Supplemental data

The Syndromes of Thrombotic Microangiopathy: A Critical Appraisal on Complement Dysregulation

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Table S1. Classification of rare variants in *CFH*, *CFI*, *CD46*, *CFB*, *C3*, *THBD*, and *CFHR1-5* found in patients with secondary thrombotic microangiopathy.

Condition	No.	Gene	cDNA	Protein	MAF (%)	PolyPhen-2/SIFT	*In vitro*	Significance[b]
STEC-HUS								
Frémeaux-Bacchi *et al.*[1] (*N*=75)	1	*CFH*	c.2850G>T[c]	p.Q950H	0.1-0.4	Prob. damaging/Del.	LOF(?)[2]	Pathogenic → **Benign**[d]
	2	*THBD*	c.1483C>T[c]	p.P495S	0.06-0.09	Benign/Tol.	LOF[3]	**Pathogenic**
	3	*CFH*	c.1145C>A	p.A382E	0	Prob. damaging/Tol.	LOF[1]	**Pathogenic**
	4	*CD46*	c.503_504insA	p.N170Kfs*7	0	N/a	LOF[1]	**Pathogenic**
	?	*C3*	c.2203C>T[c]	p.R735W	0.1-0.3	Prob. damaging/Del.	Normal[4]	VUS → **Benign**[d]
	?	*C3*	c.2203C>T[c]	p.R735W	0.1-0.3	Prob. damaging/Del.	Normal[4]	VUS → **Benign**[d]
	?	*C3*	c.2203C>T[c]	p.R735W	0.1-0.3	Prob. damaging/Del.	Normal[4]	VUS → **Benign**[d]
	?	*C3*	c.4369G>C	p.D1457H	0.1	Prob. damaging/Del.	–	VUS → **Benign**[d]
	?	*C3*	c.1618G>T	p.A540S	<0.01	Benign/Tol.	–	**VUS**
	?	*CFB*	c.978A>C[c]	p.E326D	<0.1	Benign/Tol.	–	**VUS**
	?	*CFI*	c.782G>A[c]	p.G261D	0.1	Benign/Tol.	Normal[5]	VUS → **Benign**[d]
	?	*THBD*	c.829G>T	p.G277W	0	Prob. damaging/Del.	–	**VUS**
Ahlenstiel-Grunow *et al.*[6] (*N*=25)	?	*C3*	c.476T>A	p.V159E	0	Poss. damaging/Tol.	–	**VUS**
	?	*CFI*	c.1657C>T[c]	p.P553S	0.1	Benign/Tol.	–	VUS → **Benign**[d]
Westra et al.[7] (*N*=25)	P14	*C3*	c.3656G>A[c]	p.R1219H	<0.01	Benign/Tol.	–	**VUS**
	P21	*CFH*	c.2867C>T[c]	p.T956M	0.1	Poss. damaging/Tol.	Normal[8]	**Benign**
	P25	*C3*	c.463T>G[c]	p.K155Q	02.-0.4	Benign/Tol.	GOF[9]	Pathogenic → **Benign**[d]
	P29	*CFH*	c.172T>G[c]	p.S58A	0.02	Benign/Tol.	LOF[8]	**VUS**
Total, *n*/*N*[a]	9/125							**Pathogenic**, *n*/*N*=3/125
Post-diarrheal HUS								
Frémeaux-Bacchi *et al.*[1] (*N*=33)	5	*THBD*	c.127G>A[c]	p.A43T	0.2-0.4	Benign/Tol.	LOF[3]	Pathogenic → **Benign**[d]
	6	*CFH*	c.3628C>T[c]	p.R1210C	0.02	Benign/Tol.	LOF[10]	**Pathogenic**
		C3	c.4319A>C[c]	p.D1440A	0.02-0.05	Benign/Tol.	–	**VUS**
	?	*CFH*	c.2867C>T[c]	p.T956M	0.1	Poss. damaging/Tol.	Normal[8]	VUS → **Benign**[d]
	?	*C3*	c.4855A>C[c]	p.S1619R	0.1-0.2	Poss. damaging/Tol.	Normal[11]	VUS → **Benign**[d]
	?	*C3*	c.4855A>C[c]	p.S1619R	0.1-0.2	Poss. damaging/Tol.	Normal[11]	VUS → **Benign**[d]
	?	*C3*	c.4177C>T	p.R1393W	<0.01	Poss. damaging/Del.	–	**VUS**
Total, *n*/*N*[a]	2/33							**Pathogenic**, *n*/*N*=1/33
Pneumococcal HUS								
Szilágyi *et al.*[12] (*N*=5)	3	*CFH*	c.3445C>T	p.R1149X	<0.01	N/a	–	**Pathogenic**
	4	*CFI*	c.148C>G[c]	p.P50A	<0.02	Prob. damaging/Del.	LOF[13]	**Pathogenic**
	5	*THBD*	c.131C>T	p.T44I	<0.01	Benign/Tol.	–	**VUS**
Total, *n*/*N*[a]	3/5							**Pathogenic**, *n*/*N*=2/5

