46*	c.776del p.(Gly259Valfs*39)	Pathogenic Type 1	-	NA	No	F	2	U	no
378	*CD46*	c.185A>G p.(Tyr62Cys)	Pathogenic Type 1	-	0.0004	No	F	27	Y	no
379§	*CD46*	c.565T>G; p.(Tyr189Asp)	Pathogenic Type 1	[46]	0.0018	No	M	5	N	no
380	*CD46*	c.175C>T p.(Arg59*)	Pathogenic Type 1	[47]	0.0012	No	F	11	N	no
381	*C3*	c.193A>C p.(Lys65Gln)	Pathogenic	[55]	0.0048	No	F	32	Y	yes

382	*C3*	c.193A>C p.(Lys65Gln)		Pathogenic	[55]	0.0048	No	M	11	N	no
383	*C3*	c.485C>G p.(Thr162Arg)		Pathogenic	-	NA	Yes	F	51	N	yes
384	*C3*	c.3124C>G p.(Arg1042Gly)		Pathogenic	[56]	NA	No	M	1	N	no
385	*C3*	c.3470T>C p.(Ile1157Thr)		Pathogenic	[68]	NA	No	F	2	N	no
386	*C3*	c.193A>C p.(Lys65Gln)		Pathogenic	[55]	0.0048	No	M	26	Y	no
387[§]	*C3*	c.193A>C p.(Lys65Gln)		Pathogenic	[55]	0.0048	No	F	18	U	yes
388	*C3*	c.193A>C p.(Lys65Gln)		Pathogenic	[55]	0.0048	No	F	20	Y	no
389	*C3*	c.3325C>G p.(Leu1109Val) homozygous		Pathogenic[β]	-		No	F	2	Y	no
390	*C3*	c.3124C>G p.(Arg1042Gly)		Pathogenic	[56]	NA	No	F	1	N	no
391	*CFB*	c.967A>C p.(Lys323Gln)		Pathogenic	[69]	NA	No	F	1	N	no
29	*DGKE*	c.1597A>C p.(Thr533Pro) homozygous		*In silico* analysis	-	0.0012	Yes	M	1	U	yes
31	*DGKE*	c.325A>G p.(Lys109Glu) homozygous		*In silico* analysis	[62]	NA	No	F	1	U	no
32	*DGKE*	c.236A>C p.(Gln79Pro) homozygous		*In silico* analysis	-	NA	No	F	1	U	no
35	*DGKE*	c.325A>G p.(Lys109Glu) homozygous		*In silico* analysis	[62]	NA	No	F	1	U	no
36	*DGKE*	c.966G>A p.(Trp322*) and c.1524+2T>C		*In silico* analysis and RNA studies[β]	[61, 62]	0.0099 and NA	No	M	1	Y	no
40	*DGKE*	c.966G>A p.(Trp322*) homozygous		*In silico* analysis	[62]	0.0099	No	F	1	N	no
FHAA		**Copy number**		**FHAA titre at presentation[¤]**	**Refs**	**[#]Population frequency %**	**Family history**	**Sex**	**Age at onset**	**PEX**	**ESRD**
		CFHR1	**CFHR3**								
14	FHAA	0	0	772	-	-	No	M	1	N	no
15	FHAA	0	0	4000	-	-	No	M	3	N	no
20	FHAA	0	1	1594	-	-	No	F	6	N	no
392	FHAA	0	0	>4000	-	-	No	M	5	N	no
393	FHAA	0	1	5120	-	-	No	F	7	N	no
394	FHAA	1	1	9239	-	-	No	M	13	N	no
395	FHAA	0	0	1507	-	-	No	M	8	Y	no
24	FHAA	0	0	3396	-	-	No	M	9	N	no
396	FHAA	0	0	7507	-	-	No	M	69	N	no
397	FHAA	0	1	2+	-	-	No	F	6	N	no
398	FHAA	0	0	1450	-	-	No	F	54	Y	no
Com 399	*CFH*	c.694C>T p.(Arg232*)		Type 1	-	0.0008	No	F	25	N	no
	C3	c.193A>C p.(Lys65Gln)		Pathogenic	[55]	0.0048					

