Supplemental Material

Supplemental Methods

Supplemental Methods 1

Kidney parameters (i.e proteinuria, estimated glomerular filtration rate (eGFR), nephrotic syndrome, hematuria) were assessed at first clinical evaluation and at last follow up and were retrospectively collected. Nephrotic range proteinuria and nephrotic syndrome were defined using KDIGO criteria(1). The staging of chronic kidney disease was based on the international KDIGO(2) definition. Biological stigmata of thrombotic microangiopathy (TMA) was defined by the association of mechanical hemolytic anemia (hemoglobin <10 g/dl, lactate dehydrogenase level >upper limit of normal, undetectable haptoglobin, and the presence of schistocytes on a blood smear), with thrombocytopenia (platelet count <150 G/L).

Supplemental Methods 2

For complement assessment, blood was drawn into tubes with the anticoagulant ethylenediaminetetraacetic acid. Plasma protein concentrations of C3, C4 were measured by nephelometry (Dade Behring, Deerfield, IL, USA). Soluble C5b-9 level was determined using the MicroVue sC5b-9 Plus EIA Assay (Quidel, San Diego, CA), according to manufacturer instructions. The ELISA method was used to detect anti-Factor H antibodies as previously described(3). C3NeF activity was determined by assessing the ability of purified plasma IgG to stabilize the membrane-bound C3bBb convertase in an hemolytic assay as previously described(4).

The crystal structure of C3b was obtained from the Protein Data Bank. Molecular graphic imaging of C3b with amino-acid changes were produced using a Pymol (http://www.pymol.org/) and UCSF Chimera package ((http:// www.cgl.ucsf.edu/chimera). For this study, the numbering was made according to the mature protein sequence (without the 22-amino acid long leader peptide).

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Supplemental Tables

Supplemental Table 1: Description of the 30 *CFH* rare variants identified in 38 patients with C3 glomerulopathy or Ig-MPGN

Nbr of cases	Variant	Transcript	Status	CCP Domain	Allele frequency (%)	CADD score	In vitro functional characterization [a]		FH quantification	Classification (This report)
								Variant implicating a Cysteine residue		
2 (Fam)	p.Arg53Cys °	c.157C>T	Ho/He	1	0.004	24.6	Impaired decay accelerating activity and FI cofactor activity		Normal	Pathogenic
1	p.Val72Glyfs*3	c.215_216del	He	1	novel		no		Normal [d]	Pathogenic
1	p.Leu77Stop °	c.230delT	He	1	novel		no		Low FH plasma level	Pathogenic
2 (Fam)	p.Gly94Arg	c.280G>C	He	2	novel	24,6	no		Low FH plasma level	Pathogenic
1	p.Gly122_Glu128del fs * °	c.364_383del (21nt)	He	2	novel		no		Normal [d]	Pathogenic
2	p.Asp130Asn °	c.388G>A	He	2	0.03	22.6	Minor defects in complement regulation (debatable functional deficiency)		Normal	VUS
1	p.Cys141Arg	c.421T>C	He	2	novel	27.1	no	Loss of a conserved cysteine;	Low FH plasma level	Pathogenic
1	p.Val143Ile °	c.427G>A	He	2	novel	25	no		Low FH plasma level	Pathogenic
3	p.Ala161Ser °	c.481G>T	He	3	0.006	12.1	No/small perturbed the regulatory activity of FH (debatable functional deficiency)		Normal	VUS
1	p.Arg232Stop °	c.694C>T	He	4	0.0009	34	no		Low FH plasma level	Pathogenic
1	p.Arg303Trp	c.907C>T	He	5	0.008	18.5	no		Normal	VUS
1	p.Cys431Arg	c.1291T>C	He	7	novel	23,8	no	Loss of a conserved cysteine	Low FH plasma level	Pathogenic
3 (Fam)[b]	p.Cys431Ser °	c.1291T>A	Ho	7	0.0004	23.8	no	Loss of a conserved cysteine;	Low FH plasma level	Pathogenic
1	p.Trp436Stop	c.1307G>A	He	7	novel	37	no		Low FH plasma level	Pathogenic
1	p.Arg444Cys	c.1330C>T	He	7	0.002	22.9	no		Normal	VUS

1	p.Gly498Stop	c.1492G>T	He	8	novel	37	no		Low FH plasma level	Pathogenic
1	p.Cys536Arg	c.1606T>C	Het	9	novel	24.3	no	Loss of a conserved cysteine;	Low FH plasma level	Pathogenic
1	p.Cys597Arg °	c.1789T>C	Ho	10	novel	25.1	no	Loss of a conserved cysteine;	Low FH plasma level	Pathogenic
1	p.Cys673Ser °	c.2018G>C	Ho	11	novel	26	no	Loss of a conserved cysteine;	Low FH plasma level	Pathogenic
1	p.Cys673Arg	c.2017T>C	He	11	novel	26	no	Loss of a conserved cysteine;	Low FH plasma level	Pathogenic
1	p.Val686Met	c.2056 G>A	He	11	novel	34	no		Low FH plasma level [c]	Pathogenic
2 (Fam)	p.Phe717Leu °	c.2151C>A	He	12	0.0009	13.7	no		Normal	VUS
1	IVS 15+5	c.2413+5G>A	He	splice site	novel	18.8	no		Low FH plasma level	Pathogenic
1	p.Tyr843Asp	c.2527T>G	He	14	novel	22.7	no		Normal	VUS
1	p.Gln872Stop	c.2614 C>T	He	15	novel	41	no		Low FH plasma level	Pathogenic
1	p.Gly879Arg	c.2635G>A	He	15	0.0009	25.6	no		Low FH plasma level	Pathogenic
1	p.Gly962ValfsTer13	c.2882delA	He	16	novel		no		Low FH plasma level	Pathogenic
1	p.Cys1043Ser °	c.3138G>C	He	17	novel	26.2	no	Loss of a conserved cysteine;	Low FH plasma level	Pathogenic
1	p.Arg1210Cys °	c.3628C>T	He	20	0.03	2.9	Impaired C3b binding		Normal	Pathogenic
1	p.ter 1232 IlefsTer38	c3691-3694del	He	20	novel		no		Low FH plasma level	Pathogenic

