The Genetics of Ultra-Rare Renal Disease

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Abstract

The complement-mediated renal diseases are a group of ultra-rare renal diseases that disproportionately affect children and young adults and frequently lead to irreversible renal failure. Genetic mutations in alternate pathway of complement genes are pathomechanistically involved in a significant number of these unique diseases. Here, we review our current understanding of the role of genetics in the primary complement-mediated renal diseases affecting children, with a focus on atypical hemolytic uremic syndrome and C3 glomerulopathy. Also, included is a brief discussion of the related diseases whose relationship to complement abnormality has been suspected but not yet confirmed. Advances in genetics have transformed both treatment and outcomes in these historically difficult to treat, highly morbid diseases.

Keywords
- complement
- atypical hemolytic uremic syndrome
- C3 glomerulopathy
- thrombotic microangiopathy

Introduction

Our understanding of the ultra-rare, complement-mediated renal diseases atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G) has advanced tremendously in the past 10 years. The discovery that genetic abnormalities are central to disease pathology in the majority of patients has been critical to improving patient outcomes. Here, we review the genetic background of the complement-mediated renal diseases and discuss how genetic advances have shaped both our understanding of the underlying pathology and informed treatment options.

Alternate Complement Pathway

Dysregulation of the alternate complement pathway (AP) is central to complement-mediated renal disease.[1–4] The AP plays a vital role in innate immunity, remaining constitutively active, and acting as a first-line of defense against microorganisms. The normal activity of the AP requires the complex interaction of an array of proteins. In the complement-mediated renal diseases, normal function of one or more of these proteins is lost. In the case of aHUS, the loss of complement function is often due to a genetic mutation in either a core complement enzyme protein or more commonly in a complement control protein. Less frequently, AP gene mutations also play a role in C3G.

The first protein in the AP is complement component C3 (C3) (►**Fig. 1**). C3 undergoes spontaneous hydrolysis or can be cleaved by a downstream enzyme known as the C3 convertase, producing the C3 breakdown products C3a (an anaphylotoxin) and C3b. The cleavage product C3b interacts with complement factor B (FB) to produce a proenzyme (C3bB). FB will be cleaved by complement factor D (FD) to form the active enzyme, C3 convertase (C3bBb). The C3 convertase cleaves additional C3 into C3a and C3b, thus forming an amplification loop of the AP. An additional C3b binds with the C3 convertase to form the C5 convertase (C3bBbC3b). The C5 convertase serves to cleave C5 into C5a, another anaphylotoxin, and C5b. C5b recruits the terminal complement proteins C6 thru C9 to form the membrane attack complex (MAC). The MAC forms a transmembrane channel in the wall of an invading

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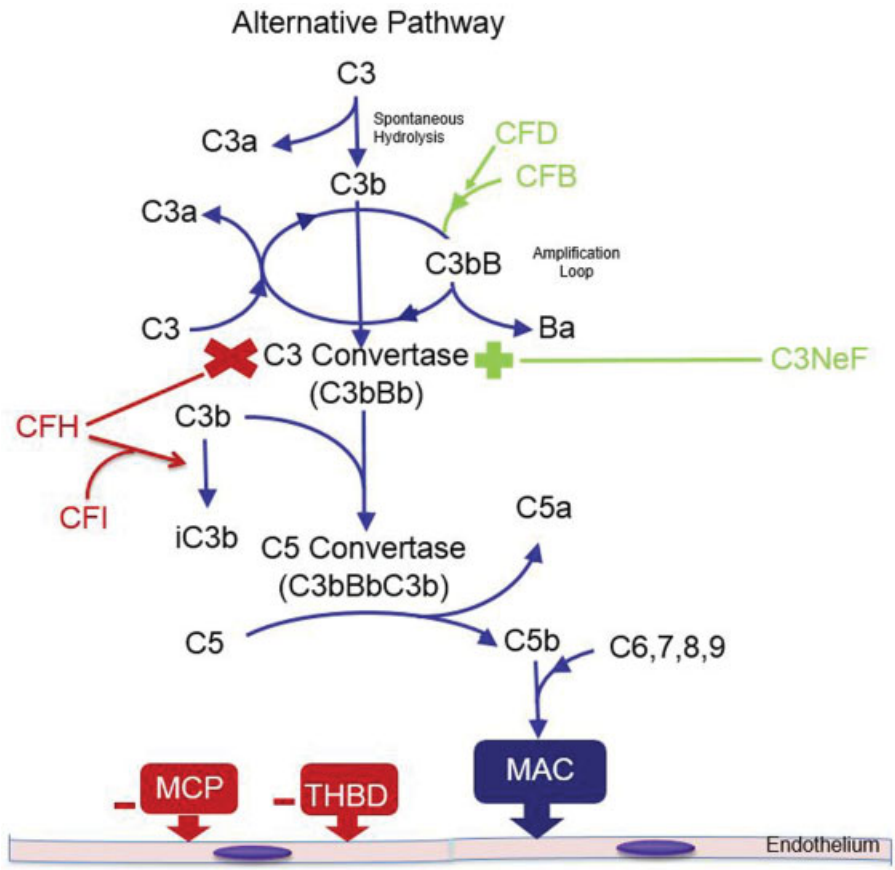

