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Evaluating the clinical utility of measuring levels of factor H and the related proteins

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ABSTRACT

After years of disappointing clinical results, the tide has finally changed and complement targeted-therapies have become a validated and accepted treatment option for several diseases. These accomplishments have revitalized the field and brought renewed attention to the prospects that complement therapeutics can offer. Streamlining diagnostics and therapeutics is imperative in this new era of clinical use of complement therapeutics. However, the incredible success in therapeutics has not been accompanied by the development of novel standardized tools for complement testing. Complement biomarkers can assist in the risk assessment and diagnosis of diseases as well as the prediction of disease progression and treatment response. Recently, a group of complement proteins has been suggested to be highly relevant in various complement-associated disorders, namely the human factor H (FH) protein family. This family of closely related proteins consists of FH, FH-like protein 1, and five factor H-related proteins, and they have been linked to eye, kidney, infectious, vascular, and autoimmune diseases as well as cancer. The goal of this review is to provide a comprehensive overview of the available data on circulating levels of FH and its related proteins in different pathologies. In addition, we examined the current literature to determine the clinical utility of measuring levels of the FH protein family in health and disease. Finally, we discuss future steps that are needed to make their clinical translation a reality.

Abbreviations: AAV, ANCA-associated vasculitis; aHUS, Atypical hemolytic uremic syndrome; AMD, Age-related macular degeneration; ANCA, Anti-neutrophil cytoplasmic antibody; AP, Alternative pathway; C3G, C3 glomerulopathy; CCP, Complement control protein; *CFH*, Human complement factor H gene; *Cfh*,, Mouse complement factor H gene; *CFHR*,, Human complement factor H-related genes; *CFHR3–1*Δ, Deletion of *CFHR3* and *CFHR1*; CRASPs, Complement regulator-acquiring surface proteins; CRP, C-reactive protein; CVD, Cardiovascular disease; FB, Factor B; FH, Factor H; fHbp, Meningococcal factor H binding protein; FHL-1, Factor H-like 1; FHRs, Factor H-related proteins; FI, Factor I; GWAS, Genome-wide association studies; IgAN, Immunoglobulin A nephropathy; MD, Meningococcal disease; PNH, Paroxysmal nocturnal hemoglobinuria; RCA, Regulators of complement activation; SLE, Systemic lupus erythematosus; SNP, Single nucleotide polymorphism.

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1. Introduction

In the past two decades, complement therapeutics have elicited tremendous excitement due to their success in achieving durable responses in previously difficult-to-treat diseases, such as paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) (Hillmen et al., 2006; Legendre et al., 2013). These accomplishments renewed interest in the potential of complement therapeutics for other clinical conditions (Garred et al., 2021). Of note, the structure and complexity of the complement system creates the opportunity to select different targets at various levels within the cascade (Ricklin et al., 2018). In addition to these various targets, there is an equally diverse arsenal of available therapeutic strategies, ranging from orally administered small-molecules to subcutaneous injected small-interfering RNAs and intravenous infused monoclonal antibodies (Mastellos et al., 2019). Consequently, multiple clinical trials are currently ongoing for various diseases with an impressive panel of complement therapeutics (Harris et al., 2018; Poppelaars and Thurman, 2020; Pouw and Ricklin, 2021; Zelek et al., 2019). In some diseases, even multiple different complement therapeutics are being evaluated. For example, in IgA nephropathy (IgAN) ongoing clinical trials are assessing the efficacy of seven distinct complement inhibitors (Poppelaars et al., 2021a). Altogether, these trials offer an early glimpse into the future of disease-tailored complement targeting therapies. Moreover, results are published at a breathtaking pace (Hasturk et al., 2021; Jaffe et al., 2021; Kulagin et al., 2021; Kulasekararaj et al., 2021; Lafayette et al., 2020; Pittock et al., 2019; Risitano et al., 2021). In 2021 alone, the positive results of three phase III clinical trials with complement therapeutics were published in the New England Journal of Medicine, namely: (i) Avacopan (an oral C5a receptor antagonist) in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (Jayne et al., 2021), (ii) Pegcetacoplan (an oral C3 inhibitor) in PNH (Hillmen et al., 2021), and (iii) Sutimlimab (a blocking monoclonal antibody against C1s) in cold agglutinin disease (Röth et al., 2021).

This incredible success is threatened to be slowed down due to the lack of clinically available complement measurements (Bomback et al., 2022; Frazer-Abel et al., 2021; Willrich et al., 2021). Complement analysis in routine clinical laboratories tends to be limited to measuring C3 and C4 with the possible addition of C1q. All other complement assays require a specialized laboratory. To further complicate matters, many of the tests in development or used in research have not been standardized and do not address potential variances in assessing complement (Bomback et al., 2022; Frazer-Abel et al., 2021; Willrich et al., 2021). Thus, streamlining the development and use of complement diagnostics in a standardized manner is imperative in this new era of clinical complement therapeutics. It is commonly accepted that complement biomarkers are valuable to assess whether the system is effectively inhibited, thereby improving the pharmacodynamics and pharmacokinetics of complement therapeutics (Bomback et al., 2022; Prohászka et al., 2018). Moreover, complement biomarkers have the potential to serve as diagnostic, prognostic, and predictive tools to help clinicians identify the presence of disease and disease stage, predict disease outcome and progression, as well as anticipate the response to treatment. It is therefore vital to identify and validate novel complement biomarkers that will be useful for physicians as well as for patients and to optimize and standardize these assays for clinical use. In this regard, multiple reports have described altered levels of a specific group of complement proteins, named the factor H (FH) protein family, in patients with complement-associated diseases. Despite the presence of several challenges and hurdles in this field (Poppelaars et al., 2021b), the results of these studies suggest significant promise for future clinical use of the FH protein family as biomarkers in complement-mediated diseases. Nevertheless, much more needs to be understood about the FH protein family, such as their role in complement biology and how they add to human disease. In the current review, we, therefore, provide an updated overview of the available data and potential clinical utility of measuring circulating levels of FH and its related proteins in different groups of diseases.

2. Measurements of the factor H protein family in disease

The FH protein family consists of seven unique proteins, namely FH, factor H-like protein 1 (FHL-1), and five factor H-related proteins (FHRs). These plasma proteins are primarily produced in the liver but extra-hepatic production has been reported for retinal pigment epithelial cells and glomerular mesangial cells (Estaller et al., 1991; McRae et al., 2001; Schwaeble et al., 1991, 1987; Van den Dobbelsteen et al., 1994). FH is one of the main regulators of the complement system by inhibiting the complement cascade and is abundantly present in blood. Specifically, FH can differentiate between self and non-self and averts complement activation in plasma as well as on cellular and non-cellular surfaces (Sánchez-Corral et al., 2018). Furthermore, FH is an important co-factor for factor I-mediated cleavage of C3b into iC3b (a C3 activation fragment that cannot promote further complement activation). FH accelerates the decay of existing alternative pathway (AP) C3-convertases and C5-convertases. Additionally, FH also competes with factor B (FB) to prevent the formation of the C3-based convertases C3(H_2O)Bb and C3bBb. FH is comprised of twenty structurally similar units commonly present in complement proteins and regulators, termed complement control protein (CCP) domains. The N-terminal domains (CCPs 1–4) of FH are responsible for the competition with FB, the decay-accelerating activity, and the FI co-factor activity, whereas an internal region located in CCPs 6–8 and the C-terminal CCPs 19–20 are needed for ligand binding and accordingly the protection of host surfaces (Ferreira et al., 2010; Kopp et al., 2012; Parente et al., 2017; Zipfel, 2001). FHL-1 was later discovered as an alternative splice variant of FH (Fontaine et al., 1989; Misasi et al., 1989; Schwaeble et al., 1987). In accordance, FHL-1 shares CCP domains 1–7 with FH but has a unique four amino acid C-terminal tail due to alternative splicing (Fontaine et al., 1989; Misasi et al., 1989; Schwaeble et al., 1987). Finally, humans also have five FH-related proteins (FHRs) encoded separately in tandem in the *CFH* locus; *CFHR3*, *CFHR1*, *CFHR4*, *CFHR2*, and *CFHR5* (Sánchez-Corral et al., 2018). FHL-1 has direct complement regulatory capabilities, identical to FH, but as it lacks the domains needed for host surface recognition it mainly seems to serve as fluid-phase regulator (Mannes et al., 2020). The functions of these altogether six related proteins are poorly understood. Nevertheless, their importance in various diseases has been established through genetic studies (Davila et al., 2010; Zipfel et al., 2020). Measuring FH and the FHRs could be of equal importance in these diseases. Measuring FH and FHR levels in disease will not only be important to understand the underlying pathological mechanisms but might also shed light on the still ambiguous function of the FHR proteins within the complement system. Below, current data is summarized on FH and FHRs levels in cancer, autoimmune and vascular diseases, kidney disease, eye disease, as well as infectious disease.

2.1. Cancer

The unexpected discovery that mice deficient in specific complement genes are protected from cancer, has prompted research into the role of complement in tumor biology (Markiewski et al., 2008). Since then, extensive research has confirmed the importance of the complement system in cancer and expanded on these findings (Thurman et al., 2020). Recent discoveries have made clear that complement is activated in many forms of tumors, and that the complement system plays a context-dependent role in anti-tumor immunity as well as carcinogenesis (Roumenina et al., 2019; Thurman et al., 2020). In the landmark paper by Laskowski et al., *Cfh* deficient mice were shown to spontaneously develop hepatocellular carcinoma, indicating a direct link between dysregulation of the FH protein family and tumor formation, at least in this organ (Laskowski et al., 2020). Furthermore, accumulating evidence shows that certain human cancer cell types can produce FH, FHL-1, FHR-1, FHR-3, and FHR-5 (DeCordova et al., 2019; Junnikkala et al., 2002; Liu et al., 2019; Zhang et al., 2019). In addition, data from The Cancer Genome Atlas has enabled the analysis of the expression of the FH family in human cancers. *CFH* is strongly expressed in the majority of the cancer types, whereas the expression of the *CFHR* is generally low or absent (Roumenina et al., 2019). A striking feature is the fact that cholangiocarcinoma is the only cancer type where all members of the FH family are highly expressed (Roumenina et al., 2019). Local expression of the FH family is also associated with prognosis in certain cancers. For example, higher expression of *CFH* and *CFHR3* has been shown to be associated with a better prognosis in patients with hepatocellular carcinoma (Laskowski et al., 2020; Liu et al., 2020). However, expression of *CFH* has also been linked to progression in cutaneous squamous cell carcinoma (Johnson et al., 2022; Riihilä et al., 2014), underscoring the context-dependent role of FH in cancer.

There are currently no published studies that measured circulating levels of the entire FH protein family in patients with cancer. Nevertheless, several pieces of evidence hint at the potential clinical utility of measuring circulating levels of FH and the related proteins in cancer patients (Table 1). For example, in patients with small-cell lung cancer, low plasma levels of FH were associated with a higher risk of cancer-related death (Xiang et al., 2021). Furthermore, within the past few years, proteomics studies have identified FHRs as possible candidate biomarkers for different cancers as well, such as thyroid cancer, hepatocellular carcinoma, ovarium cancer, colon carcinoma, and small cell lung cancer. For example, circulating levels of FHR-1 were higher in patients with thyroid cancer than in controls and FHR-1 levels were able to distinguish between subtypes (Li et al., 2020). In contrast, proteomics studies also revealed that patients with metastatic hepatocellular carcinoma have lower serum levels of FHR-1 than those without metastasis (Fu et al., 2009). This underscores that the role of FHRs in cancer is also context-dependent. Additionally, in patients with colorectal cancer, plasma levels of FHR-1, as well as FHR-4, were associated with the primary tumor location (Holm et al., 2020). Furthermore, plasma measurements of FHR-4 levels were also shown to help differentiate malignant from benign pulmonary nodules (Kuang et al., 2019). Recently, plasma-derived extracellular vesicles with FHR-4 deposits were shown to be a potential biomarker for the early diagnosis of small cell lung cancer (Pedersen et al., 2022). Proteomic analysis has also revealed that levels of FHR-4 and FHR-5 in serum of women with ovarian cancer are higher compared to controls and that these measurements might help in the early detection (Amon et al., 2010). In addition, the FH protein family has been suggested as a potential biomarker for cancer in other bodily fluids such as urinary levels of FH and FHR-1 in bladder cancer (Cheng et al., 2005), ascites levels of FHL-1 in ovarian cancer (Junnikkala et al., 2002), and FH levels in bronchoalveolar lavage samples from lung cancer patients (Pio et al., 2010). In conclusion, there is an increasing body of evidence implicating that measuring levels of the FH protein family holds great promise as novel biomarkers for the diagnosis and prognosis of certain cancers.

2.2. Autoimmune and vascular diseases

Unlike cancer, the role of the complement system in auto-immune diseases such as systemic lupus erythematosus (SLE), where tolerance to self-antigens is lost, has long been recognized (Weinstein et al., 2021). Early reports demonstrated that genetic deficiencies of the classical pathway are highly associated with the development of SLE (Brodszki et al., 2020). Initial case reports suggested that a genetic deficiency in FH might also lead to the development of SLE (Fijen et al., 1996),

Table 1
FH and FHR levels in cancer.

Cancer type	Protein	Technique (Company)	Matrix	Groups	Median/ Mean [μg/mL]	SD/ IQR [μg/mL]	N	P-value vs controls	Ref.
Ovarian cancer	FH/ FHL-1	In-house ELISA *(Abs described)*			Mean	SD			Junnikkala et al. (2002)
			Serum	Ovarian cancer	461	63	8	-	
			Ascites fluids	Ovarian cancer	758	312	16	<0.05	
				Liver cirrhosis	43	27	6	-	
Lung cancer	FH	In-house ELISA *(Abs described)*	Broncho-alveolar lavage fluids		Mean	SD			Pio et al. (2010)
				Lung disease I	1.17	1.5	22	-	
				Lung cancer I	2.61	1.88	17	<0.01	
				Lung disease II	0.41	0.46	25	-	
				Lung cancer II	2.65	2.2	26	<0.001	
Thyroid cancer	FHR-1	Commercial ELISA *(Novus/ Bio-Techne)*	Serum		Median	IQR			Li et al. (2020)
				Controls	0.00062	0.00056–0.00065	178	-	
				benign TN	0.00069	0.00062–0.00081	69	NS	
				papillary TC	0.00747	0.00064-0.00082	248	NS	
				follicular TC	0.00375	0.00302-0.00621	6	<0.001	
				medullary TC	0.01518	0.00123-0.00229	38	NS	
Ovarian cancer	FHL-1	In-house ELISA *(Abs described)*			Mean	SD			Junnikkala et al. (2002)
			Serum	Ovarian cancer	24	3	8	-	
			Ascites fluids	Ovarian cancer	130	-	16	<0.01	
				Liver cirrhosis	<2	-	6	-	
			Follicle fluids	Liver cirrhosis	18	-	6	-	

Abs – antibodies, ELISA – enzyme linked immunoassay, N – numbers, NS – not significant, TC – thyroid cancer, TN – thyroid nodules, Q – quartiles, SD – standard deviation.

however, later studies pointed towards loss of FH as an accelerator of disease rather than a cause (Bao et al., 2011; Jönsen et al., 2011). Moreover, circulating levels of FH were identified as a promising biomarker of disease activity in SLE patients (Hu et al., 2019; Tseng et al., 2018; Wang et al., 2012). Levels of FH were found to be lower in patients with active SLE than those in remission. In addition, the lowest levels of FH were found in SLE patients with renal involvement, termed lupus nephritis, and there were significant differences in the levels of FH among the various classes of lupus nephritis (Hu et al., 2019; Liu et al., 2012). Genetic studies subsequently revealed that disease susceptibility of SLE is greatly impacted by variants and alterations in the *CFHR* (Zhao et al., 2011). In this study, the *CFH-CFHRs* region was fine mapped in over 15,000 subjects from different ethnic groups to assess the association with SLE susceptibility. Intriguingly, the deletion of *CFHR3* and *CFHR1* (*CFHR3–1*Δ) showed a dose-dependent association with the risk of SLE (Zhao et al., 2011), suggesting that lower levels of FHR-1 and FHR-3 increase the risk of SLE. Yet a study by Schäfer et al. found higher, rather than lower, circulating levels of FHR-3 in SLE patients compared to controls (Schäfer et al., 2016). It is important to note that only 31 SLE patients were included in this study. Furthermore, information on the genetic background of the cohort was not provided, which can be a confounder since FHR-3 levels are largely determined by copy number variants (Pouw et al., 2016). Alternatively, this could suggest that the association found between the *CFHR3–1*Δ and SLE susceptibility is mediated via FHR-1. In another study, plasma levels of FHR-3 and FHR-5 (but not FHR-1, FHR-2, or FHR-4) were found to be increased in SLE patients with lupus nephritis and their concentrations increased with disease activity (Hu et al., 2019). These two initial studies suggest that, in addition to FH, measuring circulating levels of FHRs in SLE has potential as markers of disease activity, especially for lupus nephritis (Table 2). However, the FHRs concentrations reported by Hu et al. were much higher (10 – 50 times) than those reported by various other studies, raising important questions about the accuracy of the commercial assays used here. Nevertheless, Schäfer et al. also reported higher FHR-3 levels in SLE patients with lupus nephritis compared to those without renal involvement, making FHR-3 a potential biomarker of interest in SLE (Schäfer et al., 2016). Notably, in the same study FHR-3 concentrations were also found to be higher in patients suffering from rheumatoid arthritis, systemic sclerosis, spondylarthritis, and polymyalgia rheumatica compared to healthy controls (Schäfer et al., 2016).

Recent studies have suggested that FHRs are involved in the clearance of cellular debris as well as immune tolerance (Csincsi et al., 2017; Hebecker et al., 2010; Hebecker and Józsi, 2012; Józsi et al., 2008;

Table 2
FH and FHR levels in autoimmune and vascular diseases.