Note: Alle Frequency are given from GnomAD data base and according to ethnicity of patient

Abbreviations: Het: Heterozygous; Hom: homozygous; VUS: variants of undetermined significance, Fam, familial form, FH, factor H

[a]Functional studies reported by Wong et al and Merinero et al. ; [b] One of the three patient carried an homozygous pathogenic *CFH* variant (p.Cys431Ser) and a C3 VUS (p.Ala257Thr) and was included in the group of patients with *CFH* variant ; [c] this variant was classified benign by Merinero et al but the patient carrying this variant in our study had very low FH plasma level [d] Prediction with strong evidence of pathogenicity but normal FH plasma level. ° Cases already reported in Servais et al

Supplemental Table 2: Description of the 13 *CFI* rare variants identified in 17 patients with C3 glomerulopathy or Ig-MPGN

Nbr of cases	Variant[a]	Transcript	Allele frequency (%)	CADD score	In vitro functional characterization [b]	FI quantification	Classification (This report)
2 [c]	p.Pro50Ala*	c.148 C>G	0.01	24.8	No/small reduced expression compared to wt (debatable quantitative deficiency)	Low FI plasma level	Pathogenic
1	p.Gly119Arg °	c.355G>A	0.09	21	Significantly reduced expression compared to WT	Low FI plasma level	Pathogenic
2	p.Asn151Ser	c.452 A>G	0.002	25.5	Significantly reduced expression compared to WT	Normal	Pathogenic
1 [c]	p.Ala210Ser	c.628G>T	novel	24.4	no	Low FI plasma level	Pathogenic
1	p.Ala240Gly °	c.719 C>G	0.009	23.9	Significantly reduced expression compared to WT	Normal	Pathogenic
1	p.Val282Leu	c.844G>C	novel	7.6	no	Normal FI level	VUS
1[d]	p.Ile306Val**	c.916A>G	0.05	10.18	Comparable to Wt	Normal	VUS
1	p.Cys327Arg °	c.979T>C	0.0004	24.5	Significantly reduced expression compared to WT	Low FI plasma level	Pathogenic
3	p.Ile357Met	c.1071 T>G	0.005	23.5	Significantly reduced expression compared to WT	Low FI plasma level	Pathogenic
1	p.Arg406Cys	c. 1216 C>T	0.002	13.8	Significantly reduced expression compared to WT	Normal	Pathogenic
2	p.Ile416Leu*** °	c.1246 A>C	0.02	18.7	Significantly reduced expression compared to WT	Low FI plasma level	Pathogenic
1	p.Arg474Stop	c.1420C>T	0.006	40	Significantly reduced expression compared to WT	Low FI plasma level	Pathogenic
1	p.Ter584GlnextTer24	c.1750T>C	novel		no	Low FI plasma level	Pathogenic

Note: Alle Frequency are given from GnomAD data base and according to ethnicity of patient
Abbreviation: VUS: variants of undetermined significance. FI, factor I
[a] All reported variant are heterozygous [b] Summary of the functional studies reported by de Jong et al; [c] The patient carried two rare variants in CFI (p.Pro50Ala and p.Ala210Ser); [d] The patient carried a pathogenic variant in C3 (p.Asn1179Thr) and a CFI VUS (p.Ile306Val) and was included in the group of patients with C3 variants . * The variant p.Pro50Ala was classified as pathogenic despite conflicting results of functional studies.** The allele frequency for p.Ile306Val in African population is 0.5%; *** The allele frequency for p.Ile416Leu in African population is 1.2%.
° Cases already reported in Servais et al

Supplemental Table 3: Description of the 10 *C3* rare variants identified in 13 patients with C3-glomerulopathy or Ig-MPGN

number of cases	variant [a]	Transcript	Domain	Allele frequency, % (gnomAD)	CADD score	In vitro functional characterization[b]	Location on functional site of C3 molecule	Variant Classification (this report)
1	p.Gln216Pro	c.647A>C	MG2	novel	16.08	no		VUS
1 [c]	p.Ala257Thr	c.769G>A	MG3	0.009	25.9	no		VUS
1	p.Thr426lys	c.1277 C>A	MG4	novel	24.3	no		VUS
1	p.Gly590Ala	c.1769G>C	MG6 beta	0.0008	23.4	no		VUS
2	p.Gly637Arg	c.1909 G>C	LNK	0.03	21.9	no		VUS
2 (fam)	p. Ile756Thr	c.2327T.C	MG6 alpha	novel	17.9	Significant decrease in FH/CR1 binding		Pathogenic
1	p.Phe794Cys	c.2381T>G	MG6 alpha	novel	22.8	no		VUS
2 (fam)	p.Pro1114Leu	c.3341 C>T	TED	novel	25.2	Significant decrease in FH binding		Pathogenic
1[d]	p.Asn1179Thr	c.3536A>C	TED	novel	14.99	no	Located in the C3d binding site on CCP4 of FH	Pathogenic
1	p.Gly1224Asp *	c.3671G>A	TED	0.016	13.25	no		VUS

Note: Allele Frequency are given from GnomAD data base and according to ethnicity of patient

Abbreviation: fam, familial form, FH, factor H, VUS: variants of undetermined significance.

[a] All reported variant are heterozygous [b] Summary of the functional studies reported by Schramm et al and Chauvet et al; [c] The patient carried a C3 VUS (p.Ala257Thr) and an homozygous pathogenic *CFH* variant (p.Cys431Ser) and was included in the group of patients with *CFH* variant; [d]: The patient carried a pathogenic variant in C3 (p.Asn1179Thr) and a CFI VUS (p.Ile306Val) and was included in the group of patients with C3 variants.

* The allele frequency of the variant p.Gly1224Asp in African population is 1.8%.

Rare variants in C3 genes were positioned on molecular structure of C3b (**Figure S1**).