Fig. 1 The alternate complement pathway. The alternative complement cascade is constitutively active. C3 is spontaneously cleaved to C3b which then can enter into the C3 amplification loop in which C3 convertase (C3bBb) is generated and subsequently cleaves additional C3 into C3a and C3b leading to rapid amplification of C3b. C3b binds to C3 convertase to form C5 convertase (C3bBbC3b) which then enters the terminal complement cascade in which C5 forms C5a, an anaphylotoxin, and C5b which goes on to form the membrane attack complex. Regulation of the alternative complement cascade is controlled with CFH down regulation of the C3 amplification loop and through FI mediated inactivation of C3 to iC3b. Additionally MCP and THBD act to negatively regulate the alternate pathway at the level of the endothelium. These proteins which serve to inhibit the alternative pathway are labeled in red. CFB, which is cleaved by CFD, serve to generate C3 convertase in the C3 amplification loop. C3NeFs are autoantibodies which stabilize the amplification loop and result in persistent activation of the alternative pathway. The proteins involved in activation of the alternative pathway are labeled in green. C3, complement C3; C3NeF, C3 nephritic factor; CFB, complement factor B; CFD, complement factor D; CFH, complement factor H; CFI, complement factor I; MCP, membrane cofactor protein; THBD, thrombomodulin.

microorganism, disrupting the integrity of its cell wall, leading to cell lysis and death. Self-cells are normally protected from MAC by complement control proteins. When AP control is lost, MAC induced damage to self may occur. The role of the anaphylotoxins and their receptors in further potentiating disease is an area of continued research.

DNA variants that disrupt the normal control of this sequence of events, or that lead to a loss of self-protection from complement activation precipitate the complement-mediated renal diseases. Both complement protein deficiency, and normal quantity, abnormal function, protein states have been identified and play a role in aHUS and C3G.

Atypical Hemolytic Uremic Syndrome

aHUS is the prototypical ultra-rare complement-mediated renal disease. Of the diseases in which complement plays a role, this disease is the one with the greatest likelihood to be driven by a genetic mutation. While the incidence is unknown, it is likely to be on the order of 2 to 5 per million population.[5] Before the current decade, our limited understanding of the underlying pathology of aHUS meant that it was often a rapidly progressive condition that lead to renal failure and even death—with only marginal response to available therapies. Genetic advances have not only identified causative proteins, but have also laid the groundwork for a targeted, effective treatment strategy.

