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Extended List of Authors

MPGN / DDD / C3 Glomerulopathy Rare Disease Group[1]

[1]Rare Renal Disease Registry (RaDaR), UK Renal Registry, Bristol, UK

Su Brimble, Terence Cook, Daniel Gale, Julie Gibbs, Rodney Gilbert, Lorraine Harper, Claire Harris, Kim Jessup, Sally Johnson, Helen Jones, David Kavanagh, Adam Levine, Hannah Lomax-Browne, Andrew Longfellow, Roger Malcomson, Kevin Marchbank, Stephen Marks, Heather Maxwell, Paul McAlinden, David Milford, Matthew Pickering, Sandra Richardson, Stephen Richardson, Neil Sebire, Mark Taylor, Julie Wessels, Sarah Whittal, Edwin Wong.

National Study of MPGN/DDD/C3 Glomerulopathy Investigators

Martin Christian, Eric Finlay, Rodney Gilbert, Shivaram Hegde, Sally Johnson, Caroline Jones, Stephen Marks, Heather Maxwell, David Milford, Moin Saleem, Manish Sinha, Nick Webb

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Supplemental Table 1 Frequency of CFHR3/1 deletion in paediatric C3 glomerulopathy, immune-complex MPGN and immune-complex GN

***CFHR3/1* deletion**	**del/del**	**del/+**	**+/+**	**Frequency of del**	**Odds Ratio (95% CI)**	**P value**
All	0	13	59	0.090	0.47 (0.26-0.85)	0.01
IC-GN	0	2	7	0.111	0.59 (0.13-2.59)	0.48
IC-MPGN	0	3	25	0.054	0.27 (0.08-0.86)	0.03
DDD	0	4	9	0.143	0.85 (0.29-2.52)	0.78
C3GN	0	4	18	0.091	0.47 (0.17-1.33	0.16

CFHR3/CFHR1 gene is deleted (del) or present (+). Control cohort from (Moore et al., 2010 [8]). Allele frequency of *CFHR3/CFHR1* deletion in control cohort was 175 out of 1000.

Supplemental Table 2 Soluble plasma C5b9 levels according to complement abnormality

	Complement Abnormality Present		P-value
	Yes	No	
C3 nephritic factor	192.5 (95.21-360.10)	232.12 (119.03-448.32)	0.70
Autoantibody to Factor H	209.50 (121.15-998.3)	223.30 (109.32-424.03)	0.78
Autoantibody to C3b	328.86 (130.81-415.64)	223.30 (110.00-456.61)	0.80
Autoantibody to Factor B	110.94 (48.89-339.400)	224.55 (117.00-431.73)	0.23
Rare Genetic Variant	141.35 (55.04-141.35)	223.30 (108.65-429.16)	0.27

Soluble C5b9 levels presented as median (inter-quartile range)

Supplemental Table 3 Summary of patients with rare complement genetic variants

Disease	Gene	Base pair change	Amino acid change	Frequency in control cohort[a]	Other disease associations	C3 at diagnosis (0.68-1.38 g/L)	C4 at diagnosis (0.18-0.60 g/L)	FH (0.35-0.59 g/L)	FI (38-58 mg/L)	C3 nephritic factor	Autoantibody to FH, C3b or FB	Functional significance [9]
IC-MPGN	*CFH*	1949G>T	G650V	0.023%	Not known	0.15	0.17	0.54	63	Not Detected	Not detected	Likely benign
IC-MPGN	*CFH*	1001G>C	G334A	n/a	Not known	1.09	0.04	0.44	47	Not Detected	FB	n/a
IC-MPGN	*CFB*	621A>C	E207D	n/a	Not known	0.71	0.12	0.46	58	Not Detected	FH	n/a
IC-MPG N	*C3* *CFH*	1855G>A 2675C>T	K155Q A892V	0.22% 0.023%	AMD [10] Not known	0.23	0.12	0.67	55	Not Detected	Not detected	Likely benign Uncertain significance
C3GN	*CFI*	1657C>T	P553S	0.14%	aHUS [11] / AMD [12]	N/A	N/A	0.74	73	Not Detected	Not detected	Likely benign
DDD	*C3* *CFI*	4594C>T 355G>A	R1532W G119R	0.0077% 0.085%	Not known aHUS [11] / AMD [12]	0.11	0.26	0.52	36	Positive	Not detected	n/a Uncertain significance

a Rare genetic variants were defined as minor allele frequency <0.01 in the exome variant server database (evs.gs.washington.edu). FH= complement factor H, FI = complement factor I, FB = complement factor B, n/a – not available