Drug-induced TMA								
Le Clech *et al.*[14] (*N*=32)	3	*CFI*	c.11T>A	p.L4H	0.02	Benign/Tol.	–	**VUS**
	6	*CFH*	c.3596T>C[c]	p.F1199S	0	Poss. damaging/Del.	LOF[15]	**Pathogenic**
Total, *n*/*N*[a]	2/32							**Pathogenic**, *n*/*N*=1/32
Cancer								
Le Clech *et al.*[14] (*N*=11)	2	*THBD*	c.91G>A	p.V31I	0	Benign/Tol.	–	**VUS**
	5	*CFH*	c.3047A>G[c]	p.Y1016C	0	Prob. damaging/Del.	–	**Pathogenic**
Total, *n*/*N*[a]	2/11							**Pathogenic**, *n*/*N*=1/11
Autoimmunity								
Le Clech *et al.*[14] (*N*=26)	1	*THBD*	c.707C>G	p.A236G	0.02	Benign/Tol.	–	**VUS**
Cavero *et al.*[16] (*N*=8)	22	*CFHR1*	c.869T>C	p.L290S	<0.01	Benign/Tol.	–	Pathogenic → **VUS**[d]
		CFHR1	c.887C>T	p.A296V	<0.1	Benign/Tol.	–	Pathogenic → **VUS**[d]
Chaturverdi *et al.*[17] (*N*=10)	CAPS3	*THBD*	c.1502C>T[c]	p.P501L	0.2	Benign/Del.	LOF[3]	Pathogenic → **Benign**[d]
	CAPS6	*CFHR4*	c.860G>A	p.R287H	<0.01	Benign/Tol.	–	**VUS**
Park *et al.*[18] (*N*=10)	1	*THBD*	c.127G>A[c]	p.A43T	0.2-0.4	Benign/Tol.	LOF[3]	**Benign**
	2	*CFH*	c.184G>A[c]	p.V62I	>5	Benign/Tol.	–	**Benign**
		CFH	c.1204C>T[c]	p.H402Y	>5	Benign/Tol.	–	**Benign**
	6	*CFB*	c.724A>C[c]	p.I242L	<0.2	Benign/Tol.	–	**VUS**
		CFHR5	c.384G>T	p.S128S	0.1	Synonymous	–	**Benign**
		CD46	c.989-78G>A	N/a	35	N/a	–	**Benign**
		CFH	c.1204C>T[c]	p.H402Y	>5	Benign/Tol.	–	**Benign**
	8	*THBD*	c.1456G>T[c]	p.D486Y	0.02-0.2	Benign/Tol.	LOF[3]	**VUS**
		CFH	c.184G>A[c]	p.V62I	>5	Benign/Tol.	–	**Benign**
	9	*CD46*	c.989-78G>A	N/a	35	N/a	–	**Benign**
	11	*CFI*	c.1217G>A	p.R406H	0.1-1	Benign/Tol.	Normal[19]	**Benign**
Total, *n*/*N*[a]	5/54							**Pathogenic**, *n*/*N*=0/54
HSCT-TMA								
Jodele *et al.*[20] (*N*=34)	?	*CD46*	c.971C>T[c]	p.P324L	0.2	Prob. damaging/Del.	LOF[21]	VUS → **Benign**[d]
	?	*CFI*	c.1246A>C[c]	p.I416L	0.4	Benign/Tol.	LOF[13]	Pathogenic → **Benign**[d]
	?	*CD46*	c.796G>A[c]	p.D266N	0.3-0.4	Benign/Tol.	–	VUS → **Benign**[d]
	?	*C3*	c.1243C>A	p.P415T	0	Benign/Tol.	–	**VUS**
	?	*THBD*	c.1208G>A[c]	p.R403K	0.02-0.03	Benign/Tol.	–	**VUS**
		CFHR5	c.486_487insA	p.E163Rfs*35	0.2	N/a	–	Pathogenic → **Benign**[d]
		CFHR5	c.622T>C	p.C208R	0.2	Prob. damaging/Del.	–	VUS → **Benign**[d]
	?	*CFI*	c.1217G>A	p.R406H	0.1-1	Benign/Tol.	Normal[19]	VUS → **Benign**[d]
	?	*C3*	c.463T>G[c]	p.K155Q	0.2-0.4	Benign/Tol.	GOF[9]	Pathogenic → **Benign**[d]
	?	*CFI*	c.1534+5G>T[c]	N/a	0.9-1.1	N/a	–	Pathogenic → **Benign**[d]
	?	*CFI*	c.1534+5G>T[c]	N/a	0.9-1.1	N/a	–	Pathogenic → **Benign**[d]