Genetic mutations are reported to be causal in up to 60% of aHUS patients.[1–3] The vast majority of the mutations associated with aHUS occur in heterozygosity, in genes encoding AP regulatory proteins. Complement factor H gene mutations (*CFH)* are the most abundant.[6–25] FH plays a significant role in protecting host cells from MAC.[26–28] Found both as a circulating protein and on the host cell surfaces, FH has three major host-cell protective functions. It serves to suppress complement activity on human surfaces by competing with complement FB for binding to C3b (►**Fig. 1**) and preventing the formation of the C3 convertase and therefore AP amplification. Once the C3 convertase is formed, FH serves to accelerate its decay. Finally, FH functions as a cofactor for complement

factor I (FI), facilitating cleavage of C3b into its inactive form, iC3b. Disruption of one or more of these roles as a result of mutation may lead to complement-mediated renal disease.

The *CFH* aHUS mutation database (available at: www.FH-HUS.org) indicates that to date 315 *CFH* mutations have been identified in aHUS patients. FH is composed of 20 protein subunits or short consensus repeat domains (SCRs) that are encoded by chromosome 1q32 in the regulators of complement gene cluster. While mutations have been identified in several *CFH* SCRs, the fact that the majority are in the C-terminal end of the protein in aHUS provides an interesting phenotype–genotype correlation. The C-terminus contains the cell-surface binding domain. Binding of FH to cell-surface glycosaminoglycans via a C-terminus SCR facilitates surface protection from complement activation. A DNA variant that interferes with the cell-surface binding of FH, may directly affect FH ability to protect host cells from complement activity.

The regulators of complement gene region also contain a series of genes known as the complement factor H-related genes (*CFHR1–5*). While complement regulatory functions have been attributed to the protein products,[29–41] more study is required to fully understand the role of each gene. One of the clearest roles for pathology in this setting is related to the similarity of these genes to *CFH*. Both *CFH* and the *CFHR* genes are made of repeating, homologous elements. The homology makes this region prone to rearrangements from nonhomologous recombination. The impact of recombination depends on the location of the recombination event and the function of the genes involved. The *CFHR* have far fewer SCR than *CFH*. During recombination regulatory domains do not match up perfectly or they are completely absent in the *CFHR*. ►**Fig. 2** portrays the normal regulators of complement region (►**Fig. 2A**) and the identified recombination events that have led to fusion proteins (►**Fig. 2B–E**). The new SCR configuration (fusion gene) leads to a product with altered protein function. If a fusion protein results in an altered FH function—protection from AP activity may be lost and risk for disease results.

A new role in complement dysregulation has recently been described for the *CFHR*. It has been demonstrated that the homology of SCRs 1 and 2 of the *CFHR1*, *CFHR2*, and *CFHR5* genes facilitates the formation of both homodimers and heterodimers.[42] The heterodimers that have been identified include FHR1–FHR2 and FHR1–FHR5.[32,43] It has been hypothesized that these dimers bind C3b more effectively the FH yet do not have the same regulatory properties of FH. The functional result of competing with FH binding is an AP that is not regulated normally.

The homozygous deletion of the *CFHR3* and *CFHR1* genes is not considered a mutation, but is instead a common polymorphism (present in 2–9% of Europeans, 16% of Africans, and ~2% of Chinese[44]). However, for unclear reasons, there is a strong association of this genetic change with the production of autoantibodies to FH.[2,45–54] Around 90 to 95% of the patients with anti-FH antibodies have a complete deficiency