Supplemental Table 4 Analysis of 10 single nucleotide polymorphisms in paediatric C3 glomerulopathy, immune-complex MPGN and immune-complex GN

		C/C	C/G	G/G	Frequency of variant allele (G)	Odds Ratio (95% CI)	P (vs control)
C3	All	40	27	5	0.257	1.28 (0.87-1.85)	0.22
c.304C>G	IC-GN	7	2	0	0.111	0.47 (0.11-2.05)	0.31
p. R102G	IC-MPGN	15	9	4	0.30	1.6 (0.93-2.91)	0.09
rs2230199	DDD	2	10	1	0.462	3.14 (1.45-6.8)	0.004
	C3GN	16	6	0	0.136	0.57 (0.24-1.37	0.21
		C/C	C/T	T/T	Frequency of variant allele (T)	Odds Ratio (95% CI)	P (vs control)
C3	All	38	29	5	0.271	1.44 (1.00-2.09)	0.05
c.941C>T	IC-GN	7	2	0	0.111	0.46 (0.11-2.11)	0.34
p.P314L	IC-MPGN	16	10	2	0.250	1.29 (0.71-2.38)	0.40
rs1047286	DDD	4	8	1	0.385	2.43 (1.10-5.36)	0.03
	C3GN	11	9	2	0.295	1.63 (0.85-3.12)	0.14
	Control[1]	2702	1436	162	0.205		
		C/C	C/T	T/T	Frequency of variant allele (T)	Odds Ratio (95% CI)	P (vs control)
CFB	All	65	5	1	0.049	0.47 (0.22-1.03)	0.06
c.94C>T	IC-GN	9	0	0	0.000	0.28 (0.02-4.66)	0.37
p.R32W	IC-MPGN	26	2	0	0.034	0.33 (0.08-1.35)	0.12
rs641153	DDD	10	1	1	0.125	1.32 (0.39-4.43)	0.66
	C3GN	20	2	0	0.045	0.44 (0.11-1.82)	0.26
	Control[1]	2206	476	27	0.098		
		G/G	G/A	A/A	Frequency of variant allele (A)	Odds Ratio (95% CI)	P (vs control)
CFB	All	65	5	0	0.036	0.39 (0.16-0.95)	0.04
c.95G>A	IC-GN	8	1	0	0.059	0.60 (0.08-4.54)	0.62
p.R32Q	IC-MPGN	27	0	0	0.000	0.09 (0.01-1.52)	0.10
rs12614	DDD	11	1	0	0.045	0.46 (0.06-3.41)	0.45
	C3GN	19	3	0	0.107	1.27 (0.38-4.21)	0.70
	Control[1]	2260	429	20	0.087		
		C/C	C/T	T/T	Frequency of variant allele (T)	Odds Ratio (95% CI)	P (vs control)
CFH	All	25	21	7	0.330	1.22 (0.73-2.04)	0.45
c.-331C>T	IC-GN	3	4	1	0.440	1.98 (0.74-5.28)	0.17
	IC-MPGN	6	11	5	0.477	2.26 (1.15-4.42)	0.02