		CFI	c.1657C>T[c]	p.P553S	0.1	Benign/Tol.	–	VUS → **Benign**[d]
	?	*CFI*	c.1322A>G[c]	p.K441R	0.1	Benign/Tol.	–	Pathogenic → **Benign**[d]
		CFB	c.1697A>C[c]	p.E566A	0.7	Benign/Tol.	–	VUS → **Benign**[d]
	?	*CFB*	c.1729G>A[c]	p.V577I	0.01	Benign/Tol.	–	**VUS**
		CFB	c.2005G>C[c]	p.V669L	0.01	Benign/Tol.	–	**VUS**
Jodele *et al*.[22] (*N*=30)	1	*C3*	c.2203C>T[c]	p.R735W	0.2-0.3	Prob. damaging/Del.	Normal[4]	Pathogenic → **Benign**[d]
		CFHR3	c.839_840del	p.I280fs	0.1	N/a	–	VUS → **Benign**[d]
	2	*CFB*	c.95G>A	p.R32Q	>5	Benign/Tol.	–	VUS → **Benign**[d]
		CFHR3	c.786A>T	p.P262P	>5	N/a	–	VUS → **Benign**[d]
	3	*CFB*	c.95G>A	p.R32Q	>5	Benign/Tol.	–	VUS → **Benign**[d]
	4	*CFHR5*	c.486_487insAA	p.E163fs	0	N/a.	–	**VUS**
	5	*CFB*	c.95G>A	p.R32Q	>5	Benign/Tol.	–	VUS → **Benign**[d]
		CFH	c.2850G>T[c]	p.Q950H	0.1-0.4	Prob. damaging/Del.	LOF(?)[2]	VUS → **Benign**[d]
	6	*THBD*	c.1502C>T[c]	p.P501L	0.2	Benign/Del.	LOF[3]	Pathogenic → **Benign**[d]
	7	*CFHR3*	c.786A>T	p.P262P	>5	N/a	–	VUS → **Benign**[d]
		CFHR5	c.1067G>A	p.R356H	>2	Poss. damaging/Del.	–	**Benign**
	8	*CFB*	c.95G>A	p.R32Q	>5	Benign/Tol.	–	VUS → **Benign**[d]
	11	*CFB*	c.559G>A	p.V187I	0	Poss. damaging/Del.	–	**VUS**
		CD46	c.1058C>T[c]	p.A353V	>1	Benign/Tol.	Normal[23]	VUS → **Benign**[d]
	13	*CFB*	c.1697A>C[c]	p.E556A	0.7	Benign/Tol.	–	VUS → **Benign**[d]
	14	*CFB*	c.1697A>C[c]	p.E556A	0.7	Benign/Tol.	–	VUS → **Benign**[d]
		CFHR1	c.310C>T	p.H104Y	<0.03	Benign/Tol.	–	**VUS**
	18	*CFB*	c.1697A>C[c]	p.E556A	0.7	Benign/Tol.	–	VUS → **Benign**[d]
		CFH	c.3506T>C	p.I1169T	<0.01	Benign/Del.	–	**VUS**
Total, *n*/*N*[a]	7/64							**Pathogenic**, *n*/*N*=0/64
DGKE-HUS								
Azukaitis *et al*.[24] (*N*=44)	HUS39	*THBD*	c.1456G>T[c]	p.D486Y	0.02-0.2	Benign/Tol.	LOF[3]	Pathogenic → **VUS**[d]
	HUS40	*THBD*	c.1456G>T[c]	p.D486Y	0.02-0.2	Benign/Tol.	LOF[3]	Pathogenic → **VUS**[d]
	HUS272	*C3*	c.784G>T[c]	p.G262W	0	Prob. damaging/Del.	–	**VUS**
Total, *n*/*N*[a]	3/44							**Pathogenic**, *n*/*N*=0/44
Cobalamin C deficiency								
Beck *et al*.[25]	27	*CFH*	Unknown	N/a	N/a	N/a	N/a	**VUS**
Total, *n*/*N*[a]	1/27							**Pathogenic**, *n*/*N*=0/27

[a] Number indicates pathogenic variants and variants of uncertain significance.

[b] The classification of variants was based on international standards.[26, 27] Pathogenic variants (depicted in red) were defined as those with functional studies supporting a defect in complement regulation, including null variants in genes linked to complement regulation (not including *CFB* and *C3*) and at least one of the following: located in a mutational hotspot, located in a functional domain, and/or cluster in patients with

primary atypical hemolytic uremic syndrome.[27] Benign variants (depicted in green) were defined as those with a minor allele frequency of ≥0.1% and/or functional studies supporting normal complement regulation. Rare variants, that is, those with a minor allele frequency of <0.1%, not fulfilling these criteria have been classified as uncertain significance.

[c] Variant has been identified in the database of complement gene variants (http://www.complement-db.org/home.php).

[d] Variant has been reclassified.

Del., deleterious. DGKE, diacylglycerol kinase epsilon. GOF, gain-of-function. HSCT-TMA, hematopoietic stem cell transplantation-thrombotic microangiopathy. HUS, hemolytic uremic syndrome. LOF, loss-of-function. MAF, minor allele frequency according to the Exome Variant Server (EVS) and Genome Aggregation Database (gnomAD). Prob. damaging, probably damaging. Poss. damaging, possibly damaging. STEC, Shiga toxin-producing E. *coli*. Tol., tolerated. VUS, variant of uncertain significance.

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