	400	*CFI*	c.355G>A p.(Gly119Arg)	Type 1	[41]	0.042	No	F	28	N	yes
		FHAA	CFHR1: 2 CFHR3: 2	Titre 257	-	-					
	16	*CFI*	c.859G>A p.(Gly287Arg)	Type 1	[8]	0.0046	No	F	8	Y	no
		FHAA	CFHR1: 0 CFHR3: 0	Titre 4000	-	-					
	401§	*CD46*	c.286+2T>G and c.1127+2T>G	Pathogenic Type 1	[46]	0.0052 and NA	No	F	18	N	no
		FHAA	CFHR1: 1 CFHR3: 1	Titre 257	-	-					
	402	*CD46*	c.133dupG p.(Glu45fs)	Pathogenic Type 1	-	NA	Yes	F	2	U	no
		CFH	CFH:CFHR1 hybrid	FH hybrid	-	NA					
403		*CFH*	c.1825G>A p.(Val609Ile)	VUS	-	0.028	No	M	1	N	no
404		*CFH*	c.211T>C p.(Trp71Arg)	VUS	-	NA	No	F	23	Y	no
405		*CFH*	c.2850G>T p.(Gln950His)	VUS	-	0.39	No	M	3	N	no
406		*CFH*	c.3134-5T>C	VUS	-	4.36	No	F	28	U	no
407		*CFH*	c.3264A>C p.(Glu1088Asp)	VUS	-	0.0004	No	M	51	Y	yes
408		*CFH*	c.3568T>C, p.(Tyr1190His)	VUS	-	NA	No	F	1	Y	no
409		*CFH*	c.2500A>C p.(Lys834Gln)	VUS	-	NA	No	F	1	N	no
410		*CFH*	c.1954A>T p.(Ser652Cys)	VUS	-	NA	No	M	19	Y	no
411		*CFI*	c.1534+5G>T	VUS	-	0.87	No	F	48	Y	no
412		*CFI*	c.1534+5G>T	VUS	-	0.87	No	F	73	Y	yes
413		*CFI*	c.1534+5G>T	VUS	-	0.87	No	F	69	Y	no
414		*CD46*	c.472G>C p.(Glu158Gln)	VUS	-	0.0004	No	M	47	Y	yes
415		*CD46*	c.1058C>T p.(Ala353Val)	VUS	-	1.54	No	F	69	Y	yes
416		*CD46*	c.417A>G p.(Leu139=)	VUS	-	0.67	No	F	66	Y	no
417		*CD46*	c.1027+5G>T	VUS	-	NA	No	M	2	N	no
418		*CD46*	c.1148C>T p.(Thr383Ile)	VUS	-	0.074	No	M	42	Y	yes
419		*CFB*	c.1112A>G p.(Asp371Gly)	VUS	-	NA	No	F	24	Y	no
420		*CFB*	c.1697A>C p.(Glu566Ala)	VUS	-	1.07	No	F	10	U	no
421		*C3*	c.3023C>T p.(Ser1008Leu)	VUS	-	0.0036	No	F	3	N	no
422		*C3*	c.3466G>A p.(Asp1156Asn)	VUS	-	NA	No	F	3	Y	no
423		*C3*	c.493G>T p.(Val165Phe)	VUS	-	NA	No	M	34	Y	no
424		*C3*	c.4411C>T p.(Leu1471Phe)	VUS	-	NA	No	M	6	N	no
425		*C3*	c.1618G>T p.(Ala540Ser)	VUS	-	0.0048	No	F	4	N	no
426		*C3*	c.1855G>A p.(Val619Met)	VUS	-	0.031	No	F	22	N	no
427		nmd					No	M		U	
428		nmd					No	M	1	N	no
429		nmd					No	M	26	Y	yes
430		nmd					No	F	1	N	no
431		nmd					No	M	63	N	yes
432		nmd					No	F	77	Y	no