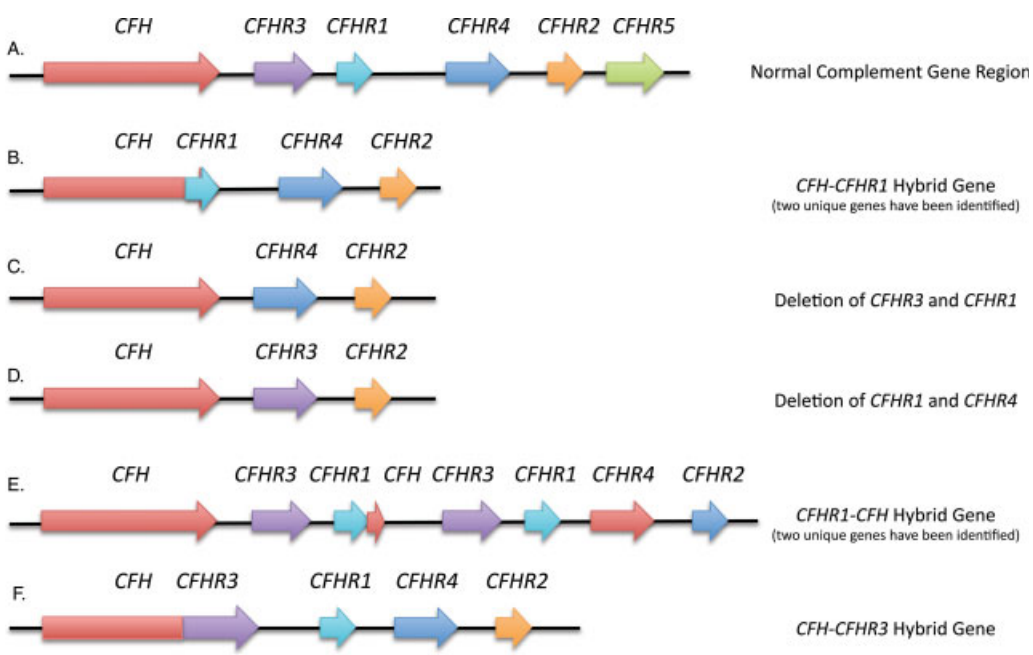

Fig. 2 Abnormal gene arrangements in the *CFH-CFHR* Region. The five *CFHR* genes are found in a tandem arrangement on the long arm of chromosome 1. Genomic duplication has led to a high sequence similarity between *CFH* and the *CFHR* genes. Sequence homology in turn results in nonallelic homologous recombination events, frequently leading to genomic changes, including deletions, duplications, and rearrangements. The most frequent change is the deletion of *CFHR3/CFHR1*. Abnormal fusion genes (triggering abnormal protein products) may also result. Nonhomologous recombination events can lead to gene deletions (B, C, D, and F), duplications (E), and hybrid genes (B, E, and F). The functional consequences at the protein level can vary and includes protein deficiency and variable function hybrid proteins. Normal gene sequence (A). *CFH*, complement factor H; *CFHR*, complement factor H related.

of FH-related proteins 3 (FHR3) and 1 (FHR1). FH autoantibodies interfere with normal FH function and account for up to 8% of aHUS cases.

In addition to *CFH* gene mutations are mutations in the complement genes *CFI*, *CFB*, *MCP*, *THBD*, and *C3*. FI plays a role in inactivating C3b and therefore limiting C3 convertase activity. Mutations in *CFI* have been estimated to occur in approximately 8% of aHUS patients.[1–3,53] FB is an integral protein of the C3 convertase. Mutations in *CFB* are classically gain-of-function mutations (facilitating an overactive C3 convertase) and account for about 1 to 4% of aHUS.[1–3,55–58] Mutations in membrane cofactor protein (MCP), the gene product of which is a cell-surface complement control protein similar to FH occurs in 5 to 9%.[1–3,59,60] Gene mutations in the thrombomodulin gene, the protein product of which is responsible for inactivating the AP anaphylotoxins C3a and C5a have been found in up to 5% of the aHUS population.[1–3] C3, a central AP complement protein may also be abnormal in aHUS. Mutations in *C3*, like those in *CFB* are often gain-of-function mutations and occur in 2 to 8% of the aHUS population.[1–3,53]

Altogether, these genetic defects result in excessive or amplified activity of the AP, ultimately resulting in the cleavage of C5. The cleavage of C5, as described previously, leads to the liberation both of C5a and of MAC at the endothelial cell surface. As endothelial injury ensues, a complement-mediated thrombotic microangiopathy (TMA) develops, precipitating the risk for the multiorgan dysfunction that is characteristic of severe aHUS.