Supplemental Table 4: Exhaustive genetic, immunological and histological characteristics of the 66 C3 glomerulopathy /Ig-MPGN patients carrying complement rare variants

Histological classification	Gene	Fam/Spo	Age at diagnosis	Genetic variant	Zygosity	C3 (mg/L)	C4 (mg/L)	sC5b-9 (ng/ml)	FH (% of normal value)	FI (% of normal value)	C3NeF	Anti Factor H Ab	Variant Classification
C3 glomerulopathy	CFH	Fam 1*1	NA	p.Gly94Arg	Het	436	209	465	78	130	N	N	Pathogenic
C3 glomerulopathy	CFH	Fam 1*2	39	p.Gly94Arg	Het	439	431	490	66	70	N	N	Pathogenic
C3 glomerulopathy	CFH	Fam 2*1	54	p.Cys431Ser	Het	740	274	328	77	130	N	N	Pathogenic
C3 glomerulopathy	CFH	Fam 2*2	49	p.Cys431Ser	Het	1020	247	793	87	120	N	N	Pathogenic
C3 glomerulopathy	CFH	Fam 2*3	3	p.Cys431Ser	Hom	97	473	2976	<10	100	N	N	Pathogenic
Ig MPGN	CFH	Fam 3*1	15	p.Phe717Leu	Het	868	101	NA	115	107	N	N	VUS
Ig MPGN	CFH	Fam 3*2	20	p.Phe717Leu	Het	923	130	NA	128	111	N	N	VUS
C3 glomerulopathy	CFH	Fam 4*1	52	p.Arg53Cys	Het	646	249	772	115	124	N	N	Pathogenic
Ig MPGN	CFH	Fam 4*2	1	p.Arg53Cys	Hom	144	234	NA	126	109	N	N	Pathogenic
C3 glomerulopathy	C3	Fam 5*1	42	p.Ile756Thr	Het	552	321	677	146	123	N	N	Pathogenic
C3 glomerulopathy	C3	Fam 5*2	45	p.Ile756Thr	Het	989	366	NA	161	146	N	N	Pathogenic
C3 glomerulopathy	C3	Fam 6*1	36	p.Pro1114Leu	Het	489	211	162	117	103	N	N	Pathogenic
Ig MPGN	C3	Fam 6*2	3	p.Pro1114Leu	Het	448	94	151	116	106	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	1	p.Cys673Arg	Het	523	141	243	51	103	P	N	Pathogenic
C3 glomerulopathy	C3	Spo	6	p.Gln216Pro	Het	51	147	352	80	112	P	N	VUS
C3 glomerulopathy	CFH	Spo	15	p.Arg232Stop	Het	538	160	755	23	86	P	N	Pathogenic
C3 glomerulopathy	CFH	Spo	29	p.Arg444Cys	Het	193	255	512	110	110	P	N	VUS
C3 glomerulopathy	CFH	Spo	55	p.Leu77Stop	Het	616	271	498	51	123	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	57	p.Cys431Arg	Het	1100	394	559	90*	120	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	59	p.Val143Ile	Het	494	223	698	53	97	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	4	p.Ala161Ser	Het	981	257	444	127	145	N	N	VUS
C3 glomerulopathy	CFI	Spo	4	p.Val282Leu	Het	625	376	761	118	107	N	N	VUS
C3 glomerulopathy	C3	Spo	6	p.Asn1179Thr	Het	257	208	967	117	134	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	7	p.Ala161Ser	Het	802	345	NA	118	113	N	N	VUS
C3 glomerulopathy	CFH	Spo	10	p.Cys1043Ser	Het	123	69	NA	53	87	P	N	Pathogenic
C3 glomerulopathy	CFI	Spo	12	p.Ile416Leu	Het	664	129	NA	81	45	N	N	Pathogenic
C3 glomerulopathy	C3	Spo	13	p.Gly637Arg	Het	850	256	248	63	85	N	N	VUS
C3 glomerulopathy	CFH	Spo	13	p.Cys536Arg	Het	605	312	NA	55	110	N	N	Pathogenic
C3 glomerulopathy	C3	Spo	14	p.Phe794Cys	Het	87	307	1807	180	130	P	N	VUS
C3 glomerulopathy	CFI	Spo	15	p.Ter584GlnextTer24	Het	933	254	NA	87	38	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	16	p.Tyr843Asp	Het	1670	279	296	112	175	N	N	VUS
C3 glomerulopathy	C3	Spo	19	p.Gly1224Asp	Het	1050	182	142	81	93	N	N	VUS
C3 glomerulopathy	CFI	Spo	19	p.Arg474Stop	Het	925	128	189	102	44	N	N	Pathogenic
C3 glomerulopathy	C3	Spo	24	p.Gly637Arg	Het	609	182	857	116	114	P	N	VUS
C3 glomerulopathy	C3	Spo	24	p.Thr426lys	Het	569	215	246	138	131	N	N	VUS
C3 glomerulopathy	CFH	Spo	24	p.Val72Glyfs*3	Het	1310	346	398	123*	131	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	25	p.Arg1210Cys	Het	794	188	414	103	93	P	N	Pathogenic
C3 glomerulopathy	CFI	Spo	27	p.Asn151Ser	Het	1360	438	254	158	96	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	29	p.Gly498*	Het	707	260	244	73	111	N	N	Pathogenic
C3 glomerulopathy	CFI	Spo	31	p.Arg406Cys	Het	885	204	356	83	98	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	32	p.Cys597Arg	Hom	179	218	3535	<10	127	N	N	Pathogenic