433	nmd					No	F	53	Y	yes
434	nmd					No	F	37	N	no
435	nmd					No	F	24	Y	no
436	nmd					No	M	39	Y	no
437	nmd					No	M	53	Y	no
438	nmd					No	M	1	N	no
439	nmd					No	F	26	Y	no
440	nmd					No	M	40	Y	no
441	nmd					No	F	2	Y	no
442	nmd					No	F	1	N	no
443	nmd					No	F	65	Y	no
444	nmd					No	F	41	N	no
445	nmd					No	F	30	Y	yes
446	nmd					No	M	19	Y	yes
447	nmd					No	M	5	Y	no
448	nmd					No	M	1	N	no
449	nmd					No	F	2	N	no
450	nmd					No	F	19	U	no
451	nmd					No	M	6	N	no
452	nmd					No	F	51	Y	yes
453	nmd					No	M	63	Y	no
454	nmd					No	F	64	N	no
455	nmd					No	M	50	N	yes
456	nmd					No	F	70	Y	no
457	nmd					No	F	26	N	no
458	nmd					No	F	20	Y	no
459	nmd					No	M	16	Y	no
460	nmd					No	F	29	N	no
461	nmd					No	F	33	Y	no
462	nmd					No	F	32	Y	no
463	nmd					No	F	29	Y	no
464	nmd					No	F	56	Y	no
465	nmd					No	M	43	Y	yes
466	nmd					No	M	59	Y	yes
467	nmd					No	M	33	Y	no
468	nmd					No	F	34	Y	no
469	nmd					No	F	29	Y	no
470	nmd					No	M	62	Y	yes
471	nmd					No	F	27	Y	yes

472	nmd					No	F	35	Y	no
473	nmd					No	F	70	Y	no
474	nmd					No	M	31	Y	no
475	nmd					No	F	72	Y	yes
476	nmd					No	F	1	N	no
477	nmd					No	M	61	Y	no
478	nmd					No	M	80	Y	no
479	nmd					No	F	29	N	yes
480	nmd					No	F	28	Y	no
481	nmd					No	M	45	N	yes
482	nmd					No	F	65	Y	no
483	nmd					No	M	48	Y	no
484	nmd					No	M	23	Y	no
485	nmd					No	F	18	Y	no
485	nmd					No	F	23	Y	no
487	nmd					No	M	54	N	no
488	nmd					No	F	62	Y	no
489	nmd					No	M	47	Y	yes
490	nmd					No	M	34	Y	yes
491	nmd					No	M	1	Y	no
492	nmd					No	M	67	N	yes
493	nmd					No	F	33	Y	no
494	nmd					No	F	30	U	yes
495	nmd					No	F	1	N	no
496	nmd					No	F	2	N	yes
497	nmd					No	F	30	Y	no
498	nmd					No	M	29	N	yes
499	nmd					No	F	68	N	
500	nmd					No	F	2	N	no
501	nmd					No	F	55	Y	no
502	nmd					No	M	40	N	no
503	nmd					No	F	2	U	no
504	nmd					No	M	1	N	no
Patient Number	**C' Gene**	**Ultimate diagnosis**		**Gene**		**Family history**	**Sex**	**Age at onset**	**PEX**	**ESRD**
505	nmd	Renal biopsy showed severe chronic damage, no TMA				No	M	13	N	yes
506	nmd	Post-partum haemorrhage				No	F	29	N	
507	nmd	Renal biopsy consistent with chronic glomerulonephritis				No	M	34	Y	yes
508	nmd	FSGS		*ACTN4*		No	F	17	N	yes