Disease	Protein	Technique (Company)	Matrix	Groups	Mean/Median [μg/mL]	SD/ IQR [μg/mL]	N	P-value vs controls	Ref.
SLE	FH	In-house ELISA *(Abs & calibration cited)*	Serum		Mean	SD			Wang et al. (2012)
				Controls	561.3	179.7	51	-	
				SLE w/o LN	705.6	196.5	38	<0.001	
				SLE with LN	409.6	192.7	241	<0.001	
SLE	FH	Commercial ELISA *(Abnova)*	Serum		Mean	SD			Tseng et al. (2018)
				active SLE	1261.9	349.7	40	-	
				remission SLE	1535.4	638.2	40	0.011	
				active SLE with LN	1414.22	140.63	29	NS	
				active SLE w/o LN	1186.31	79.70	11	NS	
				remission SLE with LN	1549.50	130.24	29	NS	
				remission SLE w/o LN	1516.56	125.13	11	NS	
AAV	FH	In-house ELISA *(Abs and calibration cited)*	Plasma		Mean	SD			Chen et al. (2015)
				Controls	559.72	87.92	65	-	
				AAV (active)	417.87	119.74	55	<0.001	
				AAV (remission)	551.33	114.12	27	NS	
				LN (active)	418.06	119.51	30	-	
AAV	FHR-1	Commercial ELISA *(RayBiotech)*	Serum		Mean	SD			Irmscher et al. (2019)
				Controls	26.50	2.30	55	-	
				Patients	69.81	3.710	313	<0.0001	
CVD	FHR-1	Commercial ELISA *(RayBiotech)*	Serum		Mean	SD			Irmscher et al. (2021)
				Controls	26.50	2.30	55	-	
				Patients	39.20	1.90	244	<0.0001	
SLE	FHR-3	In-house ELISA *(Abs and calibration described)*	Serum		Mean	Range			Schäfer et al. (2016)
				Controls (young)	1.06	0.41-2.49	21	-	
				SLE untreated	4.14	1.84-9.24	12	< 0.01	
				SLE all	2.68	0.6-9.24	33	< 0.01	
rheumatoid arthritis	FHR-3	In-house ELISA *(Abs and calibration described)*	Serum		Mean	Range			Schäfer et al. (2016)
				Controls (young)	1.06	0.41-2.49	21	-	
				Rheumatoid arthritis	3.12	0.98-12.29	46	< 0.01	
PR	FHR-3	In-house ELISA *(Abs and calibration described)*	Serum		Mean	Range			Schäfer et al. (2016)
				Controls (young)	1.06	0.41-2.49	21	-	
				PR	3.37	0.41-9.99	30	< 0.01	
SSc	FHR-3	In-house ELISA *(Abs and calibration described)*	Serum		Mean	Range			Schäfer et al. (2016)
				Controls (young)	1.06	0.41-2.49	21	-	
				SSc	1.96	0.64-5.26	16	< 0.01	
SPA	FHR-3	In-house ELISA *(Abs and calibration described)*	Serum		Mean	Range			Schäfer et al. (2016)
				Controls (young)	1.06	0.41-2.49	21	-	
				SPA	2.08	0.31-8.46	41	< 0.01	

AAV – anti-neutrophil cytoplasmic antibody-associated vasculitis, Abs – antibodies, CVD – cardiovascular disease, ELISA – enzyme linked immunoassay, LN – Lupus nephritis, N – numbers, NS – not significant, PR – polymyalgia rheumatica, SD – standard deviation, SLE – systemic lupus erythematosus, SSc – systemic sclerosis, SPA – spondylarthritis, SSc –systemic sclerosis.

Kárpáti et al., 2020; Mihlan et al., 2009). Some have suggested that the lack of FHRs is therefore linked to SLE due to defective clearance, whereas increased levels worsen disease activity of other autoimmune disorders by promoting sterile inflammation (Skerka et al., 2021). In accordance, FHR-1 was shown to bind to necrotic cells in vitro and also to necrotic sites in the glomeruli of patients with ANCA-associated vasculitis (AAV) (Irmscher et al., 2019). Furthermore, in AAV patients, serum FHR-1 levels were significantly increased compared to healthy controls (Table 2). While patients with AAV had increased serum IL-1β levels compared to healthy controls, AAV patients carrying the *CFHR3–1*Δ did not (Irmscher et al., 2019). In addition, there was also a positive correlation in AAV patients between serum FHR-1 and IL-1β levels, while serum FHR-1 levels were negatively correlated with kidney function. Correspondingly, FH levels were shown in a separate study to be lower in patients with active AAV compared to those in remission and healthy controls (Chen et al., 2015). Circulating levels of FH were also shown to negatively correlate with systemic complement activation, while FH positively correlates with kidney function in a patient with AAV (Chen et al., 2015). Moreover, Irmscher et al. found that with increasing FHR-1 serum concentrations, the relapse and death rates increased in parallel in AAV (Irmscher et al., 2019), whereas Chen et al. reported that higher FH levels were associated with a lower risk of kidney failure and death (Chen et al., 2015). Altogether, these results suggest that circulating levels of FH and FHR-1 may have significant clinical value as prognostic biomarkers in AAV.

The role of FHR-1 in vasculitis also sparked interest in the role of

Table 3
FH and FHR levels in kidney diseases.

Disease	Protein	Technique (Company)	Matrix	Groups	Mean/ Median [μg/mL]	SD/ IQR [μg/ mL]	N	P-value vs controls	Ref.
aHUS	FH	In-house ELISA #1 *(Abs and calibration described)*	Serum		Mean	SD			Nozal et al. (2014)
				Controls A	284	66	40	-	
				Patients B	297	122	24	-	
				Patients C	340	141	11	-	
				Patients D	248	128	111	-	
				Patients E	177	77	13	-	
aHUS	FH	In-house ELISA #2 *(Abs and calibration described)*	Serum		Mean	SD			Nozal et al. (2014)
				Controls A	259	73	40	-	
				Patients B	278	131	24	-	
				Patients C	282	117	11	-	
				Patients D	136	89	111	-	
				Patients E	88	44	13	-	
IgAN	FH	In-house ELISA *(Abs and calibration described)*	Plasma		Mean	SD			Tortajada et al. (2017)
				Controls					
				No	156	39	44	-	
				Het	168	49	24	-	
				Hom	176	39	8	-	
				IgAN					
				No	144	45	75	NS	
				Het	184	65	30	NS	
				Hom	104	-	1	-	
				ADPKD					
				No	146	31	25	NS	
				Het	176	51	18	NS	
				Hom	111	28	3	NS	
IgAN	FHR-1	In-house ELISA *(Abs and calibration described)*	Plasma		Mean	SD			Tortajada et al. (2017)
				Controls					
				No	122	26	44	-	
				Het	61	34	24	-	
				Hom	8	2	8	-	
				IgAN					
				No	155	45	75	<0.0001	
				Het	116	65	30	<0.0001	
				Hom	-	-	1	-	
				ADPKD					
				No	158	47	25	0.0012	
				Het	91	35	18	0.0094	
				Hom	-	-	3	-	
aHUS	FHR-3	In-house ELISA *(Abs and calibration described)*	Serum/ Plasma		Mean	SD			Pouw et al. (2018a,b)
				Controls	0.58	0.26	49	-	
				Patients	2.06	1.77	230	<0.0001	
C3G	FHR-5	In-house ELISA *(Abs and calibration described)*	Serum		Median	IQR			Garam et al. (2021)
				Controls	2.1	1.8-2.5	85	-	
				C3GN	1.8	1.5-2.6	41	-	
				DDD	1.6	1.4-2	12	-	
				IC-MPGN	1.8	1.3-2.2	67	-	
				all	1.8	1.4-2.3	120	0.0004	
C3G	FHR-5	In-house ELISA *(Abs and calibration described)*	Serum		Median	IQR			Vernon et al. (2012)
				Controls	5.5	3.4-10.1	13	-	
				Patients	4.3	1.2-7.4	23	0.02	

Abs – antibodies, ADPKD – autosomal dominant polycystic kidney disease, aHUS – atypical hemolytic uremic syndrome, C3G – C3 glomerulopathy, C3GN – C3 glomerulonephritis, DDD – dense deposit disease, ELISA – enzyme linked immunoassay, IC-MPGN – immune complex-mediated membranoproliferative glomerulonephritis, IgAN - IgA Nephropathy, IQR – interquartile range, N – numbers, *No, Het and Hom refer to the CFHR3-CFHR1Δ genotypes (Het-heterozygote, Hom-homozygote), NS – not significant, SD – standard deviation.

FHR-1 in other vascular disorders such as atherosclerotic cardiovascular disease (CVD) (Irmscher et al., 2021). Until recently, no evidence had shown that reducing inflammation improves outcomes in patients with CVD. However, the CANTOS trial demonstrated that targeting IL-1β significantly reduced the recurrent rate of cardiovascular events (Ridker et al., 2017). This finding has opened new avenues for other anti-inflammatory interventions and validates the clinical use of inflammatory biomarkers in patients with CVD. The complement system has also been suggested to be involved in the pathogenesis of CVD (Kiss and Binder, 2022). Accordingly, various complement proteins have been proposed as prognostic biomarkers of CVD (Poppelaars et al., 2018, 2016). Initial reports explored the importance of FH in CVD by analyzing the association between *CFH* polymorphisms and CVD. The results have thus far been conflicting: while previously it has been suggested to increase the risk of CVD in three large population-based studies (Jylhävä et al., 2008; Kardys et al., 2006; Volcik et al., 2008), a meta-analysis based on 48,646 individuals implied no or even an inverse correlation between *CFH* polymorphisms and CVD (Pai et al., 2007; Sofat et al., 2010). Recently, the homozygous *CFHR3–1*Δ was found to be protective in two independent cohorts of patients with CVD (Irmscher et al., 2021). Furthermore, circulating FHR-1 concentrations were significantly elevated in patients with CVD compared to healthy controls, and correlated with serum CRP, IL-6, and LDL-cholesterol levels (Table 2). Thus, these results suggest a potential pathogenic role of FHR-1 in CVD as well as being a biomarker to improve risk assessment (Irmscher et al., 2021).

2.3. Kidney disease

For incompletely understood reasons, the kidney is an organ particularly susceptible to complement-mediated damage; the fenestrated endothelium and the high pressure needed for ultrafiltration are likely contributing factors. Common and rare gene variants in complement components of the AP, as well as autoantibodies against its components, are associated with renal diseases including aHUS, C3 glomerulopathy (C3G), and IgAN (Goicoechea de Jorge et al., 2018; Lemaire et al., 2021; Poppelaars and Thurman, 2020). In this regard, alterations involving the FH protein family account for a substantial proportion of the risk factors found in these patients, and they encompass variations that may either affect protein levels or its function (Goicoechea de Jorge et al., 2018; Józsi et al., 2015; Zipfel et al., 2020). The next paragraph will discuss the recent data on measuring FH and the related proteins in the context of the aforementioned kidney diseases (Table 3).

aHUS is a rare renal disease characterized by thrombocytopenia, hemolytic anemia, and acute renal failure. Amongst the complement genes that are associated with aHUS, the *CFH* harbors the highest frequency of aHUS-associated mutations (Goodship et al., 2017). Prototypical aHUS mutations are missense genetic variants located at the C-terminus of FH (Merinero et al., 2018). As a result, FH mutants are normally expressed, but their function is altered and they show a reduced ability to regulate complement activation on cell surfaces (Martín Merinero et al., 2021). Hence, despite FH mutations, circulating FH levels in aHUS patients are usually within the normal range of variation (Nozal et al., 2014). In this case, functional assays to test for FH activity are crucial. Besides mutations in *CFH,* common and rare gene variations in the *CFHRs* have also been associated with aHUS (Goicoechea de Jorge et al., 2018; Lemaire et al., 2021; Zipfel et al., 2020). The common *CFHR3–1*Δ confers a risk to develop the disease (Zipfel et al., 2007). Importantly, this association is due to the occurrence of anti-FH antibodies in aHUS patients that are homozygous for the *CFHR3–1*Δ, but the deficiency of FHR-1 and FHR-3 itself is not a risk factor for the disease (Józsi et al., 2008). Later studies revealed that these FH autoantibodies are specifically associated with the deletion of *CFHR1,* since they are also found in patients with the much rarer *CFHR1-CFHR4* deletion (Abarrategui-Garrido et al., 2009; Bhattacharjee et al., 2015; Moore et al., 2010). Other aHUS-associated mutations in the *CFHRs* lead to the generation of mutant proteins that have a functional impact on FH, either by altering FH regulatory activity on cell surfaces or by competing with this activity (Martín Merinero et al., 2021). Examples include hybrid genes between *CFH* and *CFHR1* or *CFHR3*, resulting in the exchange of the C-terminus of FH by the C-terminus of the corresponding FHR (De Jorge et al., 2018; Heinen et al., 2006; Valoti et al., 2015; Venables et al., 2006), or missense mutations at the C-terminus of FHR-1, which generate mutant proteins that can compete with FH for the binding to C3b deposited on cell surfaces (Martin Merinero et al., 2021). Interestingly, aHUS-associated FH or FHR mutations do not generally affect protein levels, however, it has been shown that the variation of circulating levels of some FH family members may be crucial in determining aHUS susceptibility. For instance, an extended haplotype spanning *CFH* and *CFHR3,* namely *CFH-H3*, confers a risk to develop aHUS and is particularly relevant in increasing the penetrance of the disease in carriers of FH mutations (Pouw et al., 2018b). Interestingly, the *CFH-H3* haplotype has been reported to be associated with low FH and high FHR-3 plasma levels, and elevated FHR-3 plasma levels have been observed in aHUS patients compared with controls (Pouw et al., 2018b). Altogether, these observations suggest that, in addition to low levels of FH, elevated FHR-3 levels may also be helpful to assess disease risk for aHUS, although their involvement in the pathogenesis of aHUS remains unknown.

C3 glomerulopathy is a heterogeneous group of renal diseases characterized by the predominant deposition of glomerular C3. About 50% of the patients have a poor prognosis and progress to kidney failure eventually (Goodship et al., 2017; Pickering et al., 2013). Pathogenic gene variants in either *CFH* or the *CFHRs* have also been found in C3G patients. *CFH* variants leading to null alleles or variants that abrogate the regulatory activities of FH at the N-terminus of the molecule are amongst the commonest pathogenic variants found in the patients (de Córdoba, 2016; Goodship et al., 2017; Licht et al., 2006). This type of alterations, when in homozygosity, cause secondary C3 deficiency (Dragon-Durey et al., 2004; Levy et al., 1986). In this scenario, measuring FH levels is extremely informative and helps to identify the null alleles. Genomic rearrangements involving the *CFHRs* are also associated with C3G, which clearly illustrates the relevance of these proteins in the disease pathogenesis (Goicoechea de Jorge et al., 2018; Lemaire et al., 2021; Zipfel et al., 2020). Of note, FHR-1, FHR-2, and FHR-5 can dimerize due to the presence of a dimerization domain in their N-terminus (Goicoechea De Jorge et al., 2013). These FHRs can consequently form both homodimers and heterodimers, which have been suggested to impact their functionality (Goicoechea De Jorge et al., 2013; van Beek et al., 2017). Mutations that lead to duplication of the dimerization domains in FHR-1, FHR-2, and FHR-5 are prototypical of C3G, and these do not generally affect protein levels but act as gain-of-function mutations that challenge the regulatory activity of FH by promoting excessive complement activation through the AP (Goicoechea De Jorge et al., 2013; Tortajada et al., 2013). Hence, suitable functional assays would be recommended to test this type of mutations. Apart from these gain-of-function mutations, alterations in circulating levels of the FHRs also seem to be relevant in C3G. Several studies identified genomic rearrangements leading to the duplication of *CFHR3-CFHR1* in C3G patients, suggesting that increased FHR-3 and FHR-1 levels are risk factors (Loeven et al., 2021; Piras et al., 2021). Moreover, low circulating FHR-5 levels in C3G patients compared with controls have been reported in two independent studies (Garam et al., 2021; Vernon et al., 2012). Interestingly, low FHR-5 levels at presentation were associated with high evidence of complement activation and with better renal survival during the follow-up period (Garam et al., 2021). These lower FHR-5 levels in C3G patients are more likely to be due to consumption, rather than being genetically driven. Although the exact reasons for this are still unknown, these data suggest that measuring circulating FHR-5 may be useful for monitoring complement activation and for patient stratification.

IgAN is the most common primary glomerulonephritis worldwide and a frequent cause of chronic kidney disease. Although some patients may recover their renal function almost completely, up to 40% of the patients progress to chronic kidney disease and even kidney failure. The involvement of complement in IgAN comes from the observations that C3 is observed in both circulating immune-complexes and because C3 co-localizes with glomerular deposits containing IgA (Poppelaars et al., 2021a). A decade ago, genome-wide studies identified the *CFHR3–1*Δ to be associated with strong protection for the development of IgAN, supporting the involvement of AP dysregulation in the disease pathogenesis and putting the FH protein family in the spotlight (Gharavi et al., 2011; Kiryluk et al., 2014, 2012). Further mechanistic studies demonstrated in IgAN patients the *CFHR3–1*Δ was associated with lower mesangial deposition of C3, increased circulating levels of C3 and FH, reduced systemic complement activation as well as improved histologic markers of kidney injury (Jullien et al., 2018; Xie et al., 2016; Zhu et al., 2015). Consistent with these findings, IgAN patients present with abnormally elevated FHR-1 plasma levels as well as increased FHR-1/FH ratios compared to controls (Medjeral-Thomas et al., 2017; Tortajada et al., 2017). Notably, the highest FHR-1 levels or FHR-1/FH ratios were found in IgAN patients with disease progression. Interestingly, some patients presented low FH levels, of which some were carriers of a *CFH* pathogenic variant (Tortajada et al., 2017). In addition to the elevated FHR-1 levels, FHR-5 levels have also been reported to be significantly increased in IgAN patients compared to controls and, importantly, FHR-5 has also been identified as an independent risk factor of IgAN progression (Medjeral-Thomas et al., 2017; Zhu et al., 2018). Altogether, these observations illustrate the relevance of the balance between the levels of FH and the FHRs in IgAN pathogenesis and suggest that either increased FHRs levels or a decrease in FH are risk factors for the disease development and progression.

2.4. Eye disease

Among all the research conducted on levels of the FH protein family so far, the most extensively studied disease is age-related macular degeneration (AMD), and the clinical utility of these measurements in AMD are becoming extremely compelling. AMD is a multifactorial ophthalmic disease that causes retinal degeneration in the elderly. As for the other diseases discussed above, the importance of the FH protein family became apparent through genetic studies in AMD. In 2005, three independent studies demonstrated that an SNP in *CFH* substantially contributed to the susceptibility of AMD (Edwards et al., 2005; Haines et al., 2005; Klein et al., 2005). This polymorphism (rs1061170, T > C, Y402H) results in a tyrosine to histidine change in CCP 7 of FH, the domain involved in FH binding to various surfaces. Consequently, rather than altering FH concentrations, this polymorphism is believed to impact the binding affinity of FH to certain ligands (Toomey et al., 2018). Since then, other studies have identified novel genetic risk factors for AMD in the regulators of complement activation (RCA) locus, which includes the *CFH* and the *CFHRs* (Cantsilieris et al., 2018; Fritsche et al., 2010). More specifically, GWAS identified the *CFHR3–1*Δ as protective against AMD (Hughes et al., 2006). In contrast, later studies showed that rare variants in *CFHR2*, *CFHR4*, and *CFHR5* were associated with an increased AMD risk (Lorés-Motta et al., 2021, 2018a). These genetic association studies have established the FH protein family as a main driver of disease and these proteins are now being turned into useful novel biomarkers for the stratification of disease risk.