C3 glomerulopathy	CFI	Spo	32	p.Ile357Met	Het	843	308	NA	89	61	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	36	p.Ala161Ser	Het	544	321	NA	121	120	N	N	VUS
C3 glomerulopathy	CFH	Spo	37	p.Val686Met	Het	183	293	NA	12	116	N	N	Pathogenic
C3 glomerulopathy	CFI	Spo	37	p.Ile357Met	Het	990	262	NA	109	64	N	N	Pathogenic
C3 glomerulopathy	CFI	Spo	38	p.Pro50Ala	Het	1090	401	309	145	45	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	40	p.Gly962ValfsTer13	Het	663	148	NA	54	107	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	42	p.Asp130Asn	Het	878	218	321	143	147	N	N	VUS
C3 glomerulopathy	CFH	Spo	43	p.ter 1232 IlefsTer38	Het	780	383	282	49	108	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	44	p.Gly122_Glu128del fs	Het	883	254	471	88*	122	N	N	Pathogenic
C3 glomerulopathy	C3	Spo	48	p.Gly590Ala	Het	578	236	302	82	98	N	N	VUS
C3 glomerulopathy	CFI	Spo	48	p.Pro50Ala	Het	1190	226	NA	147	140	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	55	p.Gly879Arg	Het	470	332	964	45	95	N	N	Pathogenic
C3 glomerulopathy	CFI	Spo	55	p.Asn151Ser	Het	973	255	250	101	48	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	62	IVS 15+5	Het	689	259	360	60	107	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	65	p.Trp436Stop	Het	884	313	NA	66	121	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	67	p.Cys141Arg	Het	844	127	1266	60	127	N	N	Pathogenic
C3 glomerulopathy	CFI	Spo	69	p.Ala240Gly	Het	975	193	705	176	107	N	N	Pathogenic
C3 glomerulopathy	CFH	Spo	95	p.Gln872Stop	Het	565	253	367	57	107	N	N	Pathogenic
Ig MPGN	CFH	Spo	7	p.Arg303Trp	Het	989	227	NA	146	102	N	N	VUS
Ig MPGN	CFI	Spo	17	p.Ile416Leu	Het	736	252	NA	100	70	N	N	Pathogenic
Ig MPGN	CFH	Spo	18	p.Cys673Ser	Hom	46	181	1900	<10	75	N	N	Pathogenic
Ig MPGN	CFH	Spo	21	p.Asp130Asn	Het	1240	328	437	130	91	N	N	VUS
Ig MPGN	CFI	Spo	31	p.Gly119Arg	Het	103	66	NA	101	58	P	N	Pathogenic
Ig MPGN	CFI	Spo	32	p.Ile357Met	Het	574	306	NA	111	19	N	N	Pathogenic
Ig MPGN	CFI	Spo	59	p.Cys327Arg	Het	568	155	NA	104	45	N	N	Pathogenic

Abbreviations: C3NeF: C3 Nephritic Factor; Het: heterozygote; Hom: homozygote; Ig-MPGN: immunoglobulin mediated membranoproliferative glomerulonephritis; N: negative; NA: not available; P: positive; Spo: sporadic. VUS: variants of undetermined significance

* Instead of normal FH plasma level for these three CFH variants genetic abnormality allow us to anticipate FH quantitative deficiency (deletion or loss of conserved Cysteine)

Supplemental Table 5: Characteristics of inherited C3 glomerulopathy/Ig-MPGN according to age diagnosis

	Children N=20**	**Adults <50yr N=32**	**Adults >50yr N=13**	**P value**
Clinical data at diagnosis				
Male sex	12/20 (60)	16/32 (50)	8/13 (62)	0.69
Age	9 (4-15)	32 (24-42)	59 (55-66)	<0.0001
eGFR (ml/min/1,73m2)	85 (40-100)	47 (14-80)	42 (29-57)	0.03
Nephrotic Syndrome	11/19 (58)	13/26 (50)	1/13 (8)	0.01
Biological stigmata of TMA	0/20	5/30 (17)	1/13 (8)	0.14
Infectious trigger	11/15 (73)	4/25 (16)	0/9	<0.0001
Low C3 level (<660 mg/L)	11/20 (55)	13/32 (41)	6/13 (46)	0.60
High sC5b-9 (>300 ng/ml)	7/11 (64)	15/22 (68)	10/11 (91)	0.28
C3NeF	5/20 (30)	2/29 (9)	0/13	0.03
Histological data at diagnosis				
C3 glomerulopathy	15/20 (75)	27/32 (84)	12/13 (92)	0.41
Ig-MPGN	5/20 (25)	5/32 (16)	1/13 (8)	0.41
Complement rare variant identified				
CFH variant	11/20 (55)	16/32 (50)	10/13 (77)	0.25
CFI variant	4/20 (20)	9/32 (28)	3/13 (23)	0.80
C3 variant	5/20 (25)	7/32 (22)	0/13	0.15
Variant classified as pathogenic	11/20 (55)	23/32 (72)	13/13 (100)	0.02
Kidney **outcome**				
Kidney failure	11/20 (55)	23/32 (72)	8/13 (62)	0.45
Duration of evolution until kidney failure	111 (67-195)	28 (2-84)	29 (19-92)	0.02

Qualitative variables are described as frequencies (percentages), quantitative variables as median (interquartile range). Time is expressed in months.

Abbreviations: C3NeF: C3 Nephritic Factor, CFH: complement factor H, CFI: complement factor I, eGFR: estimated glomerular filtration rate, TMA: thrombotic micro angiopathy, Ig-MPGN: Immunoglobulin mediated Membranoproliferative Glomerulonephritis, sC5b-9: soluble C5b-9

*Only 65 patients are included in this analysis: age at diagnosis was unknown in one carrying *CFH* rare variant.

**Were defined as children, patients with disease onset before 18 years old.

Supplemental Table 6: Characteristics of C3 glomerulopathy /Ig-MPGN children patients carrying rare variants in *CFH, CFI, C3* genes or not

	No variant N=86	*CFH, CFI or C3* Variants N=20	P value
Clinical data at first clinical evaluation			
Male sex	40/86 (47)	12/20 (60)	0.32
Nephrotic Syndrome	39/74 (53)	11/19 (58)	0.80
eGFR (ml/min/1,73m2)	100 (43-100)	85 (40-100)	0.74
Low C3 level (<660 mg/L)	50/84 (60)	11/20 (55)	0.80
High sC5b-9 (>300 ng/ml)	54/70 (77)	7/11 (64)	0.45
C3NeF	61/84 (73)	5/20 (30)	0.0006
Histological data			
C3 glomerulopathy	73/86 (85)	15/20 (75)	0.32
Ig-MPGN	13/86 (15)	5/20 (25)	0.32

Qualitative variables are described as frequencies (percentages), quantitative variables as median (interquartile range). Time is expressed in months.
Abbreviations: C3NeF: C3 Nephritic Factor; CFH: complement factor H, CFI: complement factor I, eGFR: estimated glomerular filtration rate, Ig-MPGN: immunoglobulin mediated membranoproliferative glomerulonephritis.