rs3753394	DDD	4	2	0	0.167	0.49 (0.10-2.33)	0.37
	C3GN	12	4	1	0.132	0.46 (0.18-1.17	0.10
	Control[2]	44	43	5	0.288		
		G/G	G/A	A/A	Frequency of variant allele (A)	Odds Ratio (95% CI)	P (vs control)
CFH	All	49	20	3	0.186	0.80 (0.52-1.23)	0.31
c.184G>A	IC-GN	4	3	1	0.313	1.59 (0.55-4.59)	0.39
p.V62I	IC-MPGN	22	7	0	0.121	0.48 (0.22-1.06)	0.07
rs800292	DDD	9	4	0	0.154	0.64 (0.22-1.85)	0.41
	C3GN	14	6	2	0.227	1.03 (0.51-2.09)	0.93
	Control[1]	2601	1489	210	0.222		
		T/T	T/C	C/C	Frequency of variant allele (C)	Odds Ratio (95% CI)	P (vs control)
CFH	All	18	39	15	0.090	0.47 (0.26-0.85)	0.01
c.1204T>C	IC-GN	5	3	1	0.278	0.62 (0.22-1.74)	0.37
p.Y402H	IC-MPGN	5	18	5	0.500	1.62 (0.96-2.73)	0.07
rs1061170	DDD	3	7	3	0.500	1.62 (0.75-3.49)	0.22
	C3GN	5	11	6	0.523	1.77 (0.98-3.20)	0.06
	Control[1]	1649	2014	637	0.382		
		A/A	A/G	G/G	Frequency of variant allele (G)	Odds Ratio (95% CI)	P (vs control)
CD46	All	10	18	10	0.500	1.62 (0.92-2.83)	0.09
c.-652A>G	IC-GN	2	3	1	0.417	1.15 (0.35-3.82)	0.81
	IC-MPGN	0	11	4	0.633	2.80 (1.24-6.30)	0.01
rs2796267	DDD	2	2	1	0.400	1.08 (0.29-3.99)	0.91
	C3GN	6	3	3	0.375	0.97 (0.40-2.37)	0.95
	Control[2]	30	34	12	0.382		
		A/A	A/G	G/G	Frequency of variant allele (G)	Odds Ratio (95% CI)	P (vs control)
CD46	All	11	21	6	0.434	1.31 (0.75-2.29)	0.34
c.-366 A>G	IC-GN	2	3	1	0.412	1.22 (0.37-4.03)	0.74
	IC-MPGN	2	11	2	0.500	1.71 (0.78-3.75)	0.18
rs2796268	DDD	2	2	1	0.400	1.14 (0.31-4.21)	0.84
	C3GN	5	5	2	0.375	1.03 (0.42-2.49	0.16
	Control	33	35	12	0.369		
		T/T	T/C	C/C	Frequency of variant allele (C)	Odds Ratio (95% CI)	P (vs control)
CD46	All	17	30	7	0.315	0.94 (0.58-1.51)	0.79
c.*4070T>C	IC-GN	3	4	1	0.375	0.82 (0.29-2.34)	0.71

	IC-MPGN	6	14	2	0.409	0.94 (0.49-1.83)	0.86
rs7144	DDD	2	4	2	0.500	1.36 (0.49-3.78	0.55
	C3GN	6	8	2	0.375	0.81 (0.38-1.76	0.61
	Control[2]	36	41	21	0.423		

In an analysis of 10 single nucleotide polymorphisms (SNPs), statistical significance taken as P<0.005. Control data from [1]European American population of evs.gs.washington.edu/, or [2] **(13)**

Supplemental Table 5 Immunosuppression Regimen in Paediatric C3 glomerulopathy, immune-complex MPGN and immune-complex GN

Category	Immunosuppression (in addition to Prednisolone)		Number of patients
Prednisolone only	None		22
Prednisolone and MMF	MMF		17
Prednisolone +	MMF + Azathioprine		2
	Azathioprine		6
	Tacrolimus		2
	Azathioprine and Tacrolimus		1
Intense	MMF +	Rituximab	3
		Plasma Exchange	2
		Rituximab and ciclosporin	1
		Rituximab and plasma exchange	1
		Cyclophosphamide and plasma exchange	1
		Eculizumab	1
		Eculizumab and plasma exchange	1
	Cyclophosphamide and Azathioprine		1
	Plasma exchange		1
	Cyclophosphamide		1
	Cyclophosphamide and plasma exchange		1
Total			**60**

MMF = mycophenolate mofetil.