Multiple studies have examined the systemic levels of various members of the FH protein family in AMD using *in-house* ELISAs (Table 4). Hakobyan et al. assessed the levels of FH in an AMD case-control series and found no difference in systemic FH levels for AMD cases compared to controls (Hakobyan et al., 2008). This was supported by later studies that reported no significant differences in FH levels in AMD cases compared to controls (Ansari et al., 2013; Cipriani et al., 2021, 2020; Lorés-Motta et al., 2021). In addition to FH, circulating levels of FHRs have also been investigated as risk factors and prognostic biomarkers in AMD. The work by Ansari et al. was the first to measure plasma FHR-1 levels in AMD patients using once again an *in-house* ELISA (Ansari et al., 2013). They observed decreased concentrations of FHR-1 in the AMD case versus the control samples. In contrast, more recent work reported increased FHR-1 and FHR-2 levels in AMD patients compared to controls (Cipriani et al., 2021; Lorés-Motta et al., 2021). These differences could be explained by cross-reactivities described for the Ansari et al. ELISA with FHR-2 and FHR-5, which was compensated by mathematical normalizations (Ansari et al., 2013). These cross reactivities were not reported for the other assays (Cipriani et al., 2021, 2020; Lorés-Motta et al., 2021). Lorés-Motta et al. therefore specifically addressed this point and determined the levels of the FHR-1 hetero- and homodimers, showing also rather increased concentrations in AMD patients (Lorés-Motta et al., 2021). Additionally, FHR-1/− 2 homo- as well as heterodimers were shown to be associated with an increased risk for advanced AMD (Lorés-Motta et al., 2021). Furthermore, two independent studies demonstrated that serum levels of FHR-3 are increased in AMD patients, which fits with the observation that the *CFHR3–1*Δ is protective against AMD (Lorés-Motta et al., 2021; Schäfer et al., 2016). The results of FHR-3 levels using ELISA approaches in AMD were later confirmed by mass-spectrometry measurements that revealed similar plasma concentration ranges in healthy controls and AMD patients (Cipriani et al., 2021). Interestingly, the importance of *CFHR4* in AMD was discovered through unbiased GWAS approaches (Lorés-Motta et al., 2018b). Lorés-Motta et al. discovered that variants in *CFH* and *CFHR4* impacted the extent of systemic complement activation seen in AMD patients (Lorés-Motta et al., 2018b). In their follow-up study using two different cohorts, they found elevated systemic FHR-4 levels in AMD patients and this was shown to be genetically driven (Cipriani et al., 2020). Moreover, levels of FHR-4 are positively associated with the risk of AMD (Cipriani et al., 2020). These results corresponded to later reported concentrations determined by a different in-house ELISA and mass spectrometry approach (Cipriani et al., 2021; Lorés-Motta et al., 2021). Additionally, the same investigators described that FHR-5 levels were slightly increased in AMD patients (Cipriani et al., 2021; Lorés-Motta et al., 2021). In sum, these studies indicate that increased systemic levels of the FHR proteins, but not of FH, are a major risk factor for the development of AMD.

In addition to plasma/serum measurements, there has also been an interest in local levels of complement in ophthalmic disease (Smith et al., 2022). Detection of the complement proteins in eye liquids, such as tears, vitreous and aqueous humor could provide further insight into the contribution of complement to AMD. In the healthy retina, *CFH* expression was described for retinal, choroidal as well as pigment epithelium cells, while *CFHR* transcripts were only weakly detected in retinal cells and hardly detected in the pigment epithelium cells and the choroid (Lyu et al., 2021). Recently, FH concentrations were measured in aqueous humor of neovascular AMD patients and shown to be significantly increased compared to controls (Altay et al., 2019). However, elevated FH levels were not observed in early or intermediated AMD. A later study confirmed these results in another cohort of early AMD (Sitnilska et al., 2021). So far, FHRs haven't been reported for vitreous, aqueous humor, or tears, but this could be of major interest. Lastly, the role of the complement system has been implicated in various other ocular diseases namely autoimmune uveitis, glaucoma, and diabetes retinopathy and myopia, but the involvement of the FH protein family has thus far not been investigated (Bansal and Gupta, 2020; Clark and Bishop, 2018; Fiedorowicz et al., 2021; García-Gen et al., 2021; Gui et al., 2020; Jha et al., 2007; Rajagopal et al., 2021; Sundstrom et al., 2018; Torok et al., 2013; Youngblood et al., 2019; Zhang et al., 2020).

2.5. Infectious disease

Another disease area in which the FH protein family plays an important role and measurement of their levels is highly relevant, albeit

Table 4
FH and FHR levels in eye diseases.

Disease	Protein	Technique (Company)	Matrix	Groups	Mean/Median [μg/mL]	SD/Range/CI [μg/mL]	N	P-value vs controls	Ref.
AMD	FH	In-house ELISA *(Abs and calibration described)*	Plasma		Mean	Range			Hakobyan et al. (2008)
				Controls (young)	222.24	135.54-349.27	63	-	
				Controls (aged)	268.69	83.05-398.38	75	-	
				AMD	287.84	120.49-498.76	53	NS	
AMD	FH	In-house ELISA *(not validated)*	Plasma		Mean	Range			Ansari et al. (2013)
				Controls	428.3	302.2-541.6	201	-	
				AMD	412.6	127.8-540.2	382	< 0.001	
AMD	FH	LC-SRM-MS *(validated)*	Plasma		Mean[1]	Range[1]			Cipriani et al. (2021)
				Controls	114	111-117	252	-	
				AMD	114	112-116	352	NS	
AMD	FH	In-house ELISA *(not validated)*	Plasma		Mean	CI			Cipriani et al. (2021)
				Controls 1	349	338.9-359.4	214	-	
				AMD 1	348.6	340.2-357.2	304	NS	
				Control 2	304.7	297.3-312.2	308	-	
				AMD 2	308.7	298.0-319.8	180	NS	
AMD	FH	Commercial Multiplex-ELISA *(Merck)*	Aqueous humor		Median				Sitnilska et al. (2020)
				Controls	0.045	-	71	-	
				AMD	0.065	-	35	NS	
AMD	FH	Commercial Multiplex-ELISA *(Merck)*	Aqueous humor		Mean	SD			Altay et al. (2019)
				Controls	0.068	0.082	77	-	
				early AMD	0.123	0.176	17	NS	
				interm. AMD	0.136	0.227	27	NS	
				CNV	0.117	0.091	35	0.018	
AMD	FHL-1	LC-SRM-MS *(validated)*	Plasma		Mean[1]	Range[1]			Cipriani et al. (2021)
				Controls	0.51	0.49-0.53	252	-	
				AMD	0.55	0.54-0.57	352	1.4×10^{-3}	
AMD	FHR-1	In-house ELISA *(not validated)*	Plasma		Mean	Range			Ansari et al. (2013)
				Controls	0.99 AU	0.99-1.7 AU	201	-	
				AMD	0.94 AU	0.34-1.48 AU	382	< 0.001	
AMD	FHR-1	LC-SRM-MS *(validated)*	Plasma		Mean[1]	Range[1]			Cipriani et al. (2021)
				Controls	1.15-1.31	1.09-1.38	252	-	
				AMD	1.42-1.61	1.37-1.67	352	2.1×10^{-10}	
AMD	FHR-2	LC-SRM-MS *(validated)*	Plasma		Mean[1]	Range[1]			Cipriani et al. (2021)
				Controls	1.1-1.3	1.03-1.38	252	-	
				AMD	1.3-1.6	1.28-1.66	352	1.9×10^{-9}	
AMD	FHR-3	In-house ELISA *(Abs and calibration described)*	Serum		Mean	Range			Schäfer et al. (2016)
				Controls (young)	1.06	0.41-2.49	21	-	
				CNV	1.83	0.63-4.36	22	< 0.1	
AMD	FHR-3	LC-SRM-MS *(validated)*	Plasma		Mean[1]	Range[1]			Cipriani et al. (2021)
				Controls	0.89-1.21	0.8-1.33	252	-	
				AMD	1.07-1.45	1-1.54	352	4.4×10^{-5}	
AMD	FHR-4	In-house ELISA *(not validated)*	Serum/ Plasma		Mean	CI			Cipriani et al. (2020)
				Controls 1	5.5	4.9-6.2	214	-	
				AMD 1	6.6	6.0-7.2	304	0.016	
				Control 2	6.0	5.6-6.3	308	-	
				AMD 2	7.2	6.6-7.8	180	1.7×10^{-4}	
AMD	FHR-4	LC-SRM-MS *(validated)*	Plasma		Mean[1]	Range[1]			Cipriani et al. (2021)
				Controls	1.98-3.96	1.84-4.27	252	-	
				AMD	2.31-4.63	2.17-4.91	352	2.1×10^{-3}	
AMD	FHR-5	LC-SRM-MS *(validated)*	Plasma		Mean[1]	Range[1]			Cipriani et al. (2021)
				Controls	1.66	1.59-1.72	252	-	
				AMD	1.81	1.76-1.88	352	1.9×10^{-4}	

Abs – antibodies, AMD – age-related macular degeneration, CI – confidence interval, CNV – choroidal neovascularization, ELISA – enzyme linked immunoassay, interm. – intermediated, LC-SRM-MS – liquid-chromatography-selected reaction-monitoring mass-spectrometry, N – numbers, NS – non-significant, IQR- inter-quartile range1, SD – standard deviation/ 1 numbers are reported as nM converted into μg/mL (supplementary data).

likely not for diagnostics purposes per se, is infectious diseases. The studies outlined above show that the role of complement in homeostatic processes and diseases is increasingly recognized, but it is still primarily viewed as a defense system protecting its host from various life-threatening microbes. The destructive capabilities of complement formed a constant evolutionary pressure for human pathogens. Today, this is testified by the numerous complement evasion strategies microbes employ to evade complement-mediated destruction upon infection (reviewed by Hovingh et al., 2016; Lambris et al., 2008). This includes secreting complement inhibiting proteins (Jongerius et al., 2007), as well as mimicry of host regulators (McKenzie et al., 1992; Rosengard et al., 2002). Pathogens also exploit the human complement regulators, hijacking them to evade complement-mediated destruction. With FH as the main regulator of the AP and the amplification feedback loop within cascade, and circulating freely in our bloodstream, it is not surprising many human pathogens can bind FH to their surface to evade complement-mediated destruction (reviewed by Moore et al., 2021). Binding of human FH for complement evasion purposes has been described for viruses such as West Nile virus (Kyung et al., 2006), various parasites including *Plasmodium falciparum* (Kennedy et al., 2016; Rosa et al., 2016; Simon et al., 2013), and a wide range of bacteria, with *Neisseria meningitidis* likely being the most infamous within the field

(Madico et al., 2006; Schneider et al., 2006). Binding of FH by pathogens confers its normal complement regulatory function to their surface. One of the FH-binding proteins of *Streptococcus pneumoniae*, PspC, is even reported to enhance the regulatory capacity of FH upon binding (Herbert et al., 2015), presumably to further increase its survival chances in the host. Thus, with many pathogens exploiting human FH, genetic variations in the *CFH* locus and the plasma concentration of FH are associated with the risk of infections (Table 5) (Davila et al., 2010; Haralambous et al., 2006; Martinón-Torres et al., 2016; Pastor et al., 2013; van Beek et al., 2018). While lower levels of FH seem to be protective against infection, too low FH levels would result in inadequate control of the C3 tick-over, leading to C3 consumption and complement-mediated damage to host tissues. Likewise, increased FH levels protect the host from complement-mediated damage to its tissues, but aid the pathogen in evading complement-mediated destruction (Kasanmoentalib et al., 2019; Van Der Maten et al., 2016).

The FH-binding proteins of pathogens often target the CCPs of FH that would normally interact with ligands on human surfaces, such as CCP 6–7 or CCP 19–20. As all five FHRs also contain domains similar to CCP 6–7 and CCP 19–20 of FH, albeit to a different extent, several pathogens are also described to recruit FHRs to their surface via their FH-binding proteins (Józsi, 2017). For instance, *Borrelia burgdorferi* expresses complement regulator-acquiring surface proteins (CRASPs) that recruit FH through the binding to CCP 19–20 and are also reported to bind FHR-1, FHR-2 and FHR-5 (Haupt et al., 2007; Siegel et al., 2010). Similar, Staphylococcus aureus recruits both FH and FHR-1 by binding to Staphylococcus aureus binder of IgG (Sbi), mediating immune recognition (Haupt et al., 2008). In contrast, the FH-binding protein of N. meningitidis binds CCP 6–7 of FH and consequently also CCP 1–2 of FHR-3 (Caesar et al., 2014; Schneider et al., 2009). As the FHRs lack direct complement inhibiting activity in contrast to FH, it is tempting to hypothesize that the recruitment of FHRs by pathogens pre-disposes the pathogen for complement-mediated clearance (Józsi et al., 2015). Consequently, local competition between FH and FHRs is thought to determine the success of infection. Therefore, accurately determining the levels of FHRs and more importantly the physiological ratio between FH and the relevant FHR in plasma is highly needed to assess if such competition truly occurs in vivo and indeed dictates susceptibility towards infection. The first specific measurement of FH and all FHRs in an infectious disease has only recently been reported, namely in

Table 5
FH and FHR levels in infectious diseases.

Disease	Protein	Technique *(Company)*	Matrix	Groups	Median/ Mean [µg/mL]	Range/ IQR [µg/mL]	N	P-value vs controls	Ref.
MD	FH	In-house ELISA *(not validated)*	Serum		Median	Range			Haralambous et al. (2006)
				Controls	313	31-953	147	-	
				Acute	223	47-601	105	NS	
				Convalescent	395	94-776	89	0.001	
MD	FH	In-house ELISA *(Abs and calibration described)*	Serum		Median	Range			Van Beek et al. (2022)
				Controls	282	238-326	110	-	
				Acute	131	109-181	106	-	
				Convalescent	295	234-320	91	NS	
Bacterial meningitis	FH	Commercial ELISA *(Quidel)*	CSF		Median	IQR			Kasanmoentalib et al. (2019)
				Controls	1.12	0.93-1.55	18	-	
				Patients	11.27	6.62-15.86	362	<0.001	
Malaria	FH	In-house ELISA *(Abs and calibration described)*	Plasma		Mean	95% CI			Van Beek et al. (2022)
				Controls	257	250-264	173	-	
				Uncom. malaria	288	268-309	67	0.0016	
				Severe malaria	328	313-344	82	<0.0001	
Sepsis	FH	Commercial ELISA *(Hycult)*	Plasma		Median	IQR			Shimizu *et al.* (2021)
				Controls	114.8	100.00-158.80	10	-	
				Survivors	104.8	68.80-124.20	44	NS	
				Non-survivors	70	51.20-97.60	18	0.001	
MD	FHR-1/1	In-house ELISA *(Abs and calibration described)*	Serum		Median	IQR			Van Beek et al. (2022)
				Controls	11.36	7.39-14.26	110	-	
				Acute	5.59	3.96-8.07	104	-	
				Convalescent	11.85	7.50-14.48	89	NS	
MD	FHR-1/2	In-house ELISA *(Abs and calibration described)*	Serum		Median	IQR			Van Beek et al. (2022)
				Controls	5.40	3.92-7.01	110	-	
				Acute	2.59	1.81-3.53	104	-	
				Convalescent	5.39	3.99-6.90	89	NS	
MD	FHR-2/2	Imputed from FHR-1/1 & FHR-1/2 data	Serum		Median	IQR			Van Beek et al. (2022)
				Controls	0.64	0.40-1.11	110	-	
				Acute	0.28	0.19-0.47	104	-	
				Convalescent	0.78	0.41-0.98	89	NS	
MD	FHR-3	In-house ELISA (Abs and calibration described)	Serum		Median	IQR			Van Beek et al. (2022)
				Controls	0.57	0.38-0.80	110	-	
				Acute	0.30	0.20-0.50	104	-	
				Convalescent	0.69	0.48-0.98	89	NS	
MD	FHR-4A	In-house ELISA *(Abs and calibration described)*	Serum		Median	IQR			Van Beek et al. (2022)
				Controls	0.91	0.48-1.50	110	-	
				Acute	1.07	0.63-1.49	106	-	
				Convalescent	2.16	1.35-3.46	91	<0.0001	
MD	FHR-5	In-house ELISA *(Abs and calibration described)*	Serum		Median	IQR			Van Beek et al. (2022)
				Controls	1.23	0.92-1.47	110	-	
				Acute	0.58	0.37-0.88	106	-	
				Convalescent	1.23	0.92-1.55	91	NS	

Abs – antibodies, CSF – cerebrospinal fluid, ELISA – enzyme linked immunoassay, IQR – interquartile range, MD - Meningococcal disease, NS – non-significant, SD – standard deviation, uncom. – uncomplicated meningococcal disease (MD) (Table 5) (van Beek et al., 2022).

The causing agent of MD, *N. meningitidis*, is the archetypical example of the need for pathogens to evade complement-mediated destruction that would otherwise protect against infection. This is demonstrated by the recurrent *N. meningitidis* infections that occurs in patients with deficiencies in components of the terminal complement pathway (Rosain et al., 2017). *N. meningitidis* evades complement by expressing various proteins capable of binding FH, with FH-binding protein (fHbp) being the most well-known (Welsch and Ram, 2008). Meningococcal fHbp binds FH at CCP 6–7, mimicking the binding as it would occur on human cells (Schneider et al., 2009). In 2010, a genome-wide association study (GWAS) not only identified SNPs in the *CFH* gene to associate with MD susceptibility but also an SNP in *CFHR3* (Davila et al., 2010). As FHR-3 CCP 1–2 have the highest similarity with FH CCP 6–7 among the FHRs (91% and 85% similarity, respectively), it was hypothesized that fHbp also recruits FHR-3 to the meningococcal surface. Indeed, this was confirmed in a later study, demonstrating competition between FH and FHR-3 on fHbp at equal molar concentrations (Caesar et al., 2014). FHR-3 decreased the in vitro survival of *N. meningitidis* in human serum due to increased complement-mediated killing of the bacteria. While this model seems highly probable, some questions remain. For instance, the relatively common *CFHR3–1*Δ has not been reported to predispose for MD to date, despite the lack of the proposed protective FHR-3. More importantly, the recent measurements of FH and FHRs in MD patients revealed that the ratio between FH and FHR-3 is closer to a 100-fold difference (1.90 μM FH versus 0.019 μM FHR-3, considering an molecular weight of 155 and 36 kDa, respectively) instead of close to equal molar levels (van Beek et al., 2021). This challenges the proposed role of FHR-3 as a relevant in vivo competitor of FH for binding to fHbp, as at physiological levels and taking into account differential binding affinities of fHbp for FH and FHR-3, the majority of fHbp is likely still binding FH and thus conferring protection to the meningococci (Fig. 1). This highlights the pressing need to measure FHRs in other infectious diseases in which the FH:FHR ratio is thought to be of great clinical importance. The recent work of van Beek et al. in acute MD also reveals a major challenge when measuring FH and FHR proteins in patients during an infectious disease (van Beek et al., 2021). Ideally, measurements are done during the acute stage of disease, to determine any possible consumption of FH or FHRs by the bacteria, and any relevant shifts in the balance within the FH protein family. However, the interpretation of such measurements is greatly confounded by complications such as loss of kidney function or treatments including administration of fluids during this acute stage. Measurements of samples after convalescence will not elucidate the status of the FH protein family during the infection, but will rather shed light on possible underlying (genetic) susceptibility risks caused by altered baseline levels.

