Table S1: Complement gene abnormalities identified in index cases as well as in affected and healthy carriers with their frequency, pathogenicity and classification.

Gene	Index Cases (n)	Healthy Carriers (n)	Affected Carriers (n)	Nucleotide Change	Aminoacid Change	Variant Effect	Allele Frequncy (ExAC)	aHUS DB	Varsome	Franklin	REFERENCES (Doi, PMID)	Final Classification
C3[(1)]	1	1	1	c.193A>C	p.(Lys65Gln)	Missense	$4.77*10^{-5}$	P	VUS	VUS	#, 30046676, 22669319, 29500241 25608561	P
	1	1	0	c.199C>G	p.(Leu67Val)	Missense	ND	A	LB	VUS	-	VUS
	1	0	4	c.485C>G	p.(Thr162Arg)	Missense	ND	VUS	LB	VUS	§, 27064621, 24161037, 29500241 25608561	P
	1[A]	2	0	c.831T>G	p.(Asp277Glu)[A]	Missense	$1.19*10^{-5}$	A	LB	VUS	-	VUS
	0	2	0	c.1228A>G	p.(Ser410Gly)[I]	Missense	ND	A	VUS	VUS	-	VUS
	0	2	0	c.1518G>T	p.(Ala540Ser)[C]	Missense	ND	A	VUS	VUS	-	VUS
	1	2	1	c.1774C>T	p.(Arg592Trp)	Missense	$3.98*10^{-6}$	VUS	LP	VUS	25879158, 18796626, 31118930, 29500241 25608561	P
	1	2	0	c.2203C>T	p.(Arg735Trp)	Missense	$2.18*10^{-3}$	B	LB	VUS	18796626, 30890598, 29500241	VUS
	1	1	0	c.3133G>A	p.(Ala1045Thr)	Missense	$3.19*10^{-5}$	A	VUS	VUS	-	VUS
	1	1+1[M]	0	c.3343G>A	p.(Asp1115Asn)[L,M]	Missense	ND	P	LP	VUS	#, 30890598, 29500241, 18796626 25608561	P
	1	2	0	c.4383C>A	p.(Phe1461Leu)	Missense	ND	A	VUS	VUS	-	VUS
	1	2	0	c.4484C>T	p.(Pro1495Leu)	Missense	$2.39*10^{-5}$	A	LB	VUS	-	VUS
	1	1	0	c.4811T>C	p.(Met1604Thr)	Missense	$2.78*10^{-5}$	A	LB	VUS	-	VUS
CFB[(1)]	1	3	0	c.1407C>G	p.(Ile469Met)	Missense	$9.72*10^{-5}$	VUS	LB	VUS	29500241	VUS
CFH[(1)]	1	1	0	c.7C>G	p.(Leu3Val)	Missense	$2.43*10^{-4}$	A	LB	VUS	25814826	VUS
	1[B]	1	0	c.29T>G	p.(Leu10Arg)[B]	Missense	ND	A	VUS	VUS	-	VUS
	1[C]	6	2	c.157C>T	p.(Arg53Cys)[C]	Missense	$1.99*10^{-5}$	P	VUS	VUS	#, 25188723, 26826462, 29500241	P
	1	3	0	c.239G>C	p.(Cys80Ser)	Missense	ND	LP	VUS	VUS	29500241	LP
	1	1	3	c.388G>A	p.(Asp130Asn)	Missense	$1.4*10^{-4}$	ND	LB	VUS	22456601	VUS
	2	2	0	c.1832G>A	p.(Cys611Tyr)	Missense	ND	A	VUS	VUS	#	LP
	1	4	1	c.1873G>A	p.(Glu625Lys)	Missense	$3.99*10^{-6}$	A	LB	VUS	-	VUS
	1	4	0	c.2383G>A	p.(Gly795Arg)	Missense	ND	LP	VUS	VUS	29500241	LP
	1	1	0	c.2650T>C	p.(Ser884Pro)	Missense	$2.79*10^{-5}$	VUS	LB	VUS	29500241	VUS
	1	1	0	c.2776T>C	p.(Cys926Arg)	Missense	ND	A	VUS	VUS	31118930	LP
	4	9	0	c.2850G>T	p.(Gln950His)	Missense	$3.94*10^{-3}$	LB	B	B	#, 16621965, 24799305, 25188723, 31118930, 29500241 25733390	VUS