Supplemental Table 7: Characteristics of C3 glomerulopathy /Ig-MPGN adults under 50 patients carrying rare variants in *CFH, CFI, C3* genes or not

	No variant N=96	*CFH, CFI or C3* Variants N=32	P value
Clinical data at first clinical evaluation			
Male sex	51/96 (53)	16/32 (50)	0.84
Nephrotic Syndrome	43/79 (54)	13/26 (50)	0.82
eGFR (ml/min/1,73m2)	80 (38-100)	47 (14-80)	0.008
Low C3 level (<660 mg/L)	42/95 (44)	13/32 (41)	0.83
High sC5b-9 (>300 ng/ml)	50/77 (65)	15/22 (68)	0.99
C3NeF	31/91 (34)	2/29 (9)	0.006
Histological data			
C3 glomerulopathy	83/96 (87)	27/32 (84)	0.77
Ig-MPGN	13/96 (13)	5/32 (16)	0.77

Qualitative variables are described as frequencies (percentages), quantitative variables as median (interquartile range). Time is expressed in months.

Abbreviations: C3NeF: C3 Nephritic Factor ; CFH: complement factor H, CFI: complement factor I, eGFR: estimated glomerular filtration rate, Ig-MPGN: immunoglobulin mediated membranoproliferative glomerulonephritis.

Supplemental Table 8: Characteristics of C3 glomerulopathy /Ig-MPGN adults older than 50 patients carrying rare variants in *CFH, CFI, C3* genes or not

	No variant N=28	*CFH, CFI or C3* Variants N=13	P value
Clinical data at first clinical evaluation			
Male sex	20/28 (62)	8/13 (62)	0.72
Nephrotic Syndrome	13/21 (62)	1/13 (8)	0.003
eGFR (ml/min/1,73m2)	38 (27-57)	42 (29-57)	0.79
Low C3 level (<660 mg/L)	10/28 (36)	6/13 (46)	0.73
High sC5b-9 (>300 ng/ml)	19/25 (79)	10/11 (91)	0.64
C3NeF	7/27 (26)	0/13	0.07
Histological data			
C3 glomerulopathy	23/28 (82)	12/13 (92)	0.64
Ig-MPGN	5/28 (18)	1/13 (8)	0.64

Qualitative variables are described as frequencies (percentages), quantitative variables as median (interquartile range). Time is expressed in months.
Abbreviations: C3NeF: C3 Nephritic Factor ; CFH: complement factor H, CFI: complement factor I, eGFR: estimated glomerular filtration rate, Ig-MPGN: immunoglobulin mediated membranoproliferative glomerulonephritis.

Supplemental Table 9: Detailed histological characteristics in inherited C3 glomerulopathy/Ig-MPGN *

	Available data	All	CFH Variants N=38	CFI Variants N=16	C3 Variants N=12	P value
General Histological data						
Time from clinical knowledge of the disease to biopsy (months)	66	1 (0-12)	0 (0-11)	1 (0-39)	1 (0-7)	0.96
C3 glomerulopathy	66	55/66 (83)	32/38 (84)	12/16 (75)	11/12 (92)	0.49
Ig-MPGN	66	11/66 (17)	6/38 (16)	4/16 (25)	1/12 (8)	0.49
Glomeruli						
No of glomeruli	58	15 (10-21)	15 (10-21)	13 (10-19)	19 (14-29)	0.39
% Sclerotic glomeruli	58	9 (0-26)	12 (0-35)	0 (0-14)	18 (4-58)	0.03
Extra-capillary proliferation	64	15/64 (23)	9/37 (24)	4/16 (25)	2/11 (18)	0.90
Fibro crescents	64	5/64 (8)	2/37 (5)	1/16 (6)	2/11 (18)	0.37
MPGN pattern	64	36/64 (56)	22/37 (60)	8/16 (50)	6/11 (55)	0.81
Endocapillary proliferation	64	37/64 (58)	21/37 (57)	10/16 (63)	6/11 (55)	0.90
Mesangial hypertrophy and/or hypercellularity	64	52/64 (81)	35/37 (97)	10/16 (63)	7/11 (64)	0.006
LM Deposits	64	29/64 (45)	18/37 (47)	4/16 (25)	7/11 (64)	0.12
Interstitium						
Interstitial fibrosis / tubular atrophia	64	45/64 (70)	27/37 (73)	11/16 (69))	7/11 (64)	0.83
Interstitial inflammation	64	36/64 (56)	20/17 (54)	11/16 (69)	5/11 (45)	0.45
Vessels						
TMA lesions**	64	6/64 (9)	3/37 (8)	3/16 (19)	0/11 (0)	0.24
Arteriosclerosis and/or arteriolar hyalinosis	64	33/64 (52)	20/37 (54)	8/16 (50)	5/11 (45)	0.87

Data are expressed as mean (IDR) or n(%).

* C3 glomerulopathy or Ig-MPGN diagnosis was made on native kidney in 59 patients (n=36 in *CFH* variants, n=11 in *CFI* variants and n= 12 in *C3* variants) and on kidney graft after kidney failure of undetermined cause in 7 patients (n=2 *CFH* variants and n= 5 *CFI* variants).

Abbreviations: Ig-MPGN: Immunoglobulin mediated Membranoproliferative Glomerulonephritis, LM: Light Microscopy; MPGN: Membranoproliferative Glomerulonephritis, TMA: thrombotic micro angiopathy.