3. The current landscape of complement testing in the clinical laboratory

The complexity of the complement system becomes apparent when looking at the options for complement analysis (Willrich et al., 2021). Complement testing can be divided into five general categories: (1) measurements of complement proteins, (2) levels of activation fragments or complexes formed during activation, (3) assessment of functionality, (4) testing for auto-antibodies against complement proteins, and (5) identification of mutations or disease-associated genetic variants of complement genes. Every category as well as every individual assay comes with its own set of challenges (Bomback et al., 2022; Frazer-Abel et al., 2021; Willrich et al., 2021). For example, to accurately assess plasma levels of activation fragments, correct sample acquisition, handling and storage are vital to prevent *ex-vivo* complement activation, that would otherwise lead to incorrect results (Mollnes et al., 1988; Yang et al., 2015). Furthermore, clinical analysis of the complement system requires multiple and preferably orthogonal tests to cover the whole system and to ensure correct interpretation. For example, low functional levels can be caused by a genetic complement deficiency, but this can also be the consequence of complement consumption due to massive activation (Bomback et al., 2022; Frazer-Abel et al., 2021; Willrich et al., 2021). Despite the growing and unmistakable importance of these analyses, the number of complement tests routinely performed in clinical practice is limited. In addition, specialized complement-testing laboratories are rare and not present in every region/country. Moreover, assays for measuring FHRs as biomarkers in a clinical setting are neither commercially available nor standardized. Extensive efforts by the *IUIS/ICS Committee for the Standardization and Quality Assessment in Complement Measurements* have greatly improved the standardization of complement testing among research and clinical laboratories (Prohászka et al., 2016). Unfortunately, within the FH protein family, only serum measurements of FH are included in their standardization activities. However, this will hopefully change as measurements of the related proteins gain in popularity and commercial assays become readily available.

4. The future of clinical analysis for the factor H protein family

The clinical utility of measuring levels of FH and FHRs has the potential to assist in the risk assessment, prognosis, and diagnosis of

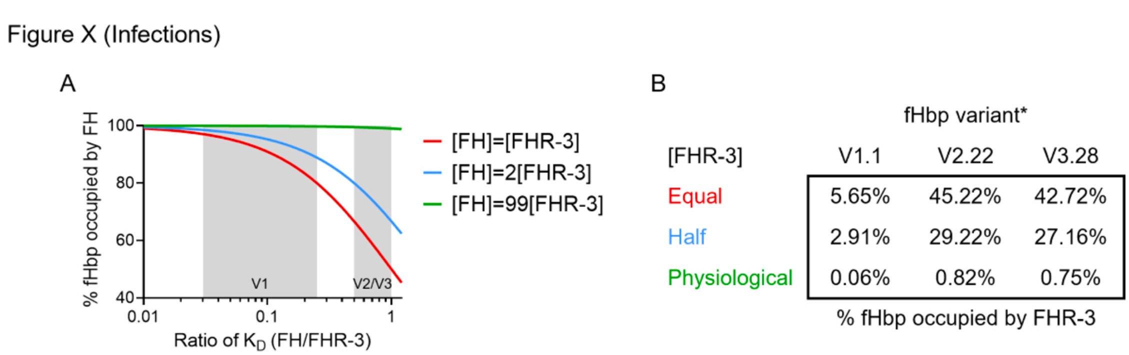

Fig. 1. Theoretical occupation of fHbp by FHR-3 considering various concentration ratios and binding affinities of fHbp variants. (A) Graphical representation of the results obtained by applying the reported physiological molar levels (green line) for FHR-3 and FH in MD patients in the theoretical model proposed by Caesar et al. to calculate the % of fHbp occupied by FH (Caesar et al., 2014; van Beek et al., 2022). Graph adjusted from by Caesar et al., the red (theoretical equal concentration) and blue line (theoretical FHR-3 concentration half of FH) were previously proposed by Caesar et al., the gray area's indicate the ratios of KD (FH/FHR-3) for variant 1, 2 and 3 of fHbp, as reported by Caesar et al. (B) Theoretical % of fHbp occupied by FHR-3 resulting from the model of by (Caesar et al., 2014) for three fHbp variants, and applying a theoretical equal and half concentrations of FHR-3 compared to FH, and the physiological ratio between FH and FHR-3 as measured by van Beek et al. (2021). *fHbp variants were selected based on those tested in Caesar et al., applying the reported affinities for FHR-3 CCP 1–2 and FH CCP 6–7. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

diseases. Based on the data discussed above, their measurements could already help assess the disease risk of aHUS, AMD, and CVD, as well as improve prognostication of C3G, IgAN, and vasculitis. This information could thus help doctors identify individuals who are at risk for disease or complications and help guide personalized interventions which can improve patients' clinical outcomes. Albeit this fundamental understanding is known, significant knowledge gaps still impede any analysis for clinical use. For example, it is not yet known, whether quantification of all members of the FH protein family simultaneously is needed or if focusing on individual proteins is sufficient for certain diseases. Nevertheless, various studies have demonstrated the context-dependent roles of the different members of the FH protein family in complement-associated diseases. Furthermore, in diseases such as IgAN and MD, the balance between the levels of FH and FHRs has been shown to be of importance (Tortajada et al., 2017; van Beek et al., 2021). Besides, functional analysis might be even more informative for other diseases such as aHUS and C3G. Ideally, clinical analysis of the FH protein family should therefore include orthogonal approaches that quantify protein concentrations, assess protein functionality and perhaps total complement activity. This can be accomplished by quantifying specific proteins, simultaneous multiplexed analysis (Prohászka and Frazer-Abel, 2021), and possibly also determining a sum parameter of the concentration of the entire FH protein family through traditional immunoassay strategies or proteomics approaches (Cipriani et al., 2021). Like in any quantitative immunoassay, the homology of these proteins makes antibody development very challenging as cross-reactivity has to be avoided (Poppelaars et al., 2021b). However, it has been demonstrated in recent years that it is feasible to develop highly-specific assays for individual FH protein family members (Pouw et al., 2018a, 2016; van Beek et al., 2017). In addition, it is of vital importance that future assays, designed and approved for clinical analyses of the FH protein family meet key requirements and are standardized and validated for robustness, specificity, sensitivity, and are easy-to-use and cost-effective. Importantly, there are first indications for the potential of robust assay development as Pouw et al.'s recent work suggests that sample handling and storage may not pose significant challenges. FHR-3 and FHR-4A levels in plasma and serum did not differ, nor were they impacted by repeated freeze/-thaw cycles (Pouw et al., 2018a, 2016). This suggests that measuring FHRs could be easier than assessing complement activation fragments. However, it should be noted, that, analysis of the FH protein family would not replace other complement testing, but instead add to current complement analysis. Nevertheless, these technical aspects need to be further evaluated and monitored to set assay specifics such as (but not limited to): the limit of blank, the limit of detection, the limit of quantitation, linearity, precision, and interference/matrix effects and batch-to-batch variation. In addition, unified protocols are needed for pre-analytical sample handling, including collection, processing, and storage thereby allowing a better comparison of test results between laboratories (Prohászka et al., 2018). Subsequently, each assay needs to be validated for each intended disease or condition by performing accuracy and cutoff studies using certified reference tests. Measuring levels of the FH protein family has most extensively been studied in patients with AMD, while the use of these measurements in other diseases is still in its infancy. For example, although proteomics studies in different types of cancer have identified FHRs as potential diagnostic and prognostic biomarkers, larger studies are needed to confirm these results. Overall, standardized clinical assays for the FH protein family are required for both fundamental studies and clinical applications.

5. Therapeutic directions

FH and FHRs could not only help as diagnostic and prognostic biomarkers, but could also form targets for disease-directed therapeutic approaches. Moss-produced recombinant human FH and mini-FH constructs have already been shown to be effective in different disease models, such as C3G and aHUS (Hebecker et al., 2013; Kamala et al., 2021; Michelfelder et al., 2017; Nichols et al., 2015). Recombinant FH protein GEM103 is already in clinical trials for AMD treatment (NCT04684394), whereas a potentiating antibody against FH (GEM307) is currently being evaluated in preclinical phase for aHUS (Dekkers et al., 2020; Pouw et al., 2019). Recombinant FH along with IgG proteins have also been considered as complementary treatment strategies in streptococcal-associated multidrug-resistant bacterial infections (Shaughnessy et al., 2021). In contrast, therapeutic targeting of the FHRs has only recently been considered. Various therapeutic approaches have been proposed, such as regulating systemic levels of FHRs by using specific antibodies, by regulating their hepatic synthesis or by the use of sequestering agents, but these strategies have not been tested in experimental settings (Chen et al., 2016; Cipriani et al., 2020; Medjeral-Thomas et al., 2017). Nevertheless, Schäfer and colleagues developed a specific monoclonal antibody against FHR-3 that can modulate its binding to C3b, thereby regulating FHR-3 deposition on the retina (Schäfer et al., 2016). In another study, gene therapy was used for a fusion homo-dimeric construct of human mini-FH and a murine FHR, that was then shown to reduce complement dysregulation in vivo in a mouse model of C3G (Kamala et al., 2021). Hence, the therapeutic targeting of FHRs still remains esoteric and is still in its early stages.

6. Conclusion

Altogether, these initial findings suggest that there is a great need, but also a great opportunity in the development of clinical assays for the FH protein family in various diseases. Simultaneous determination of levels and ratios for the entire protein family across different disease groups in validated assays and larger, diverse patient cohorts will prospectively demonstrate the path of the FH protein family into the clinic. It will advance understanding of the associated pathophysiology and help clinicians build consensus for the management of patients suffering from associated diseases. Our review has stockpiled the characteristics of the FH protein family by bringing available data on circulating concentrations of this family in one place as well as emphasized the knowledge gaps on which the future of more precise complement diagnostics could be built on and aid to advance therapeutics.

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Data Availability

No data was used for the research described in the article.

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Conflict of interest statement

ET was employed by Hycult Biotech. MS was employed by Microcoat Biotechnologie GmbH. FP has been involved as a consultant for Invizius. RBP is co-inventor of multiple patents and patent applications describing the therapeutic use of anti-FH antibodies. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. We position this overview considering our own perspective, as principal investigators of the SciFiMed Consortium, a consortium aiming to create a comprehensive analytical system for the quantitative and functional assessment of the entire FH protein family.

References

Abarrategui-Garrido, C., Martínez-Barricarte, R., López-Trascasa, M., Rodríguez De Córdoba, S., Sánchez-Corral, P., 2009. Characterization of complement factor H-related (CFHR) proteins in plasma reveals novel genetic variations of CFHR1 associated with atypical hemolytic uremic syndrome. Blood 114, 4261–4271. https://doi.org/10.1182/BLOOD-2009-05-223834.

Altay, L., Sitnilska, V., Schick, T., Widmer, G., Duchateau-Nguyen, G., Piraino, P., Jayagopal, A., Drawnel, F.M., Fauser, S., 2019. Early local activation of complement in aqueous humour of patients with age-related macular degeneration. Eye 33, 1859. https://doi.org/10.1038/S41433-019-0501-4.

Amon, L.M., Law, W., Fitzgibbon, M.P., Gross, J.A., O'Briant, K., Peterson, A., Drescher, C., Martin, D.B., McIntosh, M., 2010. Integrative proteomic analysis of serum and peritoneal fluids helps identify proteins that are up-regulated in serum of women with ovarian cancer. PLoS One 5. https://doi.org/10.1371/JOURNAL.PONE.0011137.

Ansari, M., Mckeigue, P.M., Skerka, C., Hayward, C., Rudan, I., Vitart, V., Polasek, O., Armbrecht, A.M., Yates, J.R.W., Vatavuk, Z., Bencic, G., Kolcic, I., Oostra, B.A., Van Duijn, C.M., Campbell, S., Stanton, C.M., Huffman, J., Shu, X., Khan, J.C., Shahid, H., Harding, S.P., Bishop, P.N., Deary Ian, I.J., Moore, A.T., Dhillon, B., Rudan, P., Zipfel, P.F., Sim, R.B., Hastie, N.D., Campbell, H., Wright, A.F., 2013. Genetic influences on plasma CFH and CFHR1 concentrations and their role in susceptibility to age-related macular degeneration. Hum. Mol. Genet. 22, 4857–4869. https://doi.org/10.1093/hmg/ddt336.

Bansal, R., Gupta, A., 2020. Protein biomarkers in uveitis. Front. Immunol. 11. https://doi.org/10.3389/FIMMU.2020.610428.

Bao, L., Haas, M., Quigg, R.J., 2011. Complement factor H deficiency accelerates development of lupus nephritis. J. Am. Soc. Nephrol. 22, 285–295. https://doi.org/10.1681/ASN.2010060647.

Bhattacharjee, A., Reuter, S., Trojnár, E., Kolodziejczyk, R., Hyvärinen, H.S.S., Uzonyi, B., Szilágyi, Á., Prohászka, Z., Goldman, A., Józsi, M., Jokiranta, T.S., 2015. The major autoantibody epitope on factor H in atypical hemolytic uremic syndrome is structurally different from its homologous site in factor H-related protein 1, supporting a novel model for induction of autoimmunity in this disease. J. Biol. Chem. 290, 9500–9510. https://doi.org/10.1074/jbc.M114.630871.

Bomback, A.S., Appel, G.B., Gipson, D.S., Hladunewich, M.A., Lafayette, R., Nester, C.M., Parikh, S.V., Smith, R.J.H., Trachtman, H., Heeger, P.S., Ram, S., Rovin, B.H., Ali, S., Arceneaux, N., Ashoor, I., Bailey-Wickins, L., Barratt, J., Beck, L., Cattran, D.C., Cravedi, P., Erkan, E., Fervenza, F., Frazer-Abel, A.A., Fremeaux-Bacchi, V., Fuller, L., Gbadegesin, R., Hogan, J.J., Kiryluk, K., le Quintrec-Donnette, M., Licht, C., Mahan, J.D., Pickering, M.C., Quigg, R., Rheault, M., Ronco, P., Sarwal, M. M., Sethna, C., Spino, C., Stegall, M., Vivarelli, M., Feldman, D.L., Thurman, J.M., 2022. Improving clinical trials for anticomplement therapies in complement-mediated glomerulopathies: report of a scientific workshop sponsored by the National Kidney Foundation. Am. J. Kidney Dis. 79, 570–581. https://doi.org/10.1053/J.AJKD.2021.07.025.

Brodszki, N., Frazer-Abel, A., Grumach, A.S., Kirschfink, M., Litzman, J., Perez, E., Seppänen, M.R.J., Sullivan, K.E., Jolles, S., 2020. European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) complement guideline: deficiencies, diagnosis, and management. J. Clin. Immunol. 40, 576–591. https://doi.org/10.1007/S10875-020-00754-1.

Caesar, J.J.E., Lavender, H., Ward, P.N., Exley, R.M., Eaton, J., Chittock, E., Malik, T.H., Goiecoechea De Jorge, E., Pickering, M.C., Tang, C.M., Lea, S.M., 2014. Competition between antagonistic complement factors for a single protein on N. meningitidis rules disease susceptibility. eLife 3. https://doi.org/10.7554/ELIFE.04008.

Cantsilieris, S., Nelson, B.J., Huddleston, J., Baker, C., Harshman, L., Penewit, K., Munson, K.M., Sorensen, M., Welch, A.M.E., Dang, V., Grassmann, F., Richardson, A. J., Guymer, R.H., Graves-Lindsay, T.A., Wilson, R.K., Weber, B.H.F., Baird, P.N., Allikmets, R., Eichler, E.E., 2018. Recurrent structural variation, clustered sites of selection, and disease risk for the complement factor H (CFH) gene family. Proc. Natl. Acad. Sci. USA 115, E4433–E4442. https://doi.org/10.1073/pnas.1717600115.

Chen, Q., Manzke, M., Hartmann, A., Büttner, M., Amann, K., Pauly, D., Wiesener, M., Skerka, C., Zipfel, P.F., 2016. Complement factor H-related 5-hybrid proteins anchor properdin and activate complement at self-surfaces. J. Am. Soc. Nephrol. 27, 1413–1425. https://doi.org/10.1681/ASN.2015020212.

Chen, S.F., Wang, F.M., Li, Z.Y., Yu, F., Zhao, M.H., Chen, M., 2015. Plasma complement factor H is associated with disease activity of patients with ANCA-associated vasculitis. Arthritis Res. Ther. 17. https://doi.org/10.1186/S13075-015-0656-8.

Cheng, Z.Z., Corey, M.J., Pärepalo, M., Majno, S., Hellwage, J., Zipfel, P.F., Kinders, R.J., Raitanen, M., Meri, S., Sakari Jokiranta, T., 2005. Complement factor H as a marker for detection of bladder cancer. Clin. Chem. 51, 856–863. https://doi.org/10.1373/CLINCHEM.2004.042192.

Cipriani, V., Lorés-Motta, L., He, F., Fathalla, D., Tilakaratna, V., McHarg, S., Bayatti, N., Acar, İ.E., Hoyng, C.B., Fauser, S., Moore, A.T., Yates, J.R.W., de Jong, E.K., Morgan, B.P., den Hollander, A.I., Bishop, P.N., Clark, S.J., 2020. Increased circulating levels of factor H-related protein 4 are strongly associated with age-related macular degeneration. Nat. Commun. 11. https://doi.org/10.1038/s41467-020-14499-3.

Cipriani, V., Tierney, A., Griffiths, J.R., Zuber, V., Sergouniotis, P.I., Yates, J.R.W., Moore, A.T., Bishop, P.N., Clark, S.J., Unwin, R.D., 2021. Beyond factor H: The impact of genetic-risk variants for age-related macular degeneration on circulating factor-H-like 1 and factor-H-related protein concentrations. Am. J. Hum. Genet. 108, 1385–1400. https://doi.org/10.1016/J.AJHG.2021.05.015.

Clark, S.J., Bishop, P.N., 2018. The eye as a complement dysregulation hotspot. Semin. Immunopathol. 40, 65–74. https://doi.org/10.1007/S00281-017-0649-6.

de Córdoba, S.R., 2016. Complement genetics and susceptibility to inflammatory disease. Lessons from genotype-phenotype correlations. Immunobiology 221, 709–714. https://doi.org/10.1016/j.imbio.2015.05.015.

Csincsi, Á.I., Szabó, Z., Bánlaki, Z., Uzonyi, B., Cserhalmi, M., Kárpáti, É., Tortajada, A., Caesar, J.J.E., Prohászka, Z., Jokiranta, T.S., Lea, S.M., Rodríguez de Córdoba, S., Józsi, M., 2017. FHR-1 binds to C-reactive protein and enhances rather than inhibits complement activation. J. Immunol. 199, 292–303 doi:10.4049/jimmunol.1600483.

Davila, S., Wright, V.J., Khor, C.C., Sim, K.S., Binder, A., Breunis, W.B., Inwald, D., Nadel, S., Betts, H., Carrol, E.D., de Groot, R., Hermans, P.W.M., Hazelzet, J., Emonts, M., Lim, C.C., Kuijpers, T.W., Martinon-Torres, F., Salas, A., Zenz, W., Levin, M., Hibberd, M.L., 2010. Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease. Nat. Genet. 42, 772–778. https://doi.org/10.1038/ng.640.

De Jorge, E.G., Tortajada, A., García, S.P., Gastoldi, S., Merinero, H.M., García-Fernández, J., Arjona, E., Cao, M., Remuzzi, G., Noris, M., De Córdoba, S.R., 2018. Factor H competitor generated by gene conversion events associates with atypical hemolytic uremic syndrome. J. Am. Soc. Nephrol. 29, 240–249. https://doi.org/10.1681/ASN.2017050518/-/DCSUPPLEMENTAL.