	1	2	0	c.3489C>G	p.(Cys1163Trp)	Missense	ND	LP	VUS	VUS	#, 14583443, 18796626, 29500241	LP
	1	2	0	c.3514G>T	p.(Glu1172*)	Nonsense	$1.2*10^{-5}$	LP	P	LP	#, 12697737, 29215813, 29500241	LP
	2	3	0	c.3572C>T	p.(Ser1191Leu)	Missense	ND	P	LB	VUS	#, 10577907, 19856002, 29500241	P
	1	3	0	c.3590T>C	p.(Val1197Ala)	Missense	$3.98*10^{-6}$	P	LB	VUS	#, 16470555, 31791575, 29500241	P
	1[D]	1[N]	0	c.3611G>A	p.(Gly1204Glu)[D,N]	Missense	ND	A	VUS	VUS	24799305, 25188723, 17089378	P
	1[E]+1[F]+1[G]+1[H]	6+1[O]	3	c.3628C>T	p.(Arg1210Cys)[E,F,G,H,O]	Missense	$1.43*10^{-4}$	P	LB	LP	#, 11170895, 25188723, 29500241	P
	1	6	5	c.3644G>A	p.(Arg1215Gln)	Missense	ND	LP	LP	LP	#, 24799305, 31791575, 29500241	LP
	1	3	0	c.3693_3696delATAG	p.(*1232Ilefs*38)	Frameshift	ND	LP	VUS	VUS	#, 24799305, 17599974, 27177491, 29500241	LP
CFH and Related LGR	1	3	0	CFH::CFHR1	p.CFH/CFHR1 hybrid	LGR	ND	LGR	ND	ND	20974643	P
	1	3	2	DupCFH(CFH1/CFH18)	p.?	LGR	ND	LGR	ND	ND	-	P
	1	1	0	DupCFHex23-CFHR1ex3	p.?	LGR	ND	LGR	ND	ND	-	P
	3	4	3	CFHR1::CFH	p.CFHR1/CFH hybrid	LGR	ND	LGR	ND	ND	23880784, 24904082	P
	1	4	0	CFHR3::CFHR4	p.CFHR3/CFHR4 hybrid [E]	LGR	ND	LGR	ND	ND	23880784	P
CFI[(1)]	1	2	1	c.96_110del	p.(Cys33_Lys37del)	Deletion	ND	LP	LP	VUS	29500241	LP
	1[I]	2	0	c.355G>A	p.(Gly119Arg)[i]	Missense	$4.22*10^{-4}$	VUS	LP	VUS	#, 20016463, 20513133, 27799617, 29500241	VUS
	1	2	0	c.482+8C>T	p.?	Splice site?	$3.94*10^{-4}$	A	VUS	LB	-	VUS
	1	2	0	c.805G>A	p.(Gly269Ser)	Missense	$1.43*10^{-4}$	A	VUS	VUS	#, 24656451, 26613809	VUS
	1	1	0	c.949C>T	p.(Arg317Trp)	Missense	$8.76*10^{-5}$	P	VUS	VUS	16621965, 29500241	P
	1	4	0	c.1045G>A	p.(Gly349Arg)	Missense	ND	LP	LP	VUS	29500241	LP
	0	1	0	c.1071T>G	p.(Ile357Met)[F]	Missense	$3.58*10^{-5}$	VUS	P	VUS	20106822, 29500241	VUS
	0	4	0	c.1217G>A	p.(Arg406His) [A]	Missense	$1.68*10^{-2}$	A	B	B	31312772, 15173250	VUS
	1[L]	1	0	c.1246A>C	p.(Ile416Leu) [L,M]	Missense	$1.68*10^{-2}$	VUS	B	B	20016463 23307876 29500241	VUS
	1	1	0	c.1343G>T	p.(Arg448Leu)	Missense	ND	A	VUS	VUS	-	VUS
	1	10	0	c.1555G>A	p.(Asp519Asn)[G]	Missense	$7.96*10^{-6}$	P	LP	VUS	16621965, 19877009, 17597211,	P

											29500241	
CD46[(1)]	1	0	1	c.98-1G>C	p.?	Splice site	ND	A	P	LP	16621965, 1984685	LP
	0	0	0	c.104G>A	p.(Cys35Tyr)[H,O]	Missense	$1.19*10^{-5}$	LP	VUS	VUS	#, 16621965, 25188723, 29500241	LP
	1	5	0	c.175C>T	p.(Arg59*)[H,O]	Nonsense	$1.19*10^{-5}$	P	LP	LP	#, 26054645, 29500241, 16621965	P
	4	7	1	c.286+2T>G	p.?[D,F,N]	Splice site	$5.21*10^{-5}$	LP	P	LP	#, 16762990, 25899302, 29500241	LP
	1	1	0	c.404G>A	p.(Gly135Asp)	Missense	$4.02*10^{-6}$	ND	VUS	VUS	#, 21706448, 25188723	VUS
	1	1	0	c.523T>G	p.(Phe175Val)	Missense	$7.96*10^{-6}$	A	LB	VUS	-	VUS
	2	4	0	c.565T>G	p.(Tyr189Asp)[B]	Missense	$1.59*10^{-5}$	LP	VUS	VUS	16762990, 25188723, 29644059, 29500241	LP
	1	2	0	c.664G>T	p.(Glu222*)	Nonsense	ND	A	P	LP	-	LP
	2	4	0	c.685C>T	p.(Arg229*)	Nonsense	ND	LP	P	P	#, 25443527, 29500241	LP
	3	6	0	c.1148C>T	p.(Thr383Ile)	Missense	$7.12*10^{-4}$	VUS	LB	VUS	#, 29500241, 21706448	VUS

DB= database; A= absent; B= benign; LB= likely benign; VUS= variant of unknown significance; LP=likely pathogenic; P=pathogenic; ND= not defined; LGR= large genomic rearrangement;

(1) C3: NM_000064, NP_000055; CFB: NM_001710, NP_001701; CFH: NM_000186, NP_000177; CFHR1: NM_002113, NP_002104; CFHR3: NM_021023, NP_066303; CFHR4: NM_001201550, NP_001188479, CFI: NM_000204, NP_000195; CD46: NM_002389, NP_002380;

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Letters identify members of families with multiple gene variants (from A to L identify the ten index cases; from M to O identify the three healthy carriers).

Modified STROBE Statement—checklist of items that should be included in reports of observational studies (Cohort/Cross-sectional and case-control studies)

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5

		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	-
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	-
		Case-control study—If applicable, explain how matching of cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(c) Consider use of a flow diagram	Fig.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	5-6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	tab. 2
		Cross-sectional study—Report numbers of outcome events or summary measure	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tab.2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6

Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7-8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.