509	nmd	Fungal septicaemia and DIC		No	F	37	Y	no
510	nmd	4H leukodystrophy	*POLR3B*	No	M	1	Y	no
511	nmd	STEC-HUS		No	F	1	N	no
512	nmd	STEC-HUS		No	M	10	Y	no
513	nmd	STEC-HUS		No	M	46	Y	no
514	nmd	Scleroderma		No	F	73	Y	
515	nmd	STEC-HUS		No	F	76	Y	
516	nmd	Scleroderma		No	F	37	Y	yes
517	nmd	Severe pancreatitis and multi-organ failure		No	F	15	Y	yes
518	nmd	Pneumococcal HUS		No	F	2	U	no
519	nmd	Nail patella syndrome	*LMX1B*	No	M	1	FFP	no
520	nmd	G6PD deficiency	*G6PD*	No	M	3	Y	no
521	nmd	Drug mediated TMA		No	M	38	N	no
522	nmd	Scleroderma		No	M	45	N	yes
523	nmd	Renal biopsy showed ATN		No	F	54	Y	no
524	nmd	Post-partum haemorrhage		No	F	42	Y	no
525	nmd	Disorder of cobalamin metabolism TMA	*MMACHC*	No	M	5	N	no
526	nmd	Other genetic TMA	*EXOSC3*	No	F	1	N	no
527	nmd	Other genetic TMA	*EXOSC3*	No	M	1	N	no
528	nmd	Disorder of cobalamin metabolism TMA	*MTR*	No	M	2	N	no
529	nmd	STEC-HUS		No	F	11	N	no
530	nmd	Paroxysmal nocturnal haemoglobinuria		No	F	32	N	no
531	nmd	STEC-HUS		No	F	68	N	no
532	nmd	Lupus with autoimmune haemolysis		No	F	19	N	
533	nmd	Primary hyperoxaluria	*AGXT*	No	M	1	N	yes
534	nmd	IgA nephropathy on biopsy		No	M	27	Y	yes
535	nmd	Sepsis		No	F	1	N	no
536	nmd	STEC-HUS		No	M	1	N	no
537	nmd	STEC-HUS		No	M	15	Y	no
538	nmd	STEC-HUS		No	M	17	Y	no
539	nmd	STEC-HUS		No	F	11	N	yes
540	nmd	STEC-HUS		No	M	62	N	no
541	nmd	Drug mediated TMA		No	M	36	Y	no
542	nmd	Sepsis		No	F	44	Y	no
543	nmd	Primary FSGS	*NPHS2*	No	F	29	Y	no
544	nmd	No TMA on renal biopsy		No	M	62	Y	no
545	nmd	Malignant hypertension (renal artery stenosis)		No	F	1	N	no
546	nmd	Died before definitive diagnosis made		No	F	1	N	no
547	nmd	Dihydrofolate reductase deficiency	*DHFR*	No	M	1	N	no

548	nmd	Other genetic TMA	*INF2*	Yes	F	15	Y	yes
549	nmd	Apparent mineralocorticoid excess	*HSD11B2*	No	M	8	N	no

Abbreviations: DIC, disseminated intravascular coagulation; ESRD, end stage renal disease; FFP, fresh frozen plasma; FSGS, focal segmental glomerulosclerosis; G6PD, glucose-6-phosphate dehydrogenase; HUS, haemolytic uraemic syndrome; N, no; NA, not available; nmd, no mutation detected; PEX, plasma exchange; Refs, references – evidence of pathogenicity; STEC-HUS, shiga toxin-producing *E. coli* haemolytic uraemic syndrome; TMA, thrombotic microangiopathy; U, unknown; Y, yes.

*Pathogenicity: Type 1 mutations result in low serum levels.

[¤]Where the consensus assay was performed a titre is given; if the test preceded the availability of the consensus assay then the titre was not quantifiable.

[§]These individuals in the treated cohort did not receive eculizumab at their first presentation and so were handled differently in the survival analysis

[#]Population frequency refers to that reported for each variant in the gnomAD database (all), other than: * refers to the EXaC database, [$] refers to the PAGE_STUDY, and [α] refers to TOPMED; NA = population frequency not available.

[β]In-house functional or RNA studies

[¶]This individual received ravulizumab in the ALXN1210 clinical trial

For the individuals shaded in yellow there is no survival data available

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eTable 4: Outcome data for the eculizumab treated cohort.

Patient number	C' gene	At presentation	Follow up (years)	ESKD	Death*	Stopped eculizumab	Reason for stopping eculizumab
318	*CFH*	Adult	0.0	yes	no	Yes	Non recovery of renal function
319	*CFH*	Adult	4.6	no	no	Yes	SETS
320	*CFH*	Adult	1.1	yes	yes	Yes	Non adherence
321§	*CFH*	Child	13.3	yes	no	No	
322§	*CFH*	Child	12.9	no	no	No	
323	*CFH*	Adult	8.0	yes	no	Yes	Clinician decision
324	*CFH*	Adult	4.0	no	no	No	
325	*CFH*	Adult	4.8	no	no	Yes	Clinician decision
326§	*CFH*	Adult	6.9	no	no	No	
327	*CFH*	Adult	4.3	yes	no	Yes	Non recovery of renal function
328	*CFH*	Child	7.3	no	no	No	
329	*CFH*	Child	9.3	no	no	No	
330	*CFH*	Adult	3.2	no	no	Yes	SETS
331	*CFH*	Adult	3.6	no	no	No	
332	*CFH*	Adult	7.6	no	no	No	
333§	*CFH*	Adult	4.1	yes	no	Yes	Non recovery of renal function
334	*CFH*	Adult	3.5	no	no	No	
335§	*CFH*	Child	6.9	no	no	Yes	SETS
336	*CFH*	Adult	6.6	no	no	No	
337	*CFH*	Adult	5.2	no	no	No	
338§	*CFH*	Adult	14.5	no	no	No	
339	*CFH*	Adult	9.0	no	no	No	
340§	*CFH*	Adult	8.4	no	no	No	
341	*CFH*	Adult	3.1	no	no	No	
342	*CFH*	Adult	1.7	yes	no	Yes	Non recovery of renal function
343§	*CFH*	Child	12.3	no	no	No	
344¶	*CFH*	Adult	3.2	yes	no	No	
345	*CFH*	Child	2.4	no	no	No	
346	*CFH*	Adult	4.5	no	no	No	
347	*CFH*	Child	1.6	no	no	No	
348	*CFH*	Adult	2.2	no	no	No	
349	*CFH*	Adult	4.0	no	no	Yes	Clinician decision