DeCordova, S., Abdelgany, A., Murugaiah, V., Pathan, A.A., Nayak, A., Walker, T., Shastri, A., Alrokayan, S.H., Khan, H.A., Singh, S.K., De Pennington, N., Sim, R.B., Kishore, U., 2019. Secretion of functionally active complement factor H related protein 5 (FHR5) by primary tumour cells derived from glioblastoma multiforme patients. Immunobiology 224, 625–631. https://doi.org/10.1016/j.imbio.2019.07.006.

Dekkers, G., Brouwer, M.C., Jeremiasse, J., Kamp, A., Biggs, R.M., van Mierlo, G., Lauder, S., Katti, S., Kuijpers, T.W., Rispens, T., Jongerius, I., 2020. Unraveling the effect of a potentiating anti–factor H antibody on atypical hemolytic uremic syndrome–associated factor H variants. J. Immunol. 205, 1778–1786. https://doi.org/10.4049/jimmunol.2000368.

Dragon-Durey, M.A., Frémeaux-Bacchi, V., Loirat, C., Blouin, J., Niaudet, P., Deschenes, G., Coppo, P., Fridman, W.H., Weiss, L., 2004. Heterozygous and homozygous factor h deficiencies associated with hemolytic uremic syndrome or membranoproliferative glomerulonephritis: report and genetic analysis of 16 cases. J. Am. Soc. Nephrol. 15, 787–795. https://doi.org/10.1097/01.ASN.0000115702.28859.A7.

Edwards, A.O., Ritter, R., Abel, K.J., Manning, A., Panhuysen, C., Farrer, L.A., 2005. Complement factor H polymorphism and age-related macular degeneration. Science 308, 421–424. https://doi.org/10.1126/SCIENCE.1110189/SUPPL_FILE/EDWARDS.SOM.PDF.

Estaller, C., Schwaeble, W., Dierich, M., Weiss, E.H., 1991. Human complement factor H: two factor H proteins are derived from alternatively spliced transcripts. Eur. J. Immunol. 21, 799–802. https://doi.org/10.1002/eji.1830210337.

Ferreira, V.P., Pangburn, M.K., Cortés, C., 2010. Complement control protein factor H: the good, the bad, and the inadequate. Mol. Immunol. https://doi.org/10.1016/j.molimm.2010.05.007.

Fiedorowicz, E., Cieślińska, A., Kuklo, P., Grzybowski, A., 2021. Protein biomarkers in glaucoma: a review. J. Clin. Med. 10. https://doi.org/10.3390/JCM10225388.

Fijen, C.A.P., Kuijper, E.J., Te Bulte, M.T., Van De Heuvel, M.M., Holdrinet, A.C.J.M., Sim, R.B., Daha, M.R., Dankert, J., 1996. Heterozygous and homozygous factor H

deficiency states in a Dutch family. Clin. Exp. Immunol. 105, 511–516. https://doi.org/10.1046/J.1365-2249.1996.D01-777.X.
Fontaine, M., Demares, M.J., Koistinen, V., Day, A.J., Davrinche, C., Sim, R.B., Ripoche, J., 1989. Truncated forms of human complement factor H. Biochem. J. 258, 927–930. https://doi.org/10.1042/bj2580927.
Frazer-Abel, A., Kirschfink, M., Prohászka, Z., 2021. Expanding horizons in complement analysis and quality control. Front. Immunol. 12. https://doi.org/10.3389/FIMMU.2021.697313.
Fritsche, L.G., Lauer, N., Hartmann, A., Stippa, S., Keilhauer, C.N., Oppermann, M., Pandey, M.K., Köhl, J., Zipfel, P.F., Weber, B.H.F., Skerka, C., 2010. An imbalance of human complement regulatory proteins CFHR1, CFHR3 and factor H influences risk for age-related macular degeneration (AMD. Hum. Mol. Genet. 19, 4694–4704. https://doi.org/10.1093/hmg/ddq399.
Fu, B. Sheng, Liu, W., Zhang, J. Wen, Zhang, T., Li, H., Chen, G. Hua, 2009. Serum proteomic analysis on metastasis-associated proteins of hepatocellular carcinoma. Nan Fang. Yi Ke Da Xue Xue Bao 29, 1775–1778.
Garam, N., Cserhalmi, M., Prohászka, Z., Szilágyi, A., Veszeli, N., Szabó, E., Uzonyi, B., Iliás, A., Aigner, C., Schmidt, A., Gaggl, M., Sunder-Plassmann, G., Bajcsi, D., Brunner, J., Dumfarth, A., Cejka, D., Flaschberger, S., Flögelova, H., Haris, A., Hartmann, A., Heilos, A., Mueller, T., Rusai, K., Arbeiter, K., Hofer, J., Jakab, D., Sinkó, M., Szigeti, E., Bereczki, C., Janko, V., Kelen, K., Reusz, G.S., Szabó, A.J., Klenk, N., Kóbor, K., Kojc, N., Knechtelsdorfer, M., Laganovic, M., Lungu, A.C., Meglic, A., Rus, R., Kersnik Levart, T., Macioniene, E., Miglinas, M., Pawłowska, A., Stompór, T., Podracka, L., Rudnicki, M., Mayer, G., Rysava, R., Reiterova, J., Saraga, M., Seeman, T., Zieg, J., Sládková, E., Stajic, N., Szabó, T., Capitanescu, A., Stancu, S., Tisljar, M., Galesic, K., Tislér, A., Vainumäe, I., Windpessl, M., Zaoral, T., Zlatanova, G., Józsi, M., Csuka, D., 2021. FHR-5 serum levels and CFHR5 genetic variations in patients with immune complex-mediated membranoproliferative glomerulonephritis and C3-glomerulopathy. Front. Immunol. 12 https://doi.org/10.3389/fimmu.2021.720183.
García-Gen, E., Penadés, M., Mérida, S., Desco, C., Araujo-Miranda, R., Navea, A., Bosch-Morell, F., 2021. High myopia and the complement system: factor H in myopic maculopathy. J. Clin. Med. 10. https://doi.org/10.3390/JCM10122600.
Garred, P., Tenner, A.J., Mollnes, T.E., 2021. Therapeutic targeting of the complement system: from rare diseases to pandemics. Pharmacol. Rev. 73, 792–827. https://doi.org/10.1124/PHARMREV.120.000072.
Gharavi, A.G., Kiryluk, K., Choi, M., Li, Y., Hou, P., Xie, J., Sanna-Cherchi, S., Men, C.J., Julian, B.A., Wyatt, R.J., Novak, J., He, J.C., Wang, H., Lv, J., Zhu, L., Wang, W., Wang, Z., Yasuno, K., Gunel, M., Mane, S., Umlauf, S., Tikhonova, I., Beerman, I., Savoldi, S., Magistroni, R., Ghiggeri, G.M., Bodria, M., Lugani, F., Ravani, P., Ponticelli, C., Allegri, L., Boscutti, G., Frasca, G., Amore, A., Peruzzi, L., Coppo, R., Izzi, C., Viola, B.F., Prati, E., Salvadori, M., Mignani, R., Gesualdo, L., Bertinetto, F., Mesiano, P., Amoroso, A., Scolari, F., Chen, N., Zhang, H., Lifton, R.P., 2011. Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat. Genet. 43, 321–329. https://doi.org/10.1038/ng.787.
Goicoechea de Jorge, E., López Lera, A., Bayarri-Olmos, R., Yebenes, H., Lopez-Trascasa, M., Rodríguez de Córdoba, S., 2018. Common and rare genetic variants of complement components in human disease. Mol. Immunol. 102, 42–57. https://doi.org/10.1016/j.molimm.2018.06.011.
Goicoechea De Jorge, E., Caesar, J.J.E., Malik, T.H., Patel, M., Colledge, M., Johnson, S., Hakobyan, S., Morgan, B.P., Harris, C.L., Pickering, M.C., Lea, S.M., 2013. Dimerization of complement factor H-related proteins modulates complement activation in vivo. Proc. Natl. Acad. Sci. USA 110, 4685–4690. https://doi.org/10.1073/pnas.1219260110.
Goodship, T.H.J., Cook, H.T., Fakhouri, F., Fervenza, F.C., Frémeaux-Bacchi, V., Kavanagh, D., Nester, C.M., Noris, M., Pickering, M.C., Rodríguez de Córdoba, S., Roumenina, L.T., Sethi, S., Smith, R.J.H., Alpers, C.E., Appel, G.B., Ardissino, G., Ariceta, G., Arici, M., Bagga, A., Bajema, I.M., Blasco, M., Burke, L., Cairns, T.D., Carratala, M., D'Agati, V.D., Daha, M.R., De Vriese, A.S., Dragon-Durey, M.A., Fogo, A.B., Galbusera, M., Gale, D.P., Haller, H., Johnson, S., Józsi, M., Karpman, D., Lanning, L., Le Quintrec, M., Licht, C., Loirat, C., Monfort, F., Morgan, B.P., Noël, L. H., O'Shaughnessy, M.M., Rabant, M., Rondeau, E., Ruggenenti, P., Sheerin, N.S., Smith, J., Spoleti, F., Thurman, J.M., van de Kar, N.C.A.J., Vivarelli, M., Zipfel, P.F., 2017. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 539–551. https://doi.org/10.1016/j.kint.2016.10.005.
Gui, F., You, Z., Fu, S., Wu, H., Zhang, Y., 2020. Endothelial dysfunction in diabetic retinopathy. Front. Endocrinol. 11, 591. https://doi.org/10.3389/FENDO.2020.00591/BIBTEX.
Haines, J.L., Hauser, M.A., Schmidt, S., Scott, W.K., Olson, L.M., Gallins, P., Spencer, K. L., Shu, Y.K., Noureddine, M., Gilbert, J.R., Schnetz-Boutaud, N., Agarwal, A., Postel, E.A., Pericak-Vance, M.A., 2005. Complement factor H variant increases the risk of age-related macular degeneration. Science 308, 419–421. https://doi.org/10.1126/SCIENCE.1110359/SUPPL_FILE/HAINES.SOM.PDF.
Hakobyan, S., Harris, C.L., Tortajada, A., Dejorge, E.G., Garcia-Layana, A., Fernandez-Robredo, P., De Cordoba, S.R., Paul Morgan, B., 2008. Measurement of factor H variants in plasma using variant-specific monoclonal antibodies: application to assessing risk of age-related macular degeneration. Investig. Ophthalmol. Vis. Sci. 49, 1983–1990 doi:10.1167/iovs.07-1523.
Haralambous, E., Dolly, S.O., Hibberd, M.L., Litt, D.J., Udalova, I.A., O'dwyer, C., Langford, P.R., Simon Kroll, J., Levin, M., 2006. Factor H, a regulator of complement activity, is a major determinant of meningococcal disease susceptibility in UK Caucasian patients. Scand. J. Infect. Dis. 38, 764–771. https://doi.org/10.1080/00365540600643203.
Harris, C.L., Pouw, R.B., Kavanagh, D., Sun, R., Ricklin, D., 2018. Developments in anti-complement therapy; from disease to clinical trial. Mol. Immunol. 102, 89–119. https://doi.org/10.1016/J.MOLIMM.2018.06.008.
Hasturk, H., Hajishengallis, G., Lambris, J.D., Mastellos, D.C., Yancopoulou, D., 2021. Phase IIa clinical trial of complement C3 inhibitor AMY-101 in adults with periodontal inflammation. J. Clin. Investig. 131. https://doi.org/10.1172/JCI152973.
Haupt, K., Kraiczy, P., Wallich, R., Brade, V., Skerka, C., Zipfel, P.F., 2007. Binding of human factor H-related protein 1 to serum-resistant Borrelia burgdorferi is mediated by borrelial complement regulator-acquiring surface proteins. J. Infect. Dis. 196, 124–133. https://doi.org/10.1086/518509.
Haupt, K., Reuter, M., Van Den Elsen, J., Burman, J., Hälbich, S., Richter, J., Skerka, C., Zipfel, P.F., 2008. The Staphylococcus aureus protein Sbi acts as a complement inhibitor and forms a tripartite complex with host complement factor H and C3b. PLoS Pathog. 4, e1000250 https://doi.org/10.1371/journal.ppat.1000250.
Hebecker, M., Józsi, M., 2012. Factor H-related protein 4 activates complement by serving as a platform for the assembly of alternative pathway C3 convertase via its interaction with C3b protein. J. Biol. Chem. 287, 19528–19536. https://doi.org/10.1074/jbc.M112.364471.
Hebecker, M., Okemefuna, A.I., Perkins, S.J., Mihlan, M., Huber-Lang, M., Józsi, M., 2010. Molecular basis of C-reactive protein binding and modulation of complement activation by factor H-related protein 4. Mol. Immunol. 47, 1347–1355. https://doi.org/10.1016/J.MOLIMM.2009.12.005.
Hebecker, M., Alba-Domínguez, M., Roumenina, L.T., Reuter, S., Hyvärinen, S., Dragon-Durey, M.-A., Jokiranta, T.S., Sánchez-Corral, P., Józsi, M., 2013. An engineered construct combining complement regulatory and surface-recognition domains represents a minimal-size functional factor H. J. Immunol. 191, 912–921. https://doi.org/10.4049/jimmunol.1300269.
Heinen, S., Sanchez-Corral, P., Jackson, M.S., Strain, L., Goodship, J.A., Kemp, E.J., Skerka, C., Jokiranta, T.S., Meyers, K., Wagner, E., Robitaille, P., Esparza-Gordillo, J., Rodriguez de Cordoba, S., Zipfel, P.F., Goodship, T.H.J., 2006. De novo gene conversion in the RCA gene cluster (1q32) causes mutations in complement factor H associated with atypical hemolytic uremic syndrome. Hum. Mutat. 27, 292–293. https://doi.org/10.1002/humu.9408.
Herbert, A.P., Makou, E., Chen, Z.A., Kerr, H., Richards, A., Rappsilber, J., Barlow, P.N., 2015. Complement evasion mediated by enhancement of captured factor H: implications for protection of self-surfaces from complement. J. Immunol. 195, 4986–4998. https://doi.org/10.4049/JIMMUNOL.1501388.
Hillmen, P., Young, N.S., Schubert, J., Brodsky, R.A., Socié, G., Muus, P., Röth, A., Szer, J., Elebute, M.O., Nakamura, R., Browne, P., Risitano, A.M., Hill, A., Schrezenmeier, H., Fu, C.-L., Maciejewski, J., Rollins, S.A., Mojcik, C.F., Rother, R.P., Luzzatto, L., 2006. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N. Engl. J. Med. 355, 1233–1243. https://doi.org/10.1056/NEJMOA061648.
Hillmen, P., Szer, J., Weitz, I., Röth, A., Höchsmann, B., Panse, J., Usuki, K., Griffin, M., Kiladjian, J.-J., de Castro, C., Nishimori, H., Tan, L., Hamdani, M., Deschatelets, P., Francois, C., Grossi, F., Ajayi, T., Risitano, A., de la Tour, R.P., 2021. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N. Engl. J. Med. 384, 1028–1037. https://doi.org/10.1056/nejmoa2029073.
Holm, M., Joenväärä, S., Saraswat, M., Tohmola, T., Ristimäki, A., Renkonen, R., Haglund, C., 2020. Plasma protein expression differs between colorectal cancer patients depending on primary tumor location. Cancer Med. 9, 5221–5234. https://doi.org/10.1002/CAM4.3178.
Hovingh, E.S., van den Broek, B., Jongerius, I., 2016. Hijacking complement regulatory proteins for bacterial immune evasion. Front. Microbiol. 7. https://doi.org/10.3389/FMICB.2016.02004.
Hu, X., Liu, H., Du, J., Chen, Y., Yang, M., Xie, Y., Chen, J., Yan, S., Ouyang, S., Gong, Z., 2019. The clinical significance of plasma CFHR 1–5 in lupus nephropathy. Immunobiology 224, 339–346. https://doi.org/10.1016/j.imbio.2019.03.005.
Hughes, A.E., Orr, N., Esfandiary, H., Diaz-Torres, M., Goodship, T., Chakravarthy, U., 2006. A common CFH haplotype, with deletion of CFHR1 and CFHR3, is associated with lower risk of age-related macular degeneration. Nat. Genet. 38, 1173–1177. https://doi.org/10.1038/ng1890.
Irmscher, S., Brix, S.R., Zipfel, S.L.H., Halder, L.D., Mutlutürk, S., Wulf, S., Girdauskas, E., Reichenspurner, H., Stahl, R.A.K., Jungnickel, B., Wiech, T., Zipfel, P. F., Skerka, C., 2019. Serum FHR1 binding to necrotic-type cells activates monocytic inflammasome and marks necrotic sites in vasculopathies. Nat. Commun. 10, 2961. https://doi.org/10.1038/s41467-019-10766-0.
Irmscher, S., Zipfel, S.L.H., Halder, L.D., Ivanov, L., Gonzalez-Delgado, A., Waldeyer, C., Seiffert, M., Brunner, F.J., von der Heide, M., Löschmann, I., Wulf, S., Czamara, D., Papac-Milicevic, N., Strauß, O., Lorkowski, S., Reichenspurner, H., Holers, M.V., Banda, N.K., Zeller, T., Binder, E.B., Binder, C.J., Wiech, T., Zipfel, P.F., Skerka, C., 2021. Factor H-related protein 1 (FHR-1) is associated with atherosclerotic cardiovascular disease. Sci. Rep. 11. https://doi.org/10.1038/S41598-021-02011-W.
Jaffe, G.J., Westby, K., Csaky, K.G., Monés, J., Pearlman, J.A., Patel, S.S., Joondeph, B.C., Randolph, J., Masonson, H., Rezaei, K.A., 2021. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial. Ophthalmology 128, 576–586. https://doi.org/10.1016/J.OPHTHA.2020.08.027.
Jayne, D.R.W., Merkel, P.A., Schall, T.J., Bekker, P., 2021. Avacopan for the treatment of ANCA-associated vasculitis. N. Engl. J. Med. 384, 599–609. https://doi.org/10.1056/nejmoa2023386.
Jha, P., Bora, P.S., Bora, N.S., 2007. The role of complement system in ocular diseases including uveitis and macular degeneration. Mol. Immunol. 44, 3901–3908. https://doi.org/10.1016/J.MOLIMM.2007.06.145.

Johnson, E.M., Uppalapati, C.K., Pascual, A.S., Estrada, S.I., Averitte, R.L., Leyva, K.J., Hull, E.E., 2022. Complement factor H in cSCC: evidence of a link between sun exposure and immunosuppression in skin cancer progression. Front. Oncol. 12. https://doi.org/10.3389/FONC.2022.819580.

Jongerius, I., Köhl, J., Pandey, M.K., Ruyken, M., Van Kessel, K.P.M., Van Strijp, J.A.G., Rooijakkers, S.H.M., 2007. Staphylococcal complement evasion by various convertase-blocking molecules. J. Exp. Med. 204, 2461–2471. https://doi.org/10.1084/JEM.20070818.