Supplemental Table 6 Factors predictive of remission in paediatric C3 Glomerulopathy

C3 glomerulopathy					
Parameter		Total	Remission n (%) [CR, PR]	No Remission n (%)	P value
	All patients	39	28 (71.2) [20,8]	11 (28.2)	
Histological sub-group	C3 Glomerulonephritis	25	20 (80.0) [15, 5]	5 (20.0)	0.126
	Dense deposit Disease	14	8 (57.1) [5, 3]	6 (42.9)	
Features at diagnosis	nephrotic range proteinuria *	20	14 (70.0) [10, 4]	6 (30.0)	0.618
	serum albumin <35g/l	26	14 (53.8)[11,4]	11 (46.2)	0.013
	eGFR <90 ml/min/1.73m^2	22	12 (54.5)[10,2]	10 (45.5)	0.012
	Crescentic Glomerulonephritis	4	1 (25.0)[1, 0]	1 (75.0)	0.06
Treatments used	ACE/ARB	9	9 (100.0)[7, 2]	0 (0.0)	0.008
	Pred	6	5 (83.3) [4, 1]	1 (16.6)	
	Pred / MMF	6	4 (66.7) [2, 2]	2 (33.3)	
	Pred +	5	5 (100.0) [3, 2]	0 (0.0)	
	Intense	13	5 (38.5) [4, 1]	8 (61.5)	
Complement antibodies	C3 nephritic factor	14	9 (64.3) [6, 3]	5 (35.7)	0.544
	Anti-FH autoantibodies	6	3 (50.0) [3, 0]	3 (50.0)	0.360

* nephrotic range proteinuria defined as P:Cr >300mg/mmol, A:Cr>250mg/mmol or 4+ on dipstick P:Cr = urinary protein:creatinine ratio, A:Cr = urinary albumin:creatinine ratio
eGFR = estimated glomerular filtration rate calculated by modified Schwartz formula and expressed in ml/min/1.73m^2
ACE/ARB, Angiotensin Converting Enzyme inhibitor or Angiotensin Receptor Blocker; Pred, Prednisolone; MMF, mycophenolate mofetil; Pred/+, includes patients receiving Pred in combination with Azathioprine or tacrolimus; Intense, includes patients that received any of rituximab, cyclophosphamide, plasma exchange or eculizumab.
n = number of patients, % = percentage of total number of patients, and number of patients achieving CR – complete remission and PR – partial remission.

Supplemental Table 7 Factors predictive of remission in paediatric immune-complex disease

Immune-complex disease					
Parameter		Total	Remission n (%) [CR, PR]	No Remission n (%)	P value
	All Patients	41	36 (87.8) [27, 9]	5 (12.2)	
Histological sub-group	IC-MPGN	31	28 (90.3) [21, 7]	3 (16.1)	0.353
	IC-GN	10	8 (80.0) [6, 2]	2 (20.0)	
Features at diagnosis	nephrotic range proteinuria *	30	25 (83.3) [18, 7]	5 (16.7)	0.248
	serum albumin <35g/l	31	26 (83.4) [21, 5]	5 (16.1)	0.295
	eGFR <90 ml/min/1.73m^2	11	9 (81.8) [6, 3]	2 (18.2)	0.455
Treatments used	ACE/ARB	7	7 (100.0) [3, 4]	0 (0.0)	0.655
	Pred	16	13 (81.3) [10, 3]	3 (18.8)	
	Pred / MMF	11	9 (81.8) [6, 3]	2 (18.2)	
	Pred +	6	6 (100.0) [6, 0]	0 (0.0)	
	Intense	1	1 (100.0) [1,0]	0 (0.0)	
Complement Antibodies	C3 nephritic factor	8	6 (75.0) [5, 1]	2 (25.0)	0.522
	Anti-FH autoantibodies	7	6 (85.7) [5, 1]	1 (14.3)	1.000

IC-MPGN = immune-complex membranoproliferative glomerulonephritis, IC-GN = immune-complex glomerulonephritis,* nephrotic range proteinuria defined as P:Cr >300mg/mmol, A:Cr>250mg/mmol or 4+ on dipstick P:Cr = urinary protein:creatinine ratio, A:Cr = urinary albumin:creatinine ratio

eGFR = estimated glomerular filtration rate calculated by modified Schwartz formula and expressed in ml/min/1.73m^2
ACE/ARB, Angiotensin Converting Enzyme inhibitor or Angiotensin Receptor Blocker; Pred, Prednisolone; MMF, mycophenolate mofetil; Pred/+, includes patients receiving Pred in combination with Azathioprine or tacrolimus; Intense, includes patients that received any of rituximab, cyclophosphamide, plasma exchange or eculizumab.
n = number of patients, % = percentage of total number of patients, and number of patients achieving CR – complete remission and PR – partial remission.