350	*CFH*	Child	1.4	no	no	No	
351	*CFHR1:CFH*	Adult	2.6	no	no	No	
352	*CFI*	Adult	0.0	no	yes	no	
353	*CFI*	Child	5.1	no	no	Yes	Family preference
354	*CFI*	Adult	9.2	no	no	No	
355	*CFI*	Adult	3.3	no	no	No	
356	*CFI*	Adult	7.7	no	no	No	
357	*CFI*	Adult	1.7	no	no	No	
358	*CD46*	Adult	5.7	yes	no	Yes	After transplantation
359	*CD46*	Adult	5.2	no	no	No	
360	*CD46*	Adult	4.5	no	no	No	
361	*CD46*	Child	5.1	no	no	Yes	SETS
362	*CD46*	Child	4.4	no	no	Yes	SETS
363	*CD46*	Adult	3.9	no	no	Yes	SETS
364	*CD46*	Adult	4.0	no	no	Yes	Clinician decision
365	*CD46*	Adult	3.7	no	no	No	
366§	*CD46*	Adult	3.6	no	no	Yes	Clinician decision
367	*CD46*	Adult	3.5	no	no	Yes	Side effects
368	*CD46*	Adult	3.4	no	no	Yes	Clinician decision
369	*CD46*	Adult	7.0	no	no	No	
370§	*CD46*	Child	34.0	no	no	Yes	Clinical decision
371§	*CD46*	Child	4.4	no	no	Yes	Influenza
372§	*CD46*	Adult	11.9	no	no	No	
373§	*CD46*	Child	15.1	no	no	Yes	No haematological response
374	*CD46*	Adult	1.5	no	no	No	
375	*CD46*	Child	7.1	no	no	Yes	Clinician decision
376§	*CD46*	Child	2.5	no	no	No	
377	*CD46*	Child	5.9	no	no	No	
378	*CD46*	Adult	1.7	no	no	No	
379§	*CD46*	child	4.3	no	no	Yes	Unknown
380	*CD46*	Child	2.8	no	no	Yes	Clinician decision
381	*C3*	Adult	6.6	yes	no	Yes	
382	*C3*	Child	4.9	no	no	No	
383	*C3*	Adult	7.2	yes	no	Yes	Non recovery of renal function
384	*C3*	Child	5.6	no	no	No	
385	*C3*	Child	4.9	no	no	Yes	SETS
386	*C3*	Adult	2.4	no	no	No	
387§	*C3*	Adult	16.8	yes	no	No	