Jönsen, A., Nilsson, S.C., Ahlqvist, E., Svenungsson, E., Gunnarsson, I., Eriksson, K.G., Bengtsson, A., Zickert, A., Eloranta, M.-L., Truedsson, L., Rönnblom, L., Nordmark, G., Sturfelt, G., Blom, A.M., 2011. Mutations in genes encoding complement inhibitors CD46 and CFH affect the age at nephritis onset in patients with systemic lupus erythematosus. Arthritis Res. Ther. 13, R206. https://doi.org/10.1186/ar3539.

Józsi, M., 2017. Factor H family proteins in complement evasion of microorganisms. Front. Immunol. https://doi.org/10.3389/fimmu.2017.00571.

Józsi, M., Licht, C., Strobel, S., Zipfel, S.L.H., Richter, H., Heinen, S., Zipfel, P.F., Skerka, C., 2008. Factor H autoantibodies in atypical hemolytic uremic syndrome correlate with CFHR1/CFHR3 deficiency. Blood 111, 1512–1514. https://doi.org/10.1182/BLOOD-2007-09-109876.

Józsi, M., Tortajada, A., Uzonyi, B., Goicoechea de Jorge, E., Rodríguez de Córdoba, S., 2015. Factor H-related proteins determine complement-activating surfaces. Trends Immunol. https://doi.org/10.1016/j.it.2015.04.008.

Jullien, P., Laurent, B., Claisse, G., Masson, I., Dinic, M., Thibaudin, D., Berthoux, F., Alamartine, E., Mariat, C., Maillard, N., 2018. Deletion variants of CFHR1 and CFHR3 associate with mesangial immune deposits but not with progression of IgA nephropathy. J. Am. Soc. Nephrol. 29, 661–669. https://doi.org/10.1681/ASN.2017010019.

Junnikkala, S., Hakulinen, J., Jarva, H., Manuelian, T., Bjørge, L., Bützow, R., Zipfel, P.F., Meri, S., 2002. Secretion of soluble complement inhibitors factor H and factor H-like protein (FHL-1) by ovarian tumour cells. Br. J. Cancer 87, 1119–1127. https://doi.org/10.1038/SJ.BJC.6600614.

Jylhävä, J., Eklund, C., Pessi, T., Raitakari, O.T., Juonala, M., Kähönen, M., Viikari, J.S.A., Lehtimäki, T., Hurme, M., 2008. Genetics of C-reactive protein and complement factor H have an epistatic effect on carotid artery compliance: the cardiovascular risk in Young Finns Study. Clin. Exp. Immunol. 155, 53–58. https://doi.org/10.1111/J.1365-2249.2008.03752.X.

Kamala, O., Malik, T.H., Hallam, T.M., Cox, T.E., Yang, Y., Vyas, F., Luli, S., Connelly, C., Gibson, B., Smith-Jackson, K., Denton, H., Pappworth, I.Y., Huang, L., Kavanagh, D., Pickering, M.C., Marchbank, K.J., 2021. Homodimeric minimal factor H: in vivo tracking and extended dosing studies in factor H deficient mice. Front. Immunol. 12, 5305. https://doi.org/10.3389/fimmu.2021.752916.

Kardys, I., Klaver, C.C.W., Despriet, D.D.G., Bergen, A.A.B., Uitterlinden, A.G., Hofman, A., Oostra, B.A., Van Duijn, C.M., de Jong, P.T.V.M., Witteman, J.C.M., 2006. A common polymorphism in the complement factor H gene is associated with increased risk of myocardial infarction: the Rotterdam study. J. Am. Coll. Cardiol. 47, 1568–1575. https://doi.org/10.1016/J.JACC.2005.11.076.

Kárpáti, É., Papp, A., Schneider, A.E., Hajnal, D., Cserhalmi, M., Csincsi, Á.I., Uzonyi, B., Józsi, M., 2020. Interaction of the factor H family proteins FHR-1 and FHR-5 with DNA and dead cells: implications for the regulation of complement activation and opsonization. Front. Immunol. 11. https://doi.org/10.3389/fimmu.2020.01297.

Kasanmoentalib, E.S., Valls Serón, M., Engelen-Lee, J.Y., Tanck, M.W., Pouw, R.B., Van Mierlo, G., Wouters, D., Pickering, M.C., Van Der Ende, A., Kuijpers, T.W., Brouwer, M.C., Van De Beek, D., 2019. Complement factor H contributes to mortality in humans and mice with bacterial meningitis. J. Neuroinflamm. 16. https://doi.org/10.1186/s12974-019-1675-1.

Kennedy, A.T., Schmidt, C.Q., Thompson, J.K., Weiss, G.E., Taechalertpaisarn, T., Gilson, P.R., Barlow, P.N., Crabb, B.S., Cowman, A.F., Tham, W.-H., 2016. Recruitment of factor H as a novel complement evasion strategy for blood-stage plasmodium falciparum infection. J. Immunol. 196, 1239–1248. https://doi.org/10.4049/JIMMUNOL.1501581.

Kiryluk, K., Li, Y., Sanna-Cherchi, S., Rohanizadegan, M., Suzuki, H., Eitner, F., Snyder, H.J., Choi, M., Hou, P., Scolari, F., Izzi, C., Gigante, M., Gesualdo, L., Savoldi, S., Amoroso, A., Cusi, D., Zamboli, P., Julian, B.A., Novak, J., Wyatt, R.J., Mucha, K., Perola, M., Kristiansson, K., Viktorin, A., Magnusson, P.K., Thorleifsson, G., Thorsteinsdottir, U., Stefansson, K., Boland, A., Metzger, M., Thibaudin, L., Wanner, C., Jager, K.J., Goto, S., Maixnerova, D., Karnib, H.H., Nagy, J., Panzer, U., Xie, J., Chen, N., Tesar, V., Narita, I., Berthoux, F., Floege, J., Stengel, B., Zhang, H., Lifton, R.P., Gharavi, A.G., 2012. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet. 8, e1002765 https://doi.org/10.1371/journal.pgen.1002765.

Kiryluk, K., Li, Y., Scolari, F., Sanna-Cherchi, S., Choi, M., Verbitsky, M., Fasel, D., Lata, S., Prakash, S., Shapiro, S., Fischman, C., Snyder, H.J., Appel, G., Izzi, C., Viola, B.F., Dallera, N., Del Vecchio, L., Barlassina, C., Salvi, E., Bertinetto, F.E., Amoroso, A., Savoldi, S., Rocchietti, M., Amore, A., Peruzzi, L., Coppo, R., Salvadori, M., Ravani, P., Magistroni, R., Ghiggeri, G.M., Caridi, G., Bodria, M., Lugani, F., Allegri, L., Delsante, M., Maiorana, M., Magnano, A., Frasca, G., Boer, E., Boscutti, G., Ponticelli, C., Mignani, R., Marcantoni, C., Di Landro, D., Santoro, D., Pani, A., Polci, R., Feriozzi, S., Chicca, S., Galliani, M., Gigante, M., Gesualdo, L., Zamboli, P., Battaglia, G.G., Garozzo, M., Maixnerová, D., Tesar, V., Eitner, F., Rauen, T., Floege, J., Kovacs, T., Nagy, J., Mucha, K., Pączek, L., Zaniew, M., Mizerska-Wasiak, M., Roszkowska-Blaim, M., Pawlaczyk, K., Gale, D., Barratt, J., Thibaudin, L., Berthoux, F., Canaud, G., Boland, A., Metzger, M., Panzer, U., Suzuki, H., Goto, S., Narita, I., Caliskan, Y., Xie, J., Hou, P., Chen, N., Zhang, H., Wyatt, R.J., Novak, J., Julian, B.A., Feehally, J., Stengel, B., Cusi, D., Lifton, R.P., Gharavi, A.G., 2014. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat. Genet. 46, 1187–1196. https://doi.org/10.1038/ng.3118.

Kiss, M.G., Binder, C.J., 2022. The multifaceted impact of complement on atherosclerosis. Atherosclerosis. https://doi.org/10.1016/J.ATHEROSCLEROSIS.2022.03.014.

Klein, R.J., Zeiss, C., Chew, E.Y., Tsai, J.Y., Sackler, R.S., Haynes, C., Henning, A.K., SanGiovanni, J.P., Mane, S.M., Mayne, S.T., Bracken, M.B., Ferris, F.L., Ott, J., Barnstable, C., Hoh, J., 2005. Complement factor H polymorphism in age-related macular degeneration. Science 308, 385–389. https://doi.org/10.1126/SCIENCE.1109557/SUPPL_FILE/KLEIN_SOM.PDF.

Kopp, A., Hebecker, M., Svobodová, E., Józsi, M., 2012. Factor H: a complement regulator in health and disease, and a mediator of cellular interactions. Biomolecules. https://doi.org/10.3390/biom2010046.

Kuang, M., Tao, X., Peng, Y., Zhang, W., Pan, Y., Cheng, L., Yuan, C., Zhao, Y., Mao, H., Zhuge, L., Zhou, Z., Chen, H., Sun, Y., 2019. Proteomic analysis of plasma exosomes to differentiate malignant from benign pulmonary nodules. Clin. Proteom. 16, 1–11. https://doi.org/10.1186/S12014-019-9225-5/FIGURES/7.

Kulagin, A.D., Ptushkin, V.V., Lukina, E.A., Davydkin, I.L., Korobkin, A.V., Shamrai, V.S., Konstantinova, T.S., Kaporskaya, T.S., Mitina, T.A., Ksenzova, T.I., Zuev, E.V., Markova, O.A., Gapchenko, E.V., Kudlay, D.A., 2021. Randomized multicenter noninferiority phase III clinical trial of the first biosimilar of eculizumab. Ann. Hematol. 100, 2689–2698. https://doi.org/10.1007/S00277-021-04624-7.

Kulasekararaj, A.G., Risitano, A.M., Maciejewski, J.P., Notaro, R., Browett, P., Lee, J.W., Huang, M., Geffner, M., Brodsky, R.A., 2021. Phase 2 study of danicopan in patients with paroxysmal nocturnal hemoglobinuria with an inadequate response to eculizumab. Blood 138, 1928–1938. https://doi.org/10.1182/BLOOD.2021011388.

Kyung, M.C., Liszewski, M.K., Nybakken, G., Davis, A.E., Townsend, R.R., Fremont, D.H., Atkinson, J.P., Diamond, M.S., 2006. West Nile virus nonstructural protein NS1 inhibits complement activation by binding the regulatory protein factor H. Proc. Natl. Acad. Sci. USA 103, 19111–19116. https://doi.org/10.1073/PNAS.0605668103.

Lafayette, R.A., Rovin, B.H., Reich, H.N., Tumlin, J.A., Floege, J., Barratt, J., 2020. Safety, tolerability and efficacy of narsoplimab, a novel MASP-2 inhibitor for the treatment of IgA nephropathy. Kidney Int. Rep. 5, 2032–2041. https://doi.org/10.1016/j.ekir.2020.08.003.

Lambris, J.D., Ricklin, D., Geisbrecht, B.V., 2008. Complement evasion by human pathogens. Nat. Rev. Microbiol. 6, 132–142. https://doi.org/10.1038/NRMICRO1824.

Laskowski, J., Renner, B., Pickering, M.C., Serkova, N.J., Smith-Jones, P.M., Clambey, E.T., Nemenoff, R.A., Thurman, J.M., 2020. Complement factor H–deficient mice develop spontaneous hepatic tumors. J. Clin. Investig. 140, 4039–4054. https://doi.org/10.1172/JCI135105.

Legendre, C.M., Licht, C., Muus, P., Greenbaum, L.A., Babu, S., Bedrosian, C., Bingham, C., Cohen, D.J., Delmas, Y., Douglas, K., Eitner, F., Feldkamp, T., Fouque, D., Furman, R.R., Gaber, O., Herthelius, M., Hourmant, M., Karpman, D., Lebranchu, Y., Mariat, C., Menne, J., Moulin, B., Nürnberger, J., Ogawa, M., Remuzzi, G., Richard, T., Sberro-Soussan, R., Severino, B., Sheerin, N.S., Trivelli, A., Zimmerhackl, L.B., Goodship, T., Loirat, C., 2013. Terminal complement inhibitor eculizumab in atypical hemolytic–uremic syndrome. N. Engl. J. Med. 368, 2169–2181. https://doi.org/10.1056/NEJMoa1208981.

Lemaire, M., Noone, D., Lapeyraque, A.L., Licht, C., Frémeaux-Bacchi, V., 2021. Inherited kidney complement diseases. Clin. J. Am. Soc. Nephrol. 16, 942–956. https://doi.org/10.2215/CJN.11830720.

Levy, M., Halbwachs-Mecarelli, L., Gubler, M.C., Kohout, G., Bensenouci, A., Niaudet, P., Hauptmann, G., Lesavre, P., 1986. H deficiency in two brothers with atypical dense intramembranous deposit disease. Kidney Int. 30, 949–956. https://doi.org/10.1038/KI.1986.278.

Li, D., Wu, J., Liu, Z., Qiu, L., Zhang, Y., 2020. Novel circulating protein biomarkers for thyroid cancer determined through data-independent acquisition mass spectrometry. PeerJ 8. https://doi.org/10.7717/PEERJ.9507.

Licht, C., Heinen, S., Józsi, M., Löschmann, I., Saunders, R.E., Perkins, S.J., Waldherr, R., Skerka, C., Kirschfink, M., Hoppe, B., Zipfel, P.F., 2006. Deletion of Lys224 in regulatory domain 4 of Factor H reveals a novel pathomechanism for dense deposit disease (MPGN II. Kidney Int. 70, 42–50. https://doi.org/10.1038/SJ.KI.5000269.

Liu, H., Zhang, L., Wang, P., 2019. Complement factor H-related 3 overexpression affects hepatocellular carcinoma proliferation and apoptosis. Mol. Med. Rep. 20, 2694–2702. https://doi.org/10.3892/MMR.2019.10514/HTML.

Liu, J., Li, W., Zhao, H., 2020. CFHR3 is a potential novel biomarker for hepatocellular carcinoma. J. Cell. Biochem. 121, 2970–2980. https://doi.org/10.1002/JCB.29551.

Liu, L.L., Jiang, Y., Wang, L.N., Liu, N., 2012. Urinary mannose-binding lectin is a biomarker for predicting the progression of immunoglobulin (Ig)A nephropathy. Clin. Exp. Immunol. 169, 148–155. https://doi.org/10.1111/j.1365-2249.2012.04604.x.

Loeven, M.A., Maciej-Hulme, M.L., Yanginlar, C., Hubers, M.C., Kellenbach, E., de Graaf, M., van Kuppevelt, T.H., Wetzels, J., Rabelink, T.J., Smith, R.J.H., van der Vlag, J., 2021. Selective binding of heparin/heparan sulfate oligosaccharides to factor H and factor H-related proteins: therapeutic potential for C3 glomerulopathies. Front. Immunol. 12. https://doi.org/10.3389/fimmu.2021.676662.

Lorés-Motta, L., Paun, C.C., Corominas, J., Pauper, M., Geerlings, M.J., Altay, L., Schick, T., Daha, M.R., Fauser, S., Hoyng, C.B., den Hollander, A.I., de Jong, E.K., 2018a. Genome-wide association study reveals variants in CFH and CFHR4 associated with systemic complement activation: implications in age-related macular degeneration. Ophthalmology 125, 1064–1074. https://doi.org/10.1016/j.ophtha.2017.12.023.

Lorés-Motta, L., Paun, C.C., Corominas, J., Pauper, M., Geerlings, M.J., Altay, L., Schick, T., Daha, M.R., Fauser, S., Hoyng, C.B., den Hollander, A.I., de Jong, E.K., 2018b. Genome-wide association study reveals variants in CFH and CFHR4 associated with systemic complement activation: implications in age-related macular degeneration. Ophthalmology 125, 1064–1074. https://doi.org/10.1016/j.ophtha.2017.12.023.

Lorés-Motta, L., van Beek, A.E., Willems, E., Zandstra, J., van Mierlo, G., Einhaus, A., Mary, J.L., Stucki, C., Bakker, B., Hoyng, C.B., Fauser, S., Clark, S.J., de Jonge, M.I., Nogoceke, E., Koertvely, E., Jongerius, I., Kuijpers, T.W., den Hollander, A.I., 2021. Common haplotypes at the CFH locus and low-frequency variants in CFHR2 and CFHR5 associate with systemic FHR concentrations and age-related macular degeneration. Am. J. Hum. Genet. 108, 1367–1384. https://doi.org/10.1016/J.AJHG.2021.06.002.

Lyu, Y., Zauhar, R., Dana, N., Strang, C.E., Hu, J., Wang, K., Liu, S., Pan, N., Gamlin, P., Kimble, J.A., Messinger, J.D., Curcio, C.A., Stambolian, D., Li, M., 2021. Implication of specific retinal cell-type involvement and gene expression changes in AMD progression using integrative analysis of single-cell and bulk RNA-seq profiling. Sci. Rep. 11. https://doi.org/10.1038/S41598-021-95122-3.

Madico, G., Welsch, J.A., Lewis, L.A., McNaughton, A., Perlman, D.H., Costello, C.E., Ngampasutadol, J., Vogel, U., Granoff, D.M., Ram, S., 2006. The meningococcal vaccine candidate GNA1870 binds the complement regulatory protein factor H and enhances serum resistance. J. Immunol. 177, 501–510. https://doi.org/10.4049/JIMMUNOL.177.1.501.

Mannes, M., Dopler, A., Huber-Lang, M., Schmidt, C.Q., 2020. Tuning the functionality by splicing: factor H and its alternative splice variant FHL-1 share a gene but not all functions. Front. Immunol. 11, 2667. https://doi.org/10.3389/FIMMU.2020.596415/BIBTEX.

Markiewski, M.M., DeAngelis, R.A., Benencia, F., Ricklin-Lichtsteiner, S.K., Koutoulaki, A., Gerard, C., Coukos, G., Lambris, J.D., 2008. Modulation of the antitumor immune response by complement. Nat. Immunol. 9, 1225–1235. https://doi.org/10.1038/NI.1655.

Martin Merinero, H., Subías, M., Pereda, A., Gómez-Rubio, E., Juana Lopez, L., Fernandez, C., Goicoechea de Jorge, E., Martin-Santamaria, S., Cañada, F.J., Rodríguez de Córdoba, S., 2021. Molecular bases for the association of FHR-1 with atypical hemolytic uremic syndrome and other diseases. Blood 137, 3484–3494. https://doi.org/10.1182/BLOOD.2020010069.

Martín Merinero, H., Zhang, Y., Arjona, E., del Angel, G., Goodfellow, R., Gomez-Rubio, E., Ji, R.R., Michelena, M., Smith, R.J.H., Rodríguez de Córdoba, S., 2021. Functional characterization of 105 factor H variants associated with aHUS: lessons for variant classification. Blood 138, 2185–2201. https://doi.org/10.1182/BLOOD.2021012037.