**TMA lesions consisted in: Fibrin thrombus, Double contour formation, Organizing arteriolar thrombosis, Arteriolar occlusion, Onion skin lesion

Supplemental Table 10: Characteristics of patients with inherited C3 glomerulopathy/Ig-MPGN according to histological diagnosis

	C3 glomerulopathy N=55	Ig-MPGN N=11	P value
Clinical data at first clinical evaluation			
Male sex	31/55 (56)	6/11 (55)	0.99
Age	34 (15-48)	18 (7-31)	0.05
Children	15/54 (28)	5/11 (46)	0.28
Proteinuria g/day	3 (1.1-4.1)	2.4(1.7-5.0)	0.58
Nephrotic Syndrome	26/50 (52)	4/9 (44)	0.73
eGFR (ml/min/1,73m2)	44 (23-80)	80 (60-100)	0.048
eGFR>60ml/min/1.73m2	18/51 (35)	9/11 (82)	0.007
eGFR 15 - 60ml/min/1.73m2	24/51 (47)	2/11 (18)	0.10
eGFR ≤15ml/min/1.73m2	9/51 (18)	0	0.34
Low C3 level (<660 mg/L)	25/55 (45)	6/11 (55)	0.74
High sC5b-9 (>300 ng/ml)	31/42 (74)	2/3 (67)	0.99
C3NeF	8/55 (15)	1/11 (9)	0.99
Histological findings			
No of glomeruli	15 (10-21)	16 (9-19)	0.67
% Sclerotic glomeruli	10 (0-29)	3 (0-26)	0.30
Extracapillary proliferation	11/53 (21)	4/11 (36)	0.27
Fibro crescents	4/53 (8)	1/11 (9)	0.99
MPGN pattern	26/53 (49)	10/11 (91)	0.02
Endocapillar proliferation	28/53 (53)	9/11 (82)	0.10
Mesangial hypertrophy and/or hypercellularity	43/53 (81)	9:11 (82)	0.99
LM Deposits	22/53 (42)	7/11 (64)	0.20
Interstitial fibrosis / tubular atrophia	38/53 (72)	7/11 (64)	0.72
Interstitial inflammation	30/53 (57)	5/11 (55)	0.99
TMA lesions**	5/53 (9)	1/11 (9)	0.99
Arteriosclerosis and/or arteriolar hyalinosis	29/53 (55)	4/11 (36)	0.33
Treatment			
No specific treatment	30/51 (59)	3/11 (27)	0.09
Plasma Exchange	3/51 (6)	0	0.99
Immunosuppressive treatment	18/51 (35)	8/11 (73)	0.04
Corticosteroid alone	9/51 (18)	7/11 (64)	0.004
Corticosteroid associated with other IS agent	9/51 (18)	1/11 (9)	0.67
Follow-up on native kidney			
Follow-up	84 (59-148)	197 (105-268)	0.009
Kidney function at last follow up			
eGFR>60ml/min/1.73m2	16/55 (29)	2/11 (18)	0.71
eGFR<60ml/min/1.73m2	4/55 (7)	1/11 (9)	0.99
Kidney failure (dialysis or transplantation)	35/55 (64)	8/11 (73)	0.73

Qualitative variables are described as frequencies (percentages), quantitative variables as median (interquartile range). Time is expressed in months.
Abbreviations: C3NeF: C3 Nephritic Factor ; CFH: complement factor H, CFI: complement factor I, eGFR: estimated glomerular filtration rate, Ig-MPGN: immunoglobulin mediated membranoproliferative glomerulonephritis.
**TMA lesions consisted in: Fibrin thrombus, Double contour formation, Organizing arteriolar thrombosis, Arteriolar occlusion, Onion skin lesion

Supplemental Table 11: Detailed Immunological characteristics of inherited C3 glomerulopathy/Ig-MPGN

	***CFH* Variants N=38**	***CFI* Variants N=16**	***C3* Variants N=12**	**P value**
Familial form/pedigree	4/33 (12)	0/16 (0)	2/10 (20)	0.22
Complement activation biomarkers				
C3 level[a] (mg/L)	676 (662-883)	905 (635-986)	561 (305-561)	0.04
Low C3 level	18/38 (47)	4/16 (25)	9/12 (75)	0.03
C4 level[b] (mg/L)	255 (204-315)	253 (165-308)	213 (182-294)	0.52
Low C4 level	1/38 (3)	1/16 (6)	0/12	0.62
Soluble C5b-9[c] (ng/ml)	471(360-772)	309 (250-705)	302 (162-857)	0.12
High sC5b-9	23/27 (85)	4/7 (57)	6/11 (55)	0.09
Regulatory proteins				
Factor H level (% of normal value)	75 (53-116)	103 (92-138)	117 (81-144)	0.005
Low Factor H[d]	18/38 (47)	0/16	1/12 (8)	<0.001
Factor I level (% of normal value)	111 (102-123)	60 (45-98)	131(113-146)	<0.001
Low Factor I[d]	1/38 (3)	11/16 (69)	0/12	<0.001
Associated acquired abnormalities				
Positive C3NeF	4/38 (11)	2/16 (13)	3/12 (25)	0.15
Genetic summary				
Variant classified as pathogenic	28/38 (74)	15/16 (94)	5/12 (42)	0.009

Qualitative variables are described as frequencies (percentages), quantitative variables as median (interquartile range). p value was calculated by comparing the 3 different groups *CFH*, *CFI* and *C3* variants

Abbreviations: C3Nef: C3 nephritic factor, *CFH*: complement factor H, *CFI*: complement factor I, sC5b-9: soluble C5b-9

[a] Normal values for C3 plasmatic level: 660-1250 mg/L; [b] Normal values for C4 plasmatic level: 93-380 mg/L; [c] Normal values for C4 plasmatic level: <300 ng/ml; [d] FH and FI measurement are categorized low when <70% of normal value

Supplemental Table 12: Cumulative frequency of the rare and pathogenic variants between C3 glomerulopathy / Ig-MPGN cohorts and 503 controls from the 1000 genome project

	Total N= 398	C3 glomerulopathy N=296	Ig-MPGN N=102	1000 g N=503	p (C3 glomerulopathy vs 1000g)	p (Ig-MPGN vs 1000 g)	p (C3 glomerulopathy vs Ig-MPGN)	p (C3 glomerulopathy +Ig-MPGN vs 1000g)
Rare variant (*CFH, CFI, C3*)	66 (17)	55 (19)	11 (11)	24 (5)	<0.001	0.03	0.09	<0.001
Pathogenic variant (*CFH, CFI, C3*)	48 (12)	41 (14)	7 (7)	3 (1)	<0.001	<0.001	0.08	<0.001
CFH rare variant	38 (10)	32 (11)	6 (6)	7 (0.6)	<0.001	0.01	0.17	<0.001
CFH Pathogenic variant	28 (7)	26 (9)	2 (2)	1 (0.2)	<0.001	0.07	0.02	<0.001
CFI rare variant	16 (4)	12 (4)	4 (4)	8 (2)	0.04	0.12	0.99	0.03
CFI Pathogenic variant	15 (4)	11 (4)	4 (4)	2 (0.4)	<0.001	0.008	0.99	<0.001
C3 rare variant	12 (3)	11 (4)	1 (1)	9 (2)	0.05	0.99	0.31	0.12
C3 Pathogenic variant	5 (1)	4 (1)	1 (1)	0	0.02	0.17	0.99	0.02

Variables are described as frequencies (percentages).
The cumulative allele frequency of the variants between our cohort and 503 controls from the 1000 genome project (1000g).