388		*C3*	Adult	1.0	no	no	No	
389		*C3*	Child	9.1	no	no	Yes	SETS
390		*C3*	Child	1.4	no	no	No	
391		*CFB*	Child	8.3	no	no	No	
29		*DGKE*	Child	26.1	yes	no	Yes	DGKE
31		*DGKE*	Child	15.3	no	no	No	
32		*DGKE*	Child	14.3	no	no	Yes	DGKE
35		*DGKE*	Child	11.3	no	no	No	
36		*DGKE*	Child	10.5	no	no	Yes	DGKE
40		*DGKE*	Child	2.4	no	no	Yes	DGKE
14		FHAA	Child	6.5	no	no	No	
15		FHAA	Child	6.3	no	no	Yes	SETS
20		FHAA	Child	8.5	no	no	No	
392		FHAA	Child	1.7	no	no	Yes	SETS
393		FHAA	Child	2.5	no	no	No	
394		FHAA	Child	2.0	no	no	Yes	SETS
395		FHAA	Child	5.5	no	no	No	
24		FHAA	Child	5.2	no	no	Yes	SETS
396		FHAA	Adult	1.5	no	no	No	
397		FHAA	Child	1.2	no	no	No	
398		FHAA	Adult	1.2	no	no	No	
Combined	399	*CFH* *C3*	Adult	6.7	no	no	No	
	400	*CFI* FHAA	Adult	5.7	yes	no	Yes	Non recovery of renal function
	16	*CFI* FHAA	Child	10.2	no	no	No	
	401 §	*CD46* FHAA	Adult	3.3	no	no	No	
	402	*CD46* *CFH*	Child	1.0	no	no	No	
403		VUS	Child	6.3	no	no	No	
404		VUS	Adult	6.1	no	no	No	
405		VUS	Child	9.4	no	no	No	
406		VUS	Adult	13.4	no	no	Yes	Clinician decision
407		VUS	Adult	5.8	yes	no	Yes	Non recovery of renal function
408		VUS	Child	9.6	no	no	No	
409		VUS	Child	2.6	no	no	Yes	SETS

410	VUS	Adult	1.8	no	no	No	
411	VUS	Adult	6.5	no	no	Yes	Clinician decision
412	VUS	Adult	4.1	yes	yes	Yes	Non recovery of renal function
413	VUS	Adult	6.4	no	yes	Yes	Clinician decision
414	VUS	Adult	3.5	yes	no	No	
415	VUS	Adult	1.3	yes	yes	Yes	Non recovery of renal function
416	VUS	Adult	6.7	no	no	Yes	Clinician decision
417	VUS	Child	8.6	no	no	Yes	Clinician decision
418	VUS	Adult	2.5	yes	no	Yes	Moved overseas
419	VUS	Adult	8.1	no	no	Yes	Clinician decision
420	VUS	Child	7.8	no	no	Yes;	Unknown
421	VUS	Child	4.1	no	no	No	
422	VUS	Child	8.5	no	no	No	
423	VUS	Adult	6.2	no	no	No	
424	VUS	Child	2.7	no	no	No	
425	VUS	Child	3.3	no	no	No	
426	VUS	Adult	2.4	no	no	Yes	Clinician decision
427	nmd	Adult	118.9			Unknown	
428	nmd	Child	0.0	no	yes	No	
429	nmd	Adult	3.6	yes	no	Yes	Non recovery of renal function
430	nmd	Child	6.6	no	no	No	
431	nmd	Adult	0.8	yes	yes	Yes	Non recovery of renal function
432	nmd	Adult	1.1	no	no	No	
433	nmd	Adult	0.6	yes	yes	Yes	Non recovery of renal function
434	nmd	Adult	1.4	no	no	No	
435	nmd	Adult	1.5	no	no	Yes	Clinician decision
436	nmd	Adult	2.6	no	no	No	
437	nmd	Adult	7.0	no	no	Yes	SETS
438	nmd	Child	2.7	no	no	No	
439	nmd	Adult	2.8	no	no	Yes	Clinician decision
440	nmd	Adult	1.1	no	no	No	
441	nmd	Child	1.0	no	no	Yes	Portacath infection
442	nmd	Child	8.6	no	no	Yes	Patient choice
443	nmd	Adult	8.4	no	no	No	
444	nmd	Adult	2.0	no	no	No	
445	nmd	Adult	6.2	yes	no	No	
446	nmd	Adult	7.1	yes	no	Yes	Non recovery of renal function
447	nmd	Child	8.2	no	no	Yes	Clinician decision
448	nmd	Child	6.7	no	no	Yes	Family preference