Defining aHUS as a disease of AP dysregulation has led to the discovery of the first effective pharmaceutical for the treatment of aHUS. Eculizumab, an anti-C5 monoclonal protein that inhibits the cleavage of C5 can limit the production of C5b and the subsequent downstream production of MAC. aHUS provides one of the best examples of how genetic studies have not only provided a clearer understanding of underlying pathology but have also led to a precise treatment strategy. Importantly, inhibition of the cleavage of C5 has become the most effective treatment for aHUS to date.

The genetic investigation of aHUS patients has also included noncomplement genes. Bu et al have identified several coagulation pathway gene variants in aHUS patients.[61] They identified abnormalities in the plasminogen gene (the gene that encodes plasminogen, the precursor of plasmin—involved in thrombin lysis) and the *ADAMTS13* gene (the gene for the a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 protein)[62]. The discovery of *ADAMTS-13* variants in aHUS is interesting as abnormalities in this gene are classically associated with thrombotic thrombocytopenic purpura (TTP). The authors reported that 83% of the aHUS cohort carried at least one variation of *ADAMTS13* and 38% had multiple ADAMTS-13 variations. Consistent with a possible functional effect of these DNA variations is the fact that aHUS patients have been shown to have reduced levels of ADAMTS-13 during acute disease. The precise role of ADAMTS-13 and plasminogen in aHUS remains to be defined.

The newest gene to be reported in association with aHUS is the gene encoding diacylglycerol kinase-epsilon (DGKE), a protein of the lipid kinase family.[63,64] This protein is expressed in the endothelium, on platelets and on podocytes. The aHUS clinical picture may be triggered by the activation of protein kinase C secondary to the loss of DGKE function, leading to an upregulation of prothrombotic factors and platelet activation. New evidence suggests that gene abnormalities may facilitate endothelial injury and thus set off a cascade leading to the characteristic TMA of aHUS.[65]

Secondary Thrombotic Microangiopathies

TMAs other than aHUS are major confounders for the diagnosis of aHUS. Because of the clinical similarity of these diseases with aHUS, it has been hypothesized that a genetic risk also exists for these diseases.

The term TMA is used to refer to any disorder characterized by endothelial cell injury, leading to an arteriolar and capillary thrombosis. The clinical criteria for a TMA include the clinical triad of hemolytic anemia, thrombocytopenia, and organ dysfunction; mainly renal injury or failure. Secondary TMAs are due to several underlying causes, including infection with enterohemorrhagic *Escherichia coli,* pregnancy, organ transplantation, hematopoietic stem-cell transplant (HSCT), and drugs including calcineurin inhibitors and chemotherapeutics. It remains unclear to what degree genetic abnormalities (particularly in complement genes) play a role in these diseases. Recent studies suggest, for instance, that complement protein abnormalities may indeed be found in the above diseases, however, when genetic investigations have been completed, causal genetic abnormalities have not been found, with very few exceptions (►**Table 1**). While it has been hypothesized that there is a genetic predisposition to the other TMAs, this hypothesis requires further study. Below, we discuss briefly what is known about these other rare genetic associations.

TTP is a TMA involving either a deficiency of ADAMTS-13 (a von Willebrand factor cleaving protease) or an inhibitor of ADAMTS-13.[66] TTP is often easily confused with aHUS or other forms of TMA given the clinical picture of thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. While TTP is most likely to be a disease that results from autoantibody production to ADAMTS-13, in Upshaw–Schulman, a congenital form of TTP with the same clinical picture, more than 76 mutations have been reported.[67] Of note, along with the primary pathology involving ADAMTS-13, complement activation represented by increased levels of C3a and sMAC have been observed during the acute phase of TTP, however, it has not been proven that this is related to a genetic abnormality.[68]

Infectious TMA associated with clear renal failure (referred to as HUS) most commonly includes HUS due to infection with Shiga toxin producing *E. coli* (ST-HUS) but can also result from infections such as *Streptococcus pneumoniae*, *Shigella*, and *Campylobacter* or viruses including cytomegalovirus, Epstein-Barr virus, and the influenza viruses. While uncommon, complement mutations have been described in ST-HUS patients.[69] Similarly, three of five patients with pneumococcal