Supplemental Table 13: Kidney transplant outcomes in patients with inherited C3 glomerulopathy/Ig-MPGN

	All N= 66	***CFH* Variants N=38**	***CFI* Variants N=16**	***C3* Variants N=12**	**P value**
Kidney **transplantation**	36/66 (55)	17/38 (45)	10/16 (63)	9/12 (75)	0.14
Graft Follow up (months)	51 (26-94)	48 (20-91)	48 (24-99)	74 (31-117)	0.59
Prophylactic treatment*	9/35 (26)	5/16 (31)	2/10 (20)	2/9 (22)	0.78
Documented histological recurrence	21/31 (69)	8/13 (62)	8/9 (89)	5/9 (56)	0.26
Delay for histological recurrence	12 (2-42)	28 (5-43)	5 (0-39)	11 (3-43)	0.63
Histological recurrence at 1 year	11/31 (36)	3/13 (23)	5/9 (56)	3/9 (33)	0.29
Histological recurrence at 2 years	12/31 (39)	3/13 (23)	6/9 (67)	3/9 (33)	0.11**
Anti-C5 therapy after recurrence	10/22 (46)	3/8 (38)	6/9 (67)	1/5 (20)	0.21
Graft failure due to recurrence	3/36 (8)	2/17 (12)	1/10 (10)	0/9 (0)	0.57
Graft function at last follow up					
eGFR>60ml/min/1.73m^2	13/36 (20)	6/17 (35)	3/10 (30)	4/9 (44)	0.80
eGFR<60ml/min/1.73m^2	19/36 (28)	7/17 (42)	6/10 (60)	5/9 (56)	0.59
Graft loss	5/36 (6)	4/17 (24)	1/10 (10)	0	0.23

Data are expressed as mean (IDR) or n(%). p value was calculated by comparing the 3 different groups *CFH*, *CFI* and *C3* variants. Time is expressed in months.

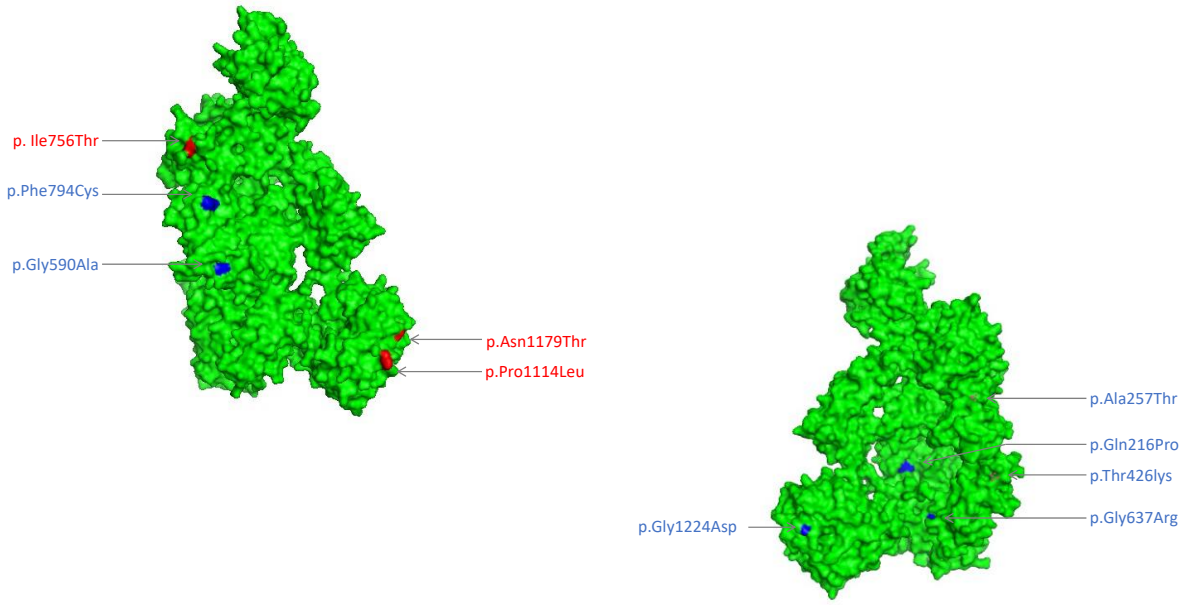
Abbreviations: *CFH*: complement factor H, *CFI:* complement factor I, eGFR: estimated glomerular filtration rate.

*Prophylactic treatment consisted in: -among patients carrying *CFH* variants: 1 plasma perfusion, 2 plasma exchange and 2 Eculizumab therapy; -among patients carrying *CFI* variants: 1 plasma exchange and 1 Eculizumab therapy; -among patients carrying C3 variants: 2 Eculizumab therapy.