449	nmd	Child	6.6	no	no	Yes	Clinician decision
450	nmd	Adult	6.2	no	no	Yes	Meningococcal sepsis
451	nmd	Child	0.0	no	yes	Yes	
452	nmd	Adult	6.2	yes	no	Yes	Non recovery of renal function
453	nmd	Adult	6.0	no	no	No	
454	nmd	Adult	6.0	no	no	Yes	Non recovery of renal function
455	nmd	Adult	0.2	yes	yes	No	
456	nmd	Adult	5.9	no	no	No	
457	nmd	Adult	5.7	no	no	No	
458	nmd	Adult	5.7	no	no	Yes	Patient choice
459	nmd	Child	4.8	no	no	Yes	Clinician decision
460	nmd	Adult	4.6	no	no	Yes	No haematological response
461	nmd	Adult	4.5	no	no	No	
462	nmd	Adult	4.4	no	no	No	
463	nmd	Adult	4.3	no	no	Yes	Patient choice
464	nmd	Adult	0.8	no	yes	No	
465	nmd	Adult	4.2	yes	no	Yes	Non recovery of renal function
466	nmd	Adult	4.2	yes	no	Yes	Non recovery of renal function
467	nmd	Adult	4.1	no	no	No	
468	nmd	Adult	3.9	no	no	Yes	Clinician decision
469	nmd	Adult	3.6	no	no	Yes;	Clinician decision
470	nmd	Adult	3.6	yes	no	Yes	Non recovery of renal function
471	nmd	Adult	3.5	yes	no	Yes	Non recovery of renal function
472	nmd	Adult	3.5	no	no	Yes	Clinician decision
473	nmd	Adult	3.4	no	no	No	
474	nmd	Adult	0.8	no	yes	Yes	Sepsis
475	nmd	Adult	0.8	yes	yes	Yes	Non recovery of renal function
476	nmd	Child	4.3	no	no	No	
477	nmd	Adult	3.2	no	no	Yes	Patient choice
478	nmd	Adult	0.1	no	yes	No	
479	nmd	Adult	1.1	yes	yes	Yes	Non adherence
480	nmd	Adult	3.1	no	no	No	
481	nmd	Adult	3.0	yes	no	Yes	Non recovery of renal function
482	nmd	Adult	3.0	no	no	No	
483	nmd	Adult	4.4	no	no	Yes	Clinician decision
484[§]	nmd	Adult	2.9	no	no	Yes	SETS
485	nmd	Adult	2.9	no	no	Yes	Clinician decision
485	nmd	Adult	2.8	no	no	No	
487	nmd	Adult	2.8	no	no	Yes	Clinician decision

488	nmd	Adult	2.7	no	no	No	
489	nmd	Adult	2.5	yes	no	Yes	Clinician decision
490	nmd	Adult	2.5	yes	no	Yes	Non recovery of renal function
491	nmd	Child	2.5	no	no	Yes	SETS
492	nmd	Adult	0.5	yes	yes	Yes	Recurrent infections
493	nmd	Adult	2.4	no	no	No	
494	nmd	Adult	2.1	yes	no	Yes	Non recovery of renal function
495	nmd	Child	2.1	no	no	No	
496	nmd	Child	2.1	yes	no	Yes	Non recovery of renal function
497	nmd	Adult	2.0	no	no	Yes	Patient choice
498	nmd	Adult	2.0	yes	no	Yes	Moved overseas
499	nmd	Adult	2.0			Unknown	
500	nmd	Child	1.5	no	no	No	
501	nmd	Adult	1.4	no	no	No	
502	nmd	Adult	1.4	no	no	Yes	Clinician decision
503	nmd	Child	7.8	no	no	No	
504	nmd	Child	6.7	no	no	Yes	No haematological response
505	Not CaHUS	Child	4.2	yes	no	Yes	Other diagnosis
506	Not CaHUS	Adult	2.4	no	no	Yes	Non recovery of renal function
507	Not CaHUS	Adult	5.8	yes	no	Yes	Non recovery of renal function
508	Not CaHUS	Child	1.8	yes	no	Yes	Non response
509	Not CaHUS	Adult	5.0	no	no	Yes	Sepsis
510	Not CaHUS	Child	4.9	no	yes	Yes	Other genetic TMA
511§	Not CaHUS	Child	2.9	no	no	Yes	STEC
512	Not CaHUS	Child	5.6	no	no	Yes	STEC
513	Not CaHUS	Adult	4.4	no	no	Yes	STEC
514	Not CaHUS	Adult	5.1			Yes	Scleroderma
515	Not CaHUS	Adult	5.8			Yes	STEC
516	Not CaHUS	Adult	5.7	yes	U	Yes	Scleroderma
517	Not CaHUS	Child	6.0	yes	no	Yes	Non recovery of renal function
518	Not CaHUS	Child	8.1	no	no	Yes	Other diagnosis
519	Not CaHUS	Child	7.3	no	no	Yes	Other genetic TMA
520	Not CaHUS	Child	7.3	no	no	Yes	Other genetic TMA
521	Not CaHUS	Adult	1.0	no	no	Yes	Drug associated TMA
522	Not CaHUS	Adult	1.2	yes	no	Yes	Scleroderma
523	Not CaHUS	Adult	1.2	no	no	Yes	No TMA on biopsy
524	Not CaHUS	Adult	1.1	no	no	Yes	PPH
525	Not CaHUS	Child	6.0	no	no	Yes	Other genetic TMA
526	Not CaHUS	Child	0.5	no	yes	Yes	Other genetic TMA