Table 1 Representative complement gene abnormalities associated with renal disease

Gene mutated	DDD	C3GN	aHUS	TTP	Infectious HUS	Solid organ transplant	HSCT	Drug induced TMA	Protein function
CFH	X[4,84,85]	X[4]	X[6–25,59]		X[69–73]	X[74]		X[79]	Regulatory protein in the alternative complement pathway
CFI		X[4]	X[1,2,53]		X[69,70]	X[74]			Regulatory protein in the alternative complement pathway responsible for inactivating C3b
CFB			X[1–3,55–58]						Protein within the alternative complement pathway which is involved in the formation of C3 convertase
C3	X[84,87]		X[1–3,53]						Central complement component of the alternate complement pathway
MCP or CD46	X[4,83]		X[1–3,59,60]					X[80]	Inhibitory complement receptor at the level of the endothelium
THBD			X[1–3]						Membrane-bound glycoprotein on the surface of endothelium. Serves as a cofactor for thrombin and modulates complement activation at the cell surface
CFHR proteins	X[43,84,88,89]	X[43,90–94]	X[48,50,54]		X[69–73]	X[74]	X[75]		Proteins of the alternative complement pathway encoded in the same region as CFH
DGKE			X[63–65]						Intracellular lipid kinase that phosphorylates diacylglycerol to phosphatidic acid localized in endothelium, platelets and podocytes
Plasminogen			X[61,62]						Precursor to plasmin in fibrinolysis
ADAMTS-13				X[61,62]				X[79]	Protease which cleaves von Willebrand factor
Autoantibodies									
CFH			X[2,45–54]				X[75]		Autoantibodies associated with CFHR3-CFHR1 deletion inhibits complement factor H
CFI			X[98]						
CFB	X[99]		X[99]						
C3NeF	X[4,84]	X[4]							Autoantibodies which bind to the C3 convertase and prevent degradation
ADAMTS-13				X[66,67]					Autoantibodies which result in decreased ADAMTS-13 function.

Abbreviations: ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic uremic syndrome; C3, complement C3; C3GN, C3 glomerulonephritis; C3NeF, C3 nephritic factor; CFB, complement factor B; CFH, complement factor H; CFHR, complement factor H related; CFI, complement factor I; DDD, dense deposit disease; DGKE, diacyl glycerol kinase epsilon; HSCT, hematopoietic stem cell transplant; MCP, membrane cofactor protein; THBD, thrombomodulin; TMA, thrombotic microangiopathies; TTP, thrombotic thrombocytopenic purpura.

HUS in one cohort carried mutations in the common AP genes *CFH*, *CFI*, and in *THBD*.[70] Complement mutations in other forms of infectious TMA have also been described, including *MCP* mutations in influenza A, *Bordetella pertussis*, and varicella zoster TMA, a *CFH* mutation in Bordetella TMA and CFH autoantibodies in varicella zoster TMA.[71–73] The relationship of these gene mutations with causality is unknown.

Complement dysregulation and known mutations in the AP have also been described in solid organ transplant-related TMA. *CFH* and *CFI* mutations were identified in 29% of patients in a cohort of 24 kidney transplant recipients who developed de novo TMA following transplant.[74] The caveat to interpreting this data are that it remains unclear whether these were previously unidentified aHUS patients and exactly what role the transplant played.