Supplemental Table 8. Summary of previously described cohorts of patients with MPGN/C3 glomerulopathy

Reference	Number of patients (child[a]/adult where specified)	Histological group (n)	Low serum C3 at diagnosis (%)	Low serum C4 at diagnosis (%)	C3NeF (%)	Anti-FH (%)	Other anti-complement antibody (%)	Complement genetic variant detected (%)	Duration of follow up (months)	ESKD (%)
[14]Iatropoulos 2018	173	C3GN 68 DDD 25 IC-MPGN 80	*(Low C3 and normal C4)* C3GN 74 DDD 84 IC-MPGN 70		**All 58%** C3GN 38 DDD 78 IC-MPGN 40			C3GN 25 DDD 16 IC-MPGN 16	Not clear	13.3
[15]Marinozzi 2017	141	C3G 118 Ig-MPGN 23	NR	NR	NR	NR	Anti-C3b 2.1 Anti-FB 4.9 Anti-C3b and anti-FB 10.6	NR	NR	NR
[16]Iatropoulos 2016	140	DDD 21 C3GN 52 Ig-MPGN 67	*(Low C3 normal C4)* DDD 86 C3GN 69 Ig-MPGN 67	Not shown separately	DDD 78 C3GN 44 Ig-MPGN 44	NR	NR	**All 17.7** Did not differ between groups	Mean 58	11.4
[17]Servias 2012	134 (52[b]/82)	MPGN 1 49 DDD 29 GNC3 56	**All 46.1** MPGN 1 46.3 DDD 59.1 GNC3 39.6	**All 1.7** MPGN 1 2.4 DDD 4.5 GNC3 0	**All 58.6** MPGN 1 53.6 DDD 86.4 GNC3 45.3	NR	NR	**All 17.9** MPGN 1 16.7 DDD 17.2 GNC3 19.6	Mean 163	**All 36.6** MPGN 1 40.8 DDD 41.4 GNC3 30.3
[18]Ravindran 2018	114	C3GN 102 DDD 12	C3GN 43 DDD 58.3	C3GN 12.2 DDD 8.3	43.5	See *other anti-complement antibody*	C4NeF or C5NeF or Anti-FB or Anti-FH 13.4	All 37.1.	Median C3GN 22.3 DDD 21.1	C3GN 10 DDD 25

[19]Bomback 2018	111 (35/76)	C3GN 87 DDD 24	C3GN 64.9 DDD 63.6	C3GN 13.9 DDD 13.6	See *other anti-complement antibody*	See *other anti-complement antibody*	C3NeF or Anti-FH or Anti-FB 35.3	23.5	Mean C3GN 69.1 DDD 83.2	C3GN 11.5 DDD 20.8
Khandelwal [20]	92 children	C3GN 26 DDD 48 IC-MPGN 18	**Persistently low C3** **C3GN 53.8%** **DDD 53.2%** **IC-MPGN16.7%**	NR	NR	NR	NR	NR	Median 52	DDD 39.6 C3GN 7.7 IC-MPGN 11.1
[21]Kirpalani 2020	85 children	42 IC-MPGN 43 C3G	**Mean C3[c]** **IC-MPGN 0.26** **C3G 0.39**	Mean C4 IC-MPGN 0.21 C3G 0.25	NR	NR	NR	NR	Mean 48	IC-MPGN 5.7 C3G 7.3
[22]Medjeral-Thomas 2014	80	DDD 21 C3GN 59	**All 59.4** DDD 79 C3GN 48	All 23.3 DDD 15 C3GN 36	NR	NR	NR	NR	Median 28	DDD 47 C3GN 23
[23]Cansick 2004	53 children	MCGN 1 31 MCGN 2 3 MCGN 3 2 Unclassified 6	71.7	24.5	NR	NR	NR	NR	Median 42	15
[24]Zhang 2012	32 (22/10)	DDD	NR	NR	78[c]	3	Anti-FB 9	NR	Median 36	34.4
[25]Holle 2018	14 children	IC-MPGN 8 C3G 6	92.9	ND	30		Anti-CFB and Anti-C3b 1	7.1	Mean 27	7.1
[26]Okuda 2015	14 children	MPGN 4 C3GN 8 Unclassified 2	NR	NR	NR	NR	NR	NR	Not stated	0
[27]Drake 2020	9 (9/0)	DDD 4 C3GN 4 Indeterminate 1	75	0	83.3	20	Anti-FB 25	20	Mean 33	11.1
[28]Sparta 2018	7 children	MPGN 1 3 C3GN 3	100	NR	14.3	NR	Anti-C3b 28.5	57.1	NR	