Martinón-Torres, F., Png, E., Khor, C.C., Davila, S., Wright, V.J., Sim, K.S., Vega, A., Fachal, L., Inwald, D., Nadel, S., Carrol, E.D., Martinón-Torres, N., Alonso, S.M., Carracedo, A., Morteruel, E., López-Bayón, J., Torre, A.C., Monge, C.C., De Aguilar, P.A.G., Torné, E.E., Martínez-Padilla, M.D.C., Martinón-Sánchez, J.M., Levin, M., Hibberd, M.L., Salas, A., Gómez-Carballa, A., Cebey, M., Sánchez, N.G., Calle, I.R., Grande, A.J., Pardo-Seco, J., Barral-Arca, R., Pischedda, S., Currás-Tuala, M.J., Rodriguez-Tenreiro, C., Redondo-Collazo, L., Sánchez, F.P., De La Cruz Moreno, J., Millán Miralles, M.L., García Rodríguez, J.L., García, S.R., Doce, A.H., Barba, Á.F., Pallares, M.O., Romero, A.R., Muñoz Bonet, J.I., Cancela, M.S., Bergara, E.O., Arriortua, A.B., Navarro Gómez, M.L., Fernández, M.S., Martínez, X.A., Ortega, Á.C., Rosso, S.P., Caballero Macarrón, C.P., Menchón, N.M., Sánchez, F.G., Garzón, M.G.R., García, M.D.M.B., Sánchez Granados, J.M., Ayestarán, O.S., Payo, R., Palazón, S.C., León León, M.C., Dominguez, S.R., Villanueba, D.A., Alonso Martín, J.A., Orayen, C.G., Iturbe, E.B., Alonso Salas, M.T., Fernández, I.Q., Booy, R., Coin, L.J.M., Eleftherohorinou, H., Faust, S., Galassini, R., Habibi, P., Haralambous, E., Kroll, S., Langford, P., Pathan, N., Pollard, A.J., Abdulla, F., Agapow, P., Bellos, E., Hamilton, S., Herberg, J.A., Hoggart, C., Kaforou, M., Mashbat, M., Mustafa, S., Sancho-Shimizu, V., 2016. Natural resistance to meningococcal disease related to CFH loci: meta-analysis of genome-wide association studies. Sci. Rep. 6 https://doi.org/10.1038/SREP35842.

Mastellos, D.C., Ricklin, D., Lambris, J.D., 2019. Clinical promise of next-generation complement therapeutics. Nat. Rev. Drug Discov. 18, 707–729. https://doi.org/10.1038/S41573-019-0031-6.

McKenzie, R., Kotwal, G.J., Moss, B., Hammer, C.H., Frank, M.M., 1992. Regulation of complement activity by vaccinia virus complement-control protein. J. Infect. Dis. 166, 1245–1250. https://doi.org/10.1093/INFDIS/166.6.1245.

McRae, J.L., Cowan, P.J., Power, D.A., Mitchelhill, K.I., Kemp, B.E., Morgan, B.P., Murphy, B.F., 2001. Human factor H-related protein 5 (FHR-5): a new complement-associated protein. J. Biol. Chem. 276, 6747–6754. https://doi.org/10.1074/jbc.M007495200.

Medjeral-Thomas, N.R., Lomax-Browne, H.J., Beckwith, H., Willicombe, M., McLean, A.G., Brookes, P., Pusey, C.D., Falchi, M., Cook, H.T., Pickering, M.C., 2017. Circulating complement factor H–related proteins 1 and 5 correlate with disease activity in IgA nephropathy. Kidney Int. 92, 942–952. https://doi.org/10.1016/J.KINT.2017.03.043.

Merinero, H.M., García, S.P., García-Fernández, J., Arjona, E., Tortajada, A., Rodríguez de Córdoba, S., 2018. Complete functional characterization of disease-associated genetic variants in the complement factor H gene. Kidney Int. 93, 470–481. https://doi.org/10.1016/j.kint.2017.07.015.

Michelfelder, S., Parsons, J., Bohlender, L.L., Hoernstein, S.N.W., Niederkrüger, H., Busch, A., Krieghoff, N., Koch, J., Fode, B., Schaaf, A., Frischmuth, T., Pohl, M., Zipfel, P.F., Reski, R., Decker, E.L., Häffner, K., 2017. Moss-produced, glycosylation-optimized human factor H for therapeutic application in complement disorders. J. Am. Soc. Nephrol. 28, 1462–1474. https://doi.org/10.1681/ASN.2015070745.

Mihlan, M., Hebecker, M., Dahse, H.M., Hälbich, S., Huber-Lang, M., Dahse, R., Zipfel, P.F., Józsi, M., 2009. Human complement factor H-related protein 4 binds and recruits native pentameric C-reactive protein to necrotic cells. Mol. Immunol. 46, 335–344. https://doi.org/10.1016/j.molimm.2008.10.029.

Misasi, R., Huemer, H.P., Schwaeble, W., Sölder, E., Larcher, C., Dierich, M.P., 1989. Human complement factor H: An additional gene product of 43kDa isolated from human plasma shows cofactor activity for the cleavage of the third component of complement. Eur. J. Immunol. 19, 1765–1768. https://doi.org/10.1002/eji.1830190936.

Mollnes, T.E., Garred, P., Bergseth, G., 1988. Effect of time, temperature and anticoagulants on in vitro complement activation: consequences for collection and preservation of samples to be examined for complement activation. Clin. Exp. Immunol. 73, 484–488.

Moore, I., Strain, L., Pappworth, I., Kavanagh, D., Barlow, P.N., Herbert, A.P., Schmidt, C.Q., Staniforth, S.J., Holmes, L.V., Ward, R., Morgan, L., Goodship, T.H.J., Marchbank, K.J., 2010. Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4, and with mutations in CFH, CFI, CD46, and C3 in patients with atypical hemolytic uremic syndrome. Blood 115, 379–387. https://doi.org/10.1182/blood-2009-05-221549.

Moore, S.R., Menon, S.S., Cortes, C., Ferreira, V.P., 2021. Hijacking factor H for complement immune evasion. Front. Immunol. 12. https://doi.org/10.3389/FIMMU.2021.602277.

Nichols, E.M., Barbour, T.D., Pappworth, I.Y., Wong, E.K.S., Palmer, J.M., Sheerin, N.S., Pickering, M.C., Marchbank, K.J., 2015. An extended mini-complement factor H molecule ameliorates experimental C3 glomerulopathy. Kidney Int. 88, 1314–1322. https://doi.org/10.1038/ki.2015.233.

Nozal, P., Garrido, S., Alba-Domínguez, M., Espinosa, L., Peña, A., Córdoba, S.R., de, Sánchez-Corral, P., López-Trascasa, M., 2014. An ELISA assay with two monoclonal antibodies allows the estimation of free factor H and identifies patients with acquired deficiency of this complement regulator. Mol. Immunol. 58, 194–200. https://doi.org/10.1016/j.molimm.2013.11.021.

Pai, J.K., Manson, J.E., Rexrode, K.M., Albert, C.M., Hunter, D.J., Rimm, E.B., 2007. Complement factor H (Y402H) polymorphism and risk of coronary heart disease in US men and women. Eur. Heart J. 28, 1297–1303. https://doi.org/10.1093/EURHEARTJ/EHM090.

Parente, R., Clark, S.J., Inforzato, A., Day, A.J., 2017. Complement factor H in host defense and immune evasion. Cell. Mol. Life Sci. https://doi.org/10.1007/s00018-016-2418-4.

Pastor, A.F., Rodrigues Moura, L., Neto, J.W.D., Nascimento, E.J.M., Calzavara-Silva, C.E., Gomes, A.L.V., Silva, A.M., da, Cordeiro, M.T., Braga-Neto, U., Crovella, S., Gil, L.H.V.G., Marques, E.T.A., Acioli-Santos, B., 2013. Complement factor H gene (CFH) polymorphisms C-257T, G257A and haplotypes are associated with protection against severe dengue phenotype, possible related with high CFH expression. Hum. Immunol. 74, 1225–1230. https://doi.org/10.1016/J.HUMIMM.2013.05.005.

Pedersen, S., Jensen, K.P., Honoré, B., Kristensen, S.R., Pedersen, C.H., Szejniuk, W.M., Maltesen, R.G., Falkmer, U., 2022. Circulating microvesicles and exosomes in small cell lung cancer by quantitative proteomics. Clin. Proteom. 19. https://doi.org/10.1186/S12014-021-09339-5.

Pickering, M.C., D'Agati, V.D., Nester, C.M., Smith, R.J., Haas, M., Appel, G.B., Alpers, C.E., Bajema, I.M., Bedrosian, C., Braun, M., Doyle, M., Fakhouri, F., Fervenza, F.C., Fogo, A.B., Frémeaux-Bacchi, V., Haas, D.P., Goicoechea de Jorge, E., Griffin, G., Harris, C.L., Holers, V.M., Johnson, S., Lavin, P.J., Medjeral-Thomas, N., Paul Morgan, B., Nast, C.C., Noel, L.-H., Peters, D.K., Rodríguez de Córdoba, S., Servais, A., Sethi, S., Song, W.-C., Tamburini, P., Thurman, J.M., Zavros, M., Cook, H.T., 2013. C3 glomerulopathy: consensus report. Kidney Int. 1079–1089. https://doi.org/10.1038/ki.2013.377.

Pio, R., Garcia, J., Corrales, L., Ajona, D., Fleischhacker, M., Pajares, M.J., Cardenal, F., Seijo, L., Zulueta, J.J., Nadal, E., Witt, C., Lozano, M.D., Schmidt, B., Montuenga, L.M., 2010. Complement factor H is elevated in bronchoalveolar lavage fluid and sputum from patients with lung cancer. Cancer Epidemiol. Biomark. Prev. 19, 2665–2672. https://doi.org/10.1158/1055-9965.EPI-10-0467.

Piras, R., Breno, M., Valoti, E., Alberti, M., Iatropoulos, P., Mele, C., Bresin, E., Donadelli, R., Cuccarolo, P., Smith, R.J.H., Benigni, A., Remuzzi, G., Noris, M., 2021. CFH and CFHR copy number variations in C3 glomerulopathy and immune complex-mediated membranoproliferative glomerulonephritis. Front. Genet. 12. https://doi.org/10.3389/fgene.2021.670727.

Pittock, S.J., Berthele, A., Fujihara, K., Kim, H.J., Levy, M., Palace, J., Nakashima, I., Terzi, M., Totolyan, N., Viswanathan, S., Wang, K.-C., Pace, A., Fujita, K.P., Armstrong, R., Wingerchuk, D.M., 2019. Eculizumab in aquaporin-4–positive neuromyelitis optica spectrum disorder. N. Engl. J. Med. 381, 614–625. https://doi.org/10.1056/NEJMOA1900866/SUPPL_FILE/NEJMOA1900866_DATA-SHARING.PDF.

Poppelaars, F., Thurman, J.M., 2020. Complement-mediated kidney diseases. Mol. Immunol. 128, 175–187. https://doi.org/10.1016/j.molimm.2020.10.015.

Poppelaars, F., da Costa, M. Gaya, Berger, S.P., Assa, S., Meter-Arkema, A.H., Daha, M.R., van Son, W.J., Franssen, C.F.M., Seelen, M.A.J., 2016. Strong predictive value of mannose-binding lectin levels for cardiovascular risk of hemodialysis patients. J. Transl. Med. 14, 236. https://doi.org/10.1186/s12967-016-0995-5.

Poppelaars, F., da Costa, M. Gaya, Faria, B., Berger, S.P., Assa, S., Daha, M.R., Medina Pestana, J.O., van Son, W.J., Franssen, C.F.M., Seelen, M.A., 2018. Intradialytic complement activation precedes the development of cardiovascular events in hemodialysis patients. Front. Immunol. 9, 2070. https://doi.org/10.3389/fimmu.2018.02070.

Poppelaars, F., Faria, B., Schwaeble, W., Daha, M.R., 2021a. The contribution of complement to the pathogenesis of IgA nephropathy: are complement-targeted