527	Not CaHUS	Child	0.1	no	yes	Yes	Other genetic TMA
528	Not CaHUS	Child	2.0	no	no	Yes	Other genetic TMA
529	Not CaHUS	Child	2.0	no	no	Yes	STEC
530	Not CaHUS	Adult	2.3	no	no	No	
531	Not CaHUS	Adult	2.1	no	no	Yes	STEC
532	Not CaHUS	Adult	2.2			Yes	Non response
533	Not CaHUS	Child	3.0	yes	no	Yes	Other diagnosis
534	Not CaHUS	Adult	3.0	yes	no	Yes	Other glomerular disease diagnosis
535	Not CaHUS	Child	3.0	no	no	Yes	Sepsis
536	Not CaHUS	Child	3.1	no	no	Yes	STEC
537	Not CaHUS	Child	3.6	no	no	Yes	STEC
538	Not CaHUS	Child	3.8	no	no	Yes	STEC
539	Not CaHUS	Child	4.0	yes	no	Yes	STEC
540	Not CaHUS	Adult	3.9	no	no	Yes	STEC
541	Not CaHUS	Adult	4.5	no	no	Yes	Drug associated TMA
542	Not CaHUS	Adult	3.1	no	no	Yes	Sepsis
543	Not CaHUS	Adult	1.6	no	no	Yes	Other glomerular disease diagnosis
544	Not CaHUS	Adult	1.5	no	no	Yes	No TMA on biopsy
545	Not CaHUS	Child	1.8	no	no	Yes	Other diagnosis
546	Not CaHUS	Child	2.9	no	yes	Yes	Non response
547	Not CaHUS	Child	0.1	no	yes	No	
548	Not CaHUS	Child	7.5	yes	no	Yes	Other genetic TMA
549	Not CaHUS	Child	6.2	no	no	Yes	Other diagnosis

Abbreviations: ACR, albumin creatinine ratio; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HUS, haemolytic uraemic syndrome; nmd, no mutation detected; PCR, protein creatinine ratio; PPH, post-partum haemorrhage; SETS, Stopping Eculizumab Treatment Safely in aHUS clinical trial; STEC-HUS, shiga toxin-producing *E. coli* haemolytic uraemic syndrome; TMA, thrombotic microangiopathy.

*Causes of death detailed in eTable 5.

eTable 5: Causes of death

Patient number	Gene	ESKD	Cause of death
320	*CFH*	Y	Non adherence
352	*CFHR1:CFH*	N	Cardiac arrest
412	VUS	Y	Unknown
413	VUS	N	Unknown
415	VUS	Y	Sepsis
428	nmd	N	Multi-organ failure
431	nmd	Y	Sepsis
433	nmd	Y	Unknown
451	nmd	N	Cerebral microangiopathic thrombosis
455	nmd	Y	Intracranial haemorrhage
464	nmd	N	Sepsis
474	nmd	N	Pulmonary embolism
475	nmd	Y	Unknown
478	nmd	N	Unknown
479	nmd	Y	Non adherence
492	nmd	Y	Unknown
510	Not CaHUS	N	Other genetic TMA, multi system disease
526	Not CaHUS	N	Other genetic TMA, multi system disease
527	Not CaHUS	N	Other genetic TMA, multi system disease
546	Not CaHUS	N	Unknown
547	Not CaHUS	N	Multi organ failure

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