		DDD 1								

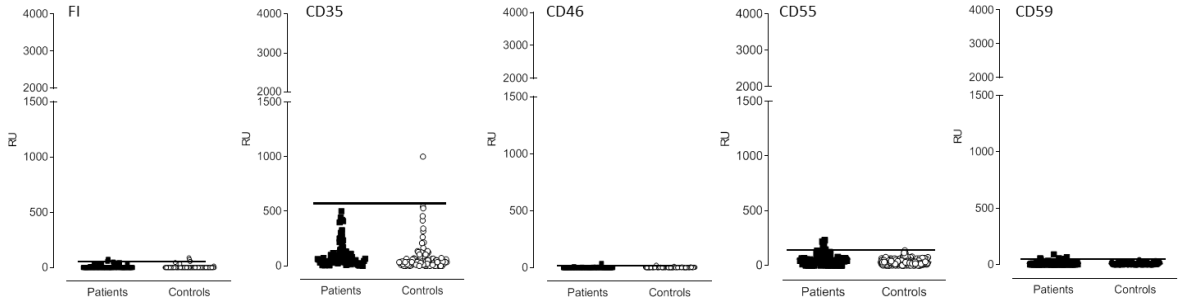
Data is reported for all patients in the cohort or sub-groups of patients (where indicated) with C3G = C3 glomerulopathy, C3GN = C3 glomerulonephritis, DDD = dense deposit disease, MPGN = membranoproliferative glomerulonephritis, MCGN = mesangiocapilliary glomerulonephritis, IC = immune-complex, Ig – immunoglobulin-associated.

NR= **not reported**

[a] Child defined as onset <18years except [b] where specified <16 years at onset.

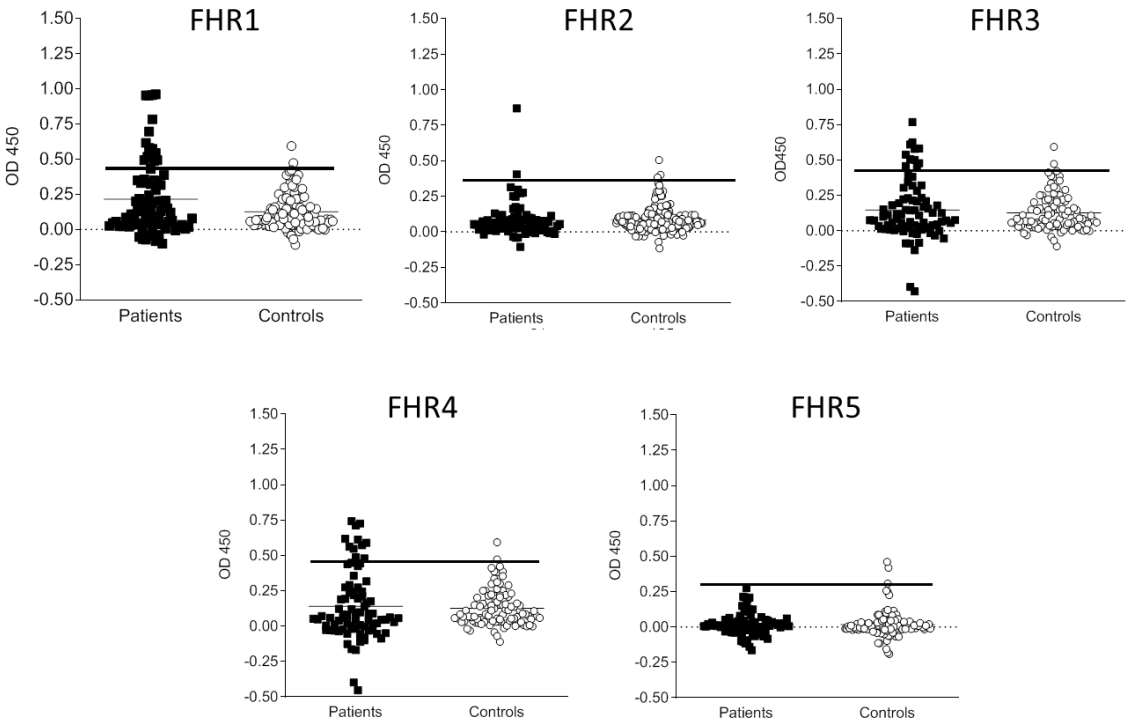
[c] Several different assays were used and this result was from the most sensitive assay