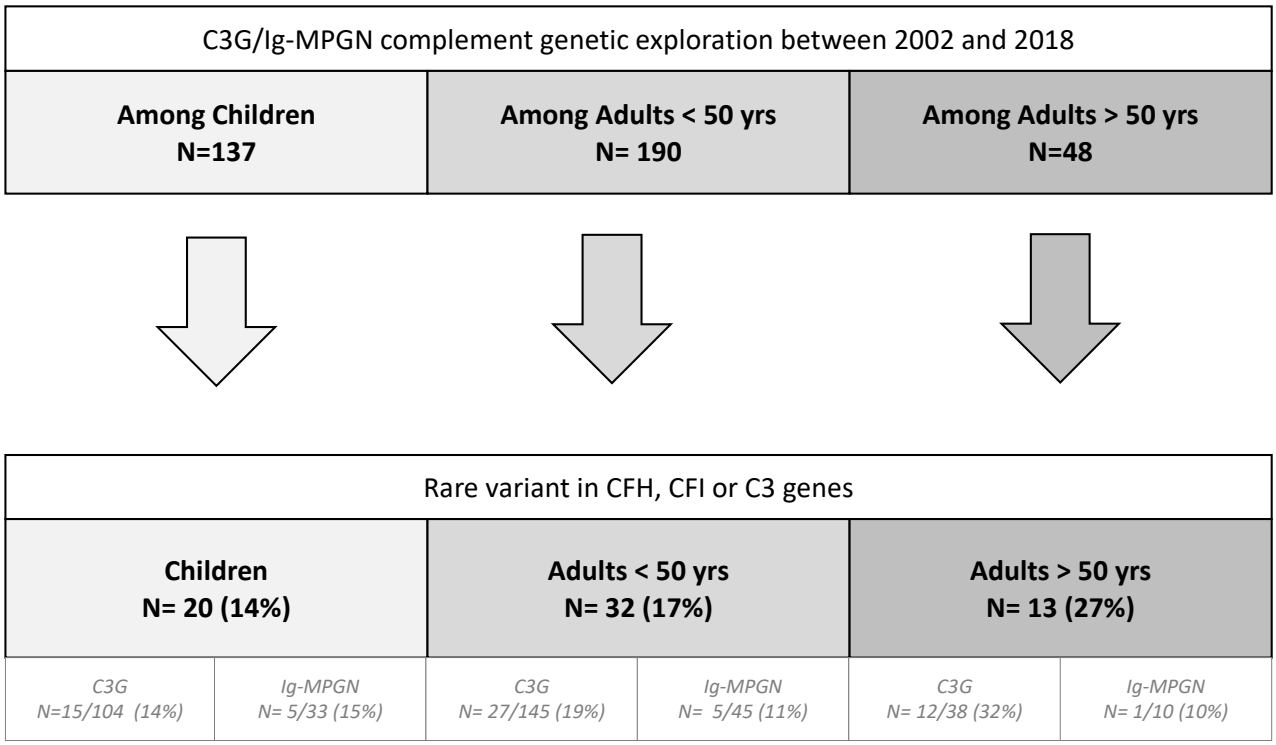
**: p=0.08 between *CFH* and *CFI* groups

Supplemental Figures

Supplemental Figure 1: C3b molecular structure with the position of rare variants of C3 identified in patients with C3 glomerulopathy/Ig-MPGN.
Pathogenic rare variants of C3b with known deleterious functional consequences are indicated in red and rare variants with unknown significance in blue.

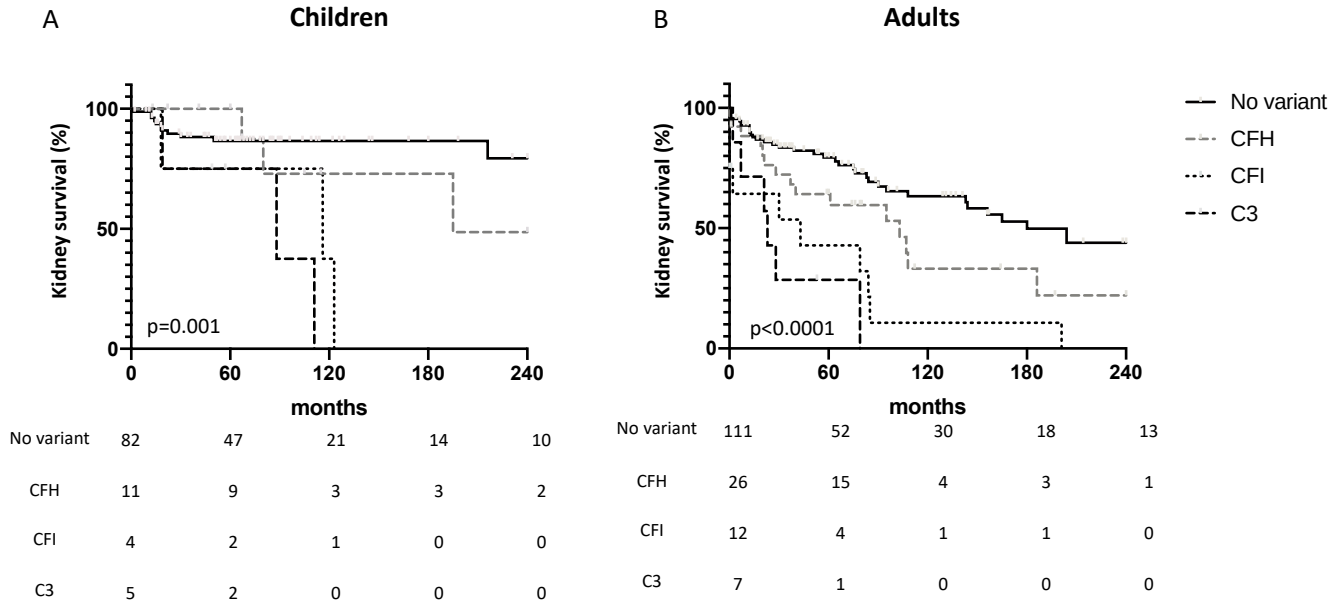


Supplemental Figure 2: C3 glomerulopathy, Ig-MPGN and CFH, CFI, C3 rare variants: patients repartition in national French registry according to age at diagnosis *Twenty-three missing values, including 1 in the variant subgroup.*



Supplemental Figure 3: Kidney survival of patients with inherited C3 glomerulopathy/Ig-MPGN.

Kaplan Meier kidney survival curve according to the complement component variant, compared to kidney survival of C3 glomerulopathy patients without complement rare variant, A) in children and B) in adults.



Supplemental Figure 4: Kidney survival of patients with inherited C3 glomerulopathy/Ig-MPGN compared to kidney survival of patients without complement rare variant receiving or not specific treatment. A) Kaplan Meier kidney survival curve in C3 glomerulopathy/Ig-MPGN patients receiving specific treatment, carrying or not complement rare variant B) Kaplan Meier kidney survival curve in C3 glomerulopathy/Ig-MPGN patients with conservative treatment, carrying or not complement rare variant.