therapies moving from rare disorders to more common diseases? J. Clin. Med. 10. https://doi.org/10.3390/JCM10204715.
Poppelaars, F., de Jorge, Goicoechea, Jongerius, E., Baeumner, I., Steiner, A.J., Józsi, M. S., Toonen, E.J.M., Pauly, D., 2021b. A family affair: addressing the challenges of factor H and the related proteins. Front. Immunol. https://doi.org/10.3389/fimmu.2021.660194.
Pouw, R.B., Ricklin, D., 2021. Tipping the balance: intricate roles of the complement system in disease and therapy. Semin. Immunopathol. 43, 757. https://doi.org/10.1007/S00281-021-00892-7.
Pouw, R.B., Brouwer, M.C., Geissler, J., Van Herpen, L.V., Zeerleder, S.S., Wuillemin, W. A., Wouters, D., Kuijpers, T.W., 2016. Complement factor H-related protein 3 serum levels are low compared to factor H and mainly determined by gene copy number variation in CFHR3. PLoS One 11. https://doi.org/10.1371/journal.pone.0152164.
Pouw, R.B., Brouwer, M.C., van Beek, A.E., Józsi, M., Wouters, D., Kuijpers, T.W., 2018a. Complement factor H-related protein 4A is the dominant circulating splice variant of CFHR4. Front. Immunol. 9, 1. https://doi.org/10.3389/fimmu.2018.00729.
Pouw, R.B., Delgado, I.G., Lera, A.L., de Córdoba, S.R., Wouters, D., Kuijpers, T.W., Sánchez-Corral, P., 2018b. High complement factor H-related (FHR)-3 levels are associated with the atypical hemolytic-uremic syndrome-risk allele CFHR3*B. Front. Immunol. 9, 24. https://doi.org/10.3389/fimmu.2018.00848.
Pouw, R.B., Brouwer, M.C., de Gast, M., van Beek, A.E., van den Heuvel, L.P., Schmidt, C. Q., van der Ende, A., Sánchez-Corral, P., Kuijpers, T.W., Wouters, D., 2019. Potentiation of complement regulator factor H protects human endothelial cells from complement attack in aHUS sera. Blood Adv. 3, 621–632. https://doi.org/10.1182/bloodadvances.2018025692.
Prohászka, Z., Frazer-Abel, A., 2021. Complement multiplex testing: concept, promises and pitfalls. Mol. Immunol. 140, 120–126. https://doi.org/10.1016/J.MOLIMM.2021.10.006.
Prohászka, Z., Nilsson, B., Frazer-Abel, A., Kirschfink, M., 2016. Complement analysis 2016: clinical indications, laboratory diagnostics and quality control. Immunobiology. https://doi.org/10.1016/j.imbio.2016.06.008.
Prohászka, Z., Kirschfink, M., Frazer-Abel, A., 2018. Complement analysis in the era of targeted therapeutics. Mol. Immunol. 102, 84–88. https://doi.org/10.1016/j.molimm.2018.06.001.
Rajagopal, R., Sylvester, B., Zhang, S., Adak, S., Wei, X., Bowers, M., Jessberger, S., Hsu, F.F., Semenkovich, C.F., 2021. Glucose-mediated de novo lipogenesis in photoreceptors drives early diabetic retinopathy. J. Biol. Chem. 297. https://doi.org/10.1016/J.JBC.2021.101104.
Ricklin, D., Mastellos, D.C., Reis, E.S., Lambris, J.D., 2018. The renaissance of complement therapeutics. Nat. Rev. Nephrol. 14, 26–47. https://doi.org/10.1038/nrneph.2017.156.
Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., Fonseca, F., Nicolau, J., Koenig, W., Anker, S.D., Kastelein, J.J.P., Cornel, J.H., Pais, P., Pella, D., Genest, J., Cifkova, R., Lorenzatti, A., Forster, T., Kobalava, Z., Vida-Simiti, L., Flather, M., Shimokawa, H., Ogawa, H., Dellborg, M., Rossi, P.R.F., Troquay, R.P.T., Libby, P., Glynn, R.J., 2017. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N. Engl. J. Med. 377, 1119–1131. https://doi.org/10.1056/NEJMOA1707914/SUPPL_FILE/NEJMOA1707914_DISCLOSURES.PDF.
Riihilä, P.M., Nissinen, L.M., Ala-Aho, R., Kallajoki, M., Grénman, R., Meri, S., Peltonen, S., Peltonen, J., Kähäri, V.M., 2014. Complement factor H: a biomarker for progression of cutaneous squamous cell carcinoma. J. Investig. Dermatol. 134, 498–506. https://doi.org/10.1038/jid.2013.346.
Risitano, A.M., Röth, A., Soret, J., Frieri, C., de Fontbrune, F.S., Marano, L., Alashkar, F., Benajiba, L., Marotta, S., Rozenberg, I., Milojevic, J., End, P., Nidamarthy, P.K., Junge, G., Peffault de Latour, R., 2021. Addition of iptacopan, an oral factor B inhibitor, to eculizumab in patients with paroxysmal nocturnal haemoglobinuria and active haemolysis: an open-label, single-arm, phase 2, proof-of-concept trial. Lancet Haematol. 8, e344–e354 doi:10.1016/S2352-3026(21)00028-4.
Rosa, T.F.A., Flammersfeld, A., Ngwa, C.J., Kiesow, M., Fischer, R., Zipfel, P.F., Skerka, C., Pradel, G., 2016. The Plasmodium falciparum blood stages acquire factor H family proteins to evade destruction by human complement. Cell. Microbiol. 18, 573–590. https://doi.org/10.1111/CMI.12535.
Rosain, J., Hong, E., Fieschi, C., Martins, P.V., El Sissy, C., Deghmane, A.E., Ouachée, M., Thomas, C., Launay, D., De Pontual, L., Suarez, F., Moshous, D., Picard, C., Taha, M. K., Frémeaux-Bacchi, V., 2017. Strains responsible for invasive meningococcal disease in patients with terminal complement pathway deficiencies. J. Infect. Dis. 215, 1331–1338. https://doi.org/10.1093/INFDIS/JIX143.
Rosengard, A.M., Liu, Y., Nie, Z., Jimenez, R., 2002. Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. Proc. Natl. Acad. Sci. USA 99, 8808–8813. https://doi.org/10.1073/PNAS.112220499.
Röth, A., Barcellini, W., D'Sa, S., Miyakawa, Y., Broome, C.M., Michel, M., Kuter, D.J., Jilma, B., Tvedt, T.H.A., Fruebis, J., Jiang, X., Lin, S., Reuter, C., Morales-Arias, J., Hobbs, W., Berentsen, S., 2021. Sutimlimab in cold agglutinin disease. N. Engl. J. Med 384, 1323–1334. https://doi.org/10.1056/NEJMOA2027760/SUPPL_FILE/NEJMOA2027760_DATA-SHARING.PDF.
Roumenina, L.T., Daugan, M.V., Petitprez, F., Sautès-Fridman, C., Fridman, W.H., 2019. Context-dependent roles of complement in cancer. Nat. Rev. Cancer 19, 698–715. https://doi.org/10.1038/s41568-019-0210-0.
Sánchez-Corral, P., Pouw, R.B., López-Trascasa, M., Józsi, M., 2018. Self-damage caused by dysregulation of the complement alternative pathway: relevance of the factor H protein family. Front. Immunol. 9, 1607. https://doi.org/10.3389/fimmu.2018.01607.
Schäfer, N., Grosche, A., Reinders, J., Hauck, S.M., Pouw, R.B., Kuijpers, T.W., Wouters, D., Ehrenstein, B., Enzmann, V., Zipfel, P.F., Skerka, C., Pauly, D., 2016. Complement regulator FHR-3 is elevated either locally or systemically in a selection of autoimmune diseases. Front. Immunol. 7, 542. https://doi.org/10.3389/fimmu.2016.00542.
Schneider, M.C., Exley, R.M., Chan, H., Feavers, I., Kang, Y.-H., Sim, R.B., Tang, C.M., 2006. Functional significance of factor H binding to Neisseria meningitidis. J. Immunol. 176, 7566–7575. https://doi.org/10.4049/JIMMUNOL.176.12.7566.
Schneider, M.C., Prosser, B.E., Caesar, J.J.E., Kugelberg, E., Li, S., Zhang, Q., Quoraishi, S., Lovett, J.E., Deane, J.E., Sim, R.B., Roversi, P., Johnson, S., Tang, C. M., Lea, S.M., 2009. Neisseria meningitidis recruits factor H using protein mimicry of host carbohydrates. Nature 458, 890–893. https://doi.org/10.1038/nature07769.
Schwaeble, W., Zwirner, J., Schulz, T.F., Linke, R.P., Dierich, M.P., Weiss, E.H., 1987. Human complement factor H: expression of an additional truncated gene product of 43 kDa in human liver. Eur. J. Immunol. 17, 1485–1489. https://doi.org/10.1002/eji.1830171015.
Schwaeble, W., Schwaiger, H., Brooimans, R.A., Barbieri, A., Möst, J., Hirsch-Kauffmann, M., Tiefenthaler, M., Lappin, D.F., Daha, M.R., Whaley, K., Dierich, M.P., 1991. Human complement factor H: Tissue specificity in the expression of three different mRNA species. Eur. J. Biochem. 198, 399–404. https://doi.org/10.1111/j.1432-1033.1991.tb16028.x.
Shaughnessy, E., Lambris, J.D., Ram, S., Anna, D., Blom, M., Magda, M., Kohl, L., 2021. Streptococcus pyogenes gram-positive bacterial pathogen therapeutic approach against the IgG chimeric proteins as a − factor H. J. Immunol. https://doi.org/10.4049/jimmunol.1700426.
Siegel, C., Hallström, T., Skerka, C., Eberhardt, H., Uzonyi, B., Beckhaus, T., Karas, M., Wallich, R., Stevenson, B., Zipfel, P.F., Kraiczy, P., 2010. Complement factor H-related proteins CFHR2 and CFHR5 represent novel ligands for the infection-associated CRASP proteins of Borrelia burgdorferi. PLoS One 5. https://doi.org/10.1371/JOURNAL.PONE.0013519.
Simon, N., Lasonder, E., Scheuermayer, M., Kuehn, A., Tews, S., Fischer, R., Zipfel, P.F., Skerka, C., Pradel, G., 2013. Malaria parasites co-opt human factor H to prevent complement-mediated lysis in the mosquito midgut. Cell Host Microbe 13, 29–41. https://doi.org/10.1016/J.CHOM.2012.11.013.
Sitnilska, V., Enders, P., Cursiefen, C., Fauser, S., Altay, L., 2021. Association of imaging biomarkers and local activation of complement in aqueous humor of patients with early forms of age-related macular degeneration. Graefes Arch. Clin. Exp. Ophthalmol. 259, 623–632. https://doi.org/10.1007/S00417-020-04910-6.
Skerka, C., Pradel, G., Halder, L.D., Zipfel, P.F., Zipfel, S.L.H., Strauß, O., 2021. Factor H-related protein 1: a complement regulatory protein and guardian of necrotic-type surfaces. Br. J. Pharmacol. 178, 2823–2831. https://doi.org/10.1111/BPH.15290.
Smith, J.M., Mandava, Nikhil, Tirado-Gonzalez, V., Garcia-Santisteban, R., Geiger, M.D., Patnaik, J.L., Frazer-Abel, A., Lynch, A.M., Mandava, Naresh, Holers, V.M., Wagner, B.D., Sanchez-Santos, I., Meizner, D., Quiroz-Mercado, H., Palestine, A.G., 2022. Correlation of complement activation in aqueous and vitreous in patients with proliferative diabetic retinopathy. Transl. Vis. Sci. Technol. 11, 13. https://doi.org/10.1167/TVST.11.4.13.
Sofat, R., Casas, J.P., Kumari, M., Talmud, P.J., Ireland, H., Kivimaki, M., Marmot, M., Hughes, A.D., Thom, S., Ebrahim, S., Whittaker, J.C., Smeeth, L., Lawlor, D.A., Humphries, S.E., Hingorani, A.D., 2010. Genetic variation in complement factor H and risk of coronary heart disease: eight new studies and a meta-analysis of around 48,000 individuals. Atherosclerosis 213, 184–190. https://doi.org/10.1016/j.atherosclerosis.2010.07.021.
Sundstrom, J.M., Hernández, C., Weber, S.R., Zhao, Y., Dunklebarger, M., Tiberti, N., Laremore, T., Simó-Servat, O., Garcia-Ramirez, M., Barber, A.J., Gardner, T.W., Simó, R., 2018. Proteomic analysis of early diabetic retinopathy reveals mediators of neurodegenerative brain diseases. Investig. Ophthalmol. Vis. Sci. 59, 2264–2274. https://doi.org/10.1167/IOVS.17-23678.
Thurman, J.M., Laskowski, J., Nemenoff, R.A., 2020. Complement and cancer—a dysfunctional relationship. Antibodies 9, 61. https://doi.org/10.3390/antib9040061.
Toomey, C.B., Johnson, L.V., Bowes Rickman, C., 2018. Complement factor H in AMD: bridging genetic associations and pathobiology. Prog. Retin. Eye Res. 62, 38. https://doi.org/10.1016/J.PRETEYERES.2017.09.001.
Torok, Z., Peto, T., Csosz, E., Tukacs, E., Molnar, A., Maros-Szabo, Z., Berta, A., Tozser, J., Hajdu, A., Nagy, V., Domokos, B., Csutak, A., 2013. Tear fluid proteomics multimarkers for diabetic retinopathy screening. BMC Ophthalmol. 13, 1–8. https://doi.org/10.1186/1471-2415-13-40/FIGURES/3.
Tortajada, A., Yébenes, H., Abarrategui-Garrido, C., Anter, J., García-Fernández, J.M., Martínez-Barricarte, R., Alba-Domínguez, M., Malik, T.H., Bedoya, R., Pérez, R.C., Trascasa, M.L., Pickering, M.C., Harris, C.L., Sánchez-Corral, P., Llorca, O., De Córdoba, S.R., 2013. C3 glomerulopathy-associated CFHR1 mutation alters FHR oligomerization and complement regulation. J. Clin. Investig. 123, 2434–2446. https://doi.org/10.1172/JCI68280.
Tortajada, A., Gutiérrez, E., Goicoechea de Jorge, E., Anter, J., Segarra, A., Espinosa, M., Blasco, M., Roman, E., Marco, H., Quintana, L.F., Gutiérrez, J., Pinto, S., Lopez-Trascasa, M., Praga, M., Rodriguez de Córdoba, S., 2017. Elevated factor H–related protein 1 and factor H pathogenic variants decrease complement regulation in IgA nephropathy. Kidney Int. 92, 953–963. https://doi.org/10.1016/j.kint.2017.03.041.
Tseng, M.-H., Lin, S.-H., Wu, C.-Y., Chien, H.-P., Yang, H.-Y., Chen, Y.-C., Chou, Y.-C., Huang, J.-L., Tseng, M.-H., Lin, S.-H., Wu, C.-Y., Chien, H.-P., Yang, H.-Y., Chen, Y.-C., Chou, Y.-C., Huang, J.-L., 2018. Serum complement factor I is associated with disease activity of systemic lupus erythematosus. Oncotarget 9, 8502–8511. https://doi.org/10.18632/ONCOTARGET.23907.
Valoti, E., Alberti, M., Tortajada, A., Garcia-Fernandez, J., Gastoldi, S., Besso, L., Bresin, E., Remuzzi, G., Rodriguez De Cordoba, S., Noris, M., 2015. A novel atypical hemolytic uremic syndrome-associated hybrid CFHR1/CFH gene encoding a fusion protein that antagonizes factor H-dependent complement regulation. J. Am. Soc. Nephrol. 26, 209–219. https://doi.org/10.1681/ASN.2013121339.

van Beek, A.E., Pouw, R.B., Brouwer, M.C., van Mierlo, G., Geissler, J., Ooijevaar-de Heer, P., de Boer, M., van Leeuwen, K., Rispens, T., Wouters, D., Kuijpers, T.W., 2017. Factor H-related (FHR)-1 and FHR-2 form homo- and heterodimers, while FHR-5 circulates only as homodimer in human plasma. Front. Immunol. 8. https://doi.org/10.3389/fimmu.2017.01328.
van Beek, A.E., Sarr, I., Correa, S., Nwakanma, D., Brouwer, M.C., Wouters, D., Secka, F., Anderson, S.T.B., Conway, D.J., Walther, M., Levin, M., Kuijpers, T.W., Cunnington, A.J., 2018. Complement factor H levels associate with plasmodium falciparum malaria susceptibility and severity. Open Forum Infect. Dis. 5. https://doi.org/10.1093/OFID/OFY166.
van Beek, A.E., Pouw, R.B., Wright, V.J., Sallah, N., Inwald, D., Hoggart, C., Brouwer, M. C., Galassini, R., Thomas, J., Calvo-Bado, L., Fink, C., Jongerius, I., Hibberd, M., Wouters, D., Levin, M., Kuijpers, T.W., 2021. Loss of factor H family proteins associates with meningococcal disease severity, 2021.02.05.21251142 medRxiv. https://doi.org/10.1101/2021.02.05.21251142.
van Beek, A.E., Pouw, R.B., Wright, V.J., Sallah, N., Inwald, D., Hoggart, C., Brouwer, M. C., Galassini, R., Thomas, J., Calvo-Bado, L., Fink, C.G., Jongerius, I., Hibberd, M., Wouters, D., Levin, M., Kuijpers, T.W., 2022. Low levels of factor H family proteins during meningococcal disease indicate systemic processes rather than specific depletion by Neisseria meningitidis. Front. Immunol. 13, 2554. https://doi.org/10.3389/fimmu.2022.876776.
Van den Dobbelsteen, M.E.A., Verhasselt, V., Kaashoek, J.G.J., Timmerman, J.J., Schroeijers, W.E.M., Verweij, C.L., Van der Woude, F.J., Van Es, L.A., Daha, M.R., 1994. Regulation of C3 and factor H synthesis of human glomerular mesangial cells by IL-1 and interferon-gamma. Clin. Exp. Immunol. 95, 173–180. https://doi.org/10.1111/j.1365-2249.1994.tb06033.x.
Van Der Maten, E., Westra, D., Van Selm, S., Langereis, J.D., Bootsma, H.J., Van Opzeeland, F.J.H., De Groot, R., Ruseva, M.M., Pickering, M.C., Van Den Heuvel, L.P. W.J., Van De Kar, N.C.A.J., De Jonge, M.I., Van Der Flier, M., 2016. Complement factor H serum levels determine resistance to pneumococcal invasive disease. J. Infect. Dis. 213, 1820–1827. https://doi.org/10.1093/INFDIS/JIW029.
Venables, J.P., Strain, L., Routledge, D., Bourn, D., Powell, H.M., Warwicker, P., Diaz-Torres, M.L., Sampson, A., Mead, P., Webb, M., Pirson, Y., Jackson, M.S., Hughes, A., Wood, K.M., Goodship, J.A., Goodship, T.H.J., 2006. Atypical haemolytic uraemic syndrome associated with a hybrid complement gene. PLoS Med. 3, 1957–1967. https://doi.org/10.1371/journal.pmed.0030431.
Vernon, K.A., Goicoechea De Jorge, E., Hall, A.E., Fremeaux-Bacchi, V., Aitman, T.J., Cook, H.T., Hangartner, R., Koziell, A., Pickering, M.C., 2012. Acute presentation and persistent glomerulonephritis following streptococcal infection in a patient with heterozygous complement factor H-related protein 5 deficiency. Am. J. Kidney Dis. 60, 121–125. https://doi.org/10.1053/j.ajkd.2012.02.329.
Volcik, K.A., Ballantyne, C.M., Braun, M.C., Coresh, J., Mosley, T.H., Boerwinkle, E., 2008. Association of the complement factor H Y402H polymorphism with cardiovascular disease is dependent upon hypertension status: the ARIC study. Am. J. Hypertens. 21, 533–538. https://doi.org/10.1038/AJH.2007.81/2/M_AJH.533.T4.JPEG.
Wang, F.M., Yu, F., Tan, Y., Song, D., Zhao, M.H., 2012. Serum complement factor H is associated with clinical and pathological activities of patients with lupus nephritis. Rheumatology 51, 2269–2277. https://doi.org/10.1093/RHEUMATOLOGY/KES218.
Weinstein, A., Alexander, R.V., Zack, D.J., 2021. A review of complement activation in SLE. Curr. Rheumatol. Rep. 23. https://doi.org/10.1007/S11926-021-00984-1.
Welsch, J.A., Ram, S., 2008. Factor H and neisserial pathogenesis. Vaccine 26 (Suppl. 8). https://doi.org/10.1016/J.VACCINE.2008.11.060.
Willrich, M.A.V., Braun, K.M.P., Moyer, A.M., Jeffrey, D.H., Frazer-Abel, A., 2021. Complement testing in the clinical laboratory. Crit. Rev. Clin. Lab. Sci. 58, 447–478. https://doi.org/10.1080/10408363.2021.1907297.
Xiang, M., Zhang, H., Kou, L., Chen, J., Xu, Z., He, J., 2021. Low level of complement factor H increases the risk of cancer-related death in patients with small-cell lung cancer. Postgrad. Med. J. https://doi.org/10.1136/POSTGRADMEDJ-2021-141186.
Xie, J., Kiryluk, K., Li, Y., Mladkova, N., Zhu, L., Hou, P., Ren, H., Wang, W., Zhang, H., Chen, N., Gharavi, A.G., 2016. Fine mapping implicates a deletion of CFHR1 and CFHR3 in protection from IgA nephropathy in Han Chinese. J. Am. Soc. Nephrol. 27, 3187–3194. https://doi.org/10.1681/ASN.2015111210.
Yang, S., McGookey, M., Wang, Y., Cataland, S.R., Wu, H.M., 2015. Effect of blood sampling, processing, and storage on the measurement of complement activation biomarkers. Am. J. Clin. Pathol. 143, 558–565. https://doi.org/10.1309/AJCPXPD7ZQXNTIAL.
Youngblood, H., Robinson, R., Sharma, A., Sharma, S., 2019. Proteomic biomarkers of retinal inflammation in diabetic retinopathy. Int. J. Mol. Sci. 20, 4755 20, 4755. doi: 10.3390/IJMS20194755.
Zelek, W.M., Xie, L., Morgan, B.P., Harris, C.L., 2019. Compendium of current complement therapeutics. Mol. Immunol. 114, 341–352. https://doi.org/10.1016/J.MOLIMM.2019.07.030.
Zhang, J., Zhang, M., Zhao, H., Xu, X., 2020. Identification of proliferative diabetic retinopathy-associated genes on the protein–protein interaction network by using heat diffusion algorithm. Biochim. Biophys. Acta Mol. Basis Dis. 1866, 165794 https://doi.org/10.1016/J.BBADIS.2020.165794.
Zhang, M.F., Huang, J., Zhang, Y.M., Qu, Z., Wang, X., Wang, F., Meng, L.Q., Cheng, X.Y., Cui, Z., Liu, G., Zhao, M.H., 2019. Complement activation products in the circulation and urine of primary membranous nephropathy. BMC Nephrol. 20. https://doi.org/10.1186/s12882-019-1509-5.
Zhao, J., Wu, H., Khosravi, M., Cui, H., Qian, X., Kelly, J.A., Kaufman, K.M., Langefeld, C. D., Williams, A.H., Comeau, M.E., Ziegler, J.T., Marion, M.C., Adler, A., Glenn, S.B., Alarcón-Riquelme, M.E., Network, B.I.O.L.U.P.U.S., Network, G.E.N.L.E.S., Pons-Estel, B.A., Harley, J.B., Bae, S.C., Bang, S.Y., Cho, S.K., Jacob, C.O., Vyse, T.J., Niewold, T.B., Gaffney, P.M., Moser, K.L., Kimberly, R.P., Edberg, J.C., Brown, E.E., Alarcon, G.S., Petri, M.A., Ramsey-Goldman, R., Vilá, L.M., Reveille, J.D., James, J. A., Gilkeson, G.S., Kamen, D.L., Freedman, B.I., Anaya, J.M., Merrill, J.T., Criswell, L.A., Scofield, R.H., Stevens, A.M., Guthridge, J.M., Chang, D.M., Song, Y. W., Park, J.A., Lee, E.Y., Boackle, S.A., Grossman, J.M., Hahn, B.H., Goodship, T.H. J., Cantor, R.M., Yu, C.Y., Shen, N., Tsao, B.P., 2011. Association of genetic variants in complement factor H and factor H-related genes with systemic lupus erythematosus susceptibility. PLoS Genet. 7. https://doi.org/10.1371/journal.pgen.1002079.
Zhu, L., Zhai, Y.L., Wang, F.M., Hou, P., Lv, J.C., Xu, D.M., Shi, S.F., Liu, L.J., Yu, F., Zhao, M.H., Novak, J., Gharavi, A.G., Zhang, H., 2015. Variants in complement factor H and complement factor H-related protein genes, CFHR3 and CFHR1, affect complement activation in IgA. Nephrop. J. Am. Soc. Nephrol. 26, 1195–1204. https://doi.org/10.1681/ASN.2014010096.
Zhu, L., Guo, W. Yi, Shi, S. Fang, Liu, L. Jun, Lv, J. Cheng, Medjeral-Thomas, N.R., Lomax-Browne, H.J., Pickering, M.C., Zhang, H., 2018. Circulating complement factor H–related protein 5 levels contribute to development and progression of IgA nephropathy. Kidney Int. 94, 150–158. https://doi.org/10.1016/j.kint.2018.02.023.
Zipfel, P.F., 2001. Complement factor H: physiology and pathophysiology. Semin. Thromb. Hemost. 191–199. https://doi.org/10.1055/s-2001-15248.
Zipfel, P.F., Edey, M., Heinen, S., Józsi, M., Richter, H., Misselwitz, J., Hoppe, B., Routledge, D., Strain, L., Hughes, A.E., Goodship, J.A., Licht, C., Goodship, T.H.J., Skerka, C., 2007. Deletion of complement factor H-related genes CFHR1 and CFHR3 is associated with atypical hemolytic uremic syndrome. PLoS Genet. 3, 0387–0392. https://doi.org/10.1371/journal.pgen.0030041.
Zipfel, P.F., Wiech, T., Stea, E.D., Skerka, C., 2020. CFHR gene variations provide insights in the pathogenesis of the kidney diseases atypical hemolytic uremic syndrome and C3 glomerulopathy. J. Am. Soc. Nephrol. https://doi.org/10.1681/ASN.2019050515.