Supplemental Figure 1



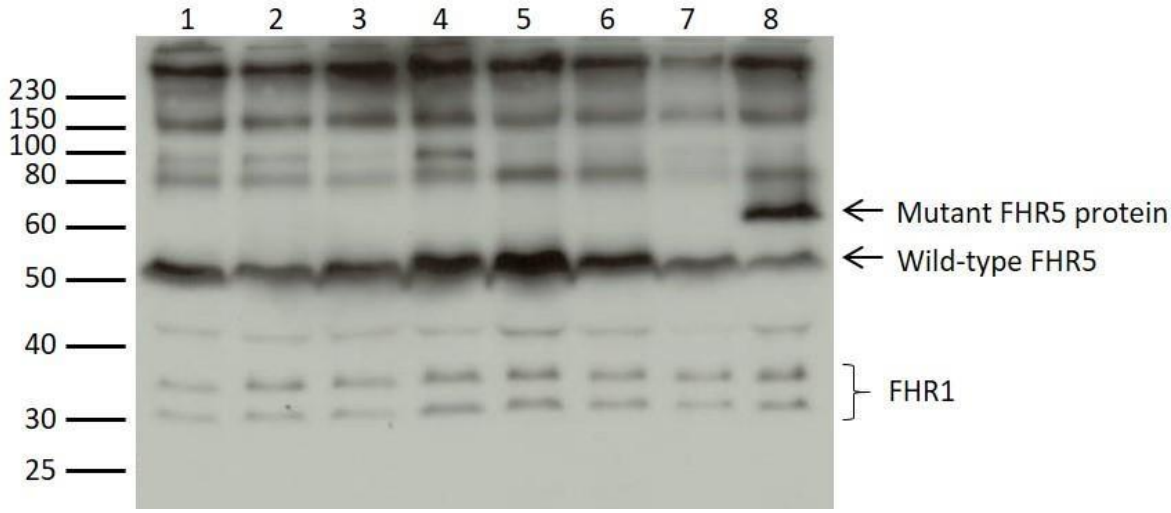
Screening serum from patients with C3 glomerulonephritis, dense deposit disease, immune-complex MPGN and immune-complex GN following central pathology review for auto-antibodies against complement factor I (FI), CD46, CD35, CD55 or CD59. Controls = local blood donors, line indicates 97.5th percentile, the minimum threshold for identifying an autoantibody. RU = relative unit to standard published in (Watson et al, 2015). No evidence of specific autoantibodies were identified. Positive findings were not confirmed in western blot testing.

Supplemental Figure 2



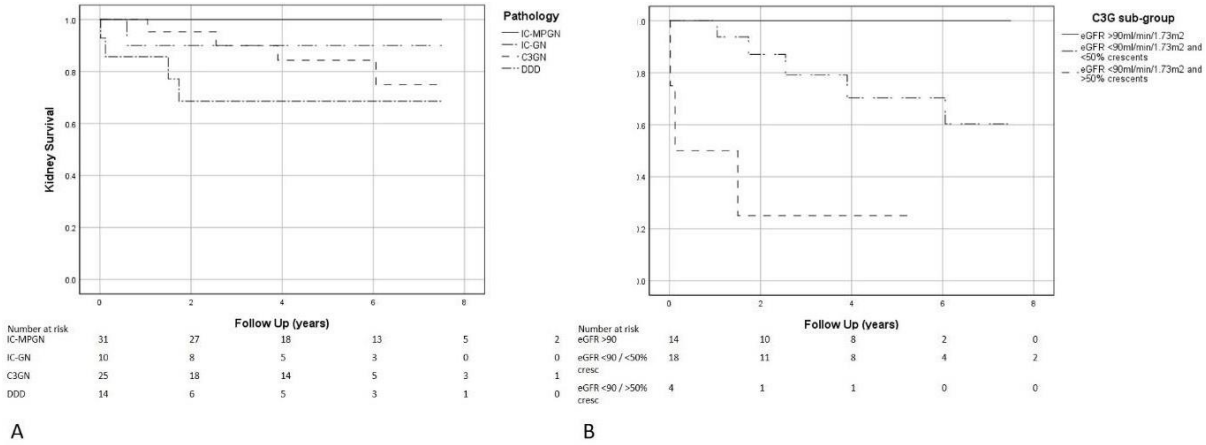
Screening serum from patients with C3 glomerulonephritis, dense deposit disease, immune-complex MPGN and immune-complex GN for auto-antibodies against complement factor H related proteins 1-5 (FHR1- 5). Line indicates 97.5th percentile of the blood donor control group, the minimum threshold for identifying an autoantibody. Potential autoantibodies were identified against CFHR1-4 using this cut off however positive findings were not confirmed in western blot testing.

Supplemental Figure 3



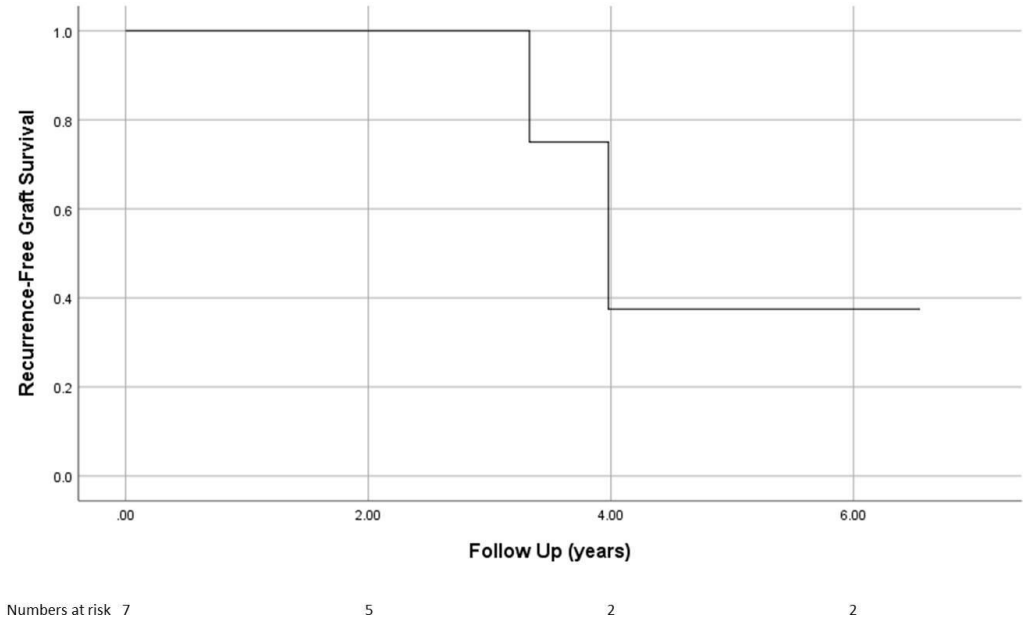
Western blot to detect factor H-related protein 5 (FHR5). Lanes 1-7 represent sera from cases. Lane 8 is sera from a patient with CFHR5 nephropathy. The wild-type FHR5 band is indicated by the arrow and is seen in all lanes. The mutant FHR5 protein associated with CFHR5 nephropathy is seen in lane 8 but is absent in the other cases. Western blotting was performed under non-reducing conditions using 10% gel. 0.5 and 1 µl of sera was loaded per lane for the FH and FHR5 gels respectively. Molecular weight (MW) markers in kDa are indicated.

Supplemental Figure 4



Kaplan-Meier analysis of kidney survival a) whole cohort by pathology and b) C3 glomerulopathy by stratified sub-groups.

Supplemental Figure 5



Kaplan-Meier analysis of transplant graft survival in patients with C3 glomerulopathy