The evidence is less convincing in HSCT-associated TMA. Jodele et al reported that five of six HSCT recipients had a *CFHR3–CFHR1* heterozygous gene deletion. While this statistic is interesting, we must keep in mind that the 3/1 deletion is a polymorphism and not a causal DNA change. During the time of their TMA, three patients in their cohort were also found to have FH autoantibodies—suggesting that their disease was triggered by autoimmune-related complement dysregulation. No patients in the cohort had identifiable mutations in *CFI*, *CFH*, *MCP*, *CFB*, or *CFHR5* genes.[75]

The role of complement in pregnancy-related TMA remains an area of interest. Pregnancy-related TTP cases tend to occur in the second and third trimesters of pregnancy due to a decrease in ADAMTS-13 activity presumably as a result of increased release of VWF toward the end of pregnancy.[76] Alternatively, 21% of adult female aHUS patients present during pregnancy with approximately 80% presenting during the postpartum period. A total of 86% of these women had identified complement abnormalities. Considering pregnancy and aHUS further, Fakhouri et al reported in their cohort, aHUS was triggered by pregnancy in 20% of patients with *CFH* mutations, 28% with *C3*, 11% with *CFI*, and 17% with *MCP* mutations.[77] More than one mutation was seen in four aHUS patients presenting during pregnancy. TMA during pregnancy has also been linked to verotoxin exposure and vascular endothelial growth factor (VEGF) deficiency.[76]

Many drugs have been reported to cause drug-induced TMA including calcineurin inhibitors, mTOR inhibitors, quinine, chemotherapy agents, VEGF inhibitors, antiplatelet medications, and cocaine.[78] It has been proposed that drug-induced TMA results from an environmental trigger that dysregulates complement in a genetically susceptible host. There have only been a few studies to support this theory. One was a report of four patients with ticlopidine-induced TMA. All four patients were found to be deficient in ADAMTS-13 activity with ADAMTS-13 inhibitors and all four were found to be homozygous or heterozygous for three different *CFH* polymorphisms, two with known functional significance.[79] Another report describes a 2-year-old male patient with likely cisplatin-induced TMA who was found to have a heterozygous *MCP* splice mutation. This patient exhibited clinical improvement with eculizumab therapy.[80]

In the absence of confirmed genetic mutations in the majority of the diseases that make up the secondary TMAs (with the possible exception of pregnancy-associated TMA), it remains impossible to label the majority of TMAs in these settings as genetic-related rare disease.

C3 Glomerulopathy

C3G is another rare renal disease that involves the abnormal regulation of the AP. In this setting, disease is not manifest by a TMA, but rather the deposition of C3 breakdown products within the glomeruli of the kidney. The pathological term used to describe this entity is C3-dominant glomerulonephritis[81] with the disease syndrome being called C3G. C3G includes dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). DDD is diagnosed when linear electron-dense deposits are found within the lamina densa (middle layer) of the glomerular basement membrane on electron microscopy in the setting of a C3-dominant glomerulonephritis. C3GN is used to designate the remainder of cases of C3G and in general represents those with less dense deposits by electron microscopy. C3GN deposits may involve any combination of mesangial, subepithelial, subendothelial, and less discrete, discontinuous intramembranous deposits.[81]

As with aHUS, C3G is an ultra-rare disease. The incidence of biopsy-proven C3G is estimated to be 1 to 2 per million with equal incidence in both the sexes.[82] Those affected tend to be children and young adults.[82] The disease presentation encompasses a spectrum from a relatively mild glomerulonephritis to a severe, rapidly progressive disease that may lead quickly to end-stage kidney disease. There are currently no reliable treatment options for C3G, making this an area ripe for continued genetic and translational research.

While autoimmunity to the C3 convertase (the so called "C3 nephritic factor"—present in up to 85% of the patients) is believed to be central to disease for the majority of C3G patients, complement gene abnormalities play a pathological role in C3G also. Servais et al studied a series of 134 patients with idiopathic membranoproliferative glomerulonephritis type I (another form of primary glomerulonephritis, $n = 48$), DDD ($n = 29$), and C3GN ($n = 56$). Mutation screening of the complement genes revealed mutations in *CFH* in 17 (12.7%), *CFI* in 6 (4.5%), and *MCP* in 1 (0.7%).[4,83]

DDD more specifically has been shown to be associated with mutations in *C3*, *CFH*, and the *CFHR* genes.[84] Five of 29 DDD patients were reported to have mutations within the *CFH* gene in the 2012 Servais et al study.[4] One of which had been described previously in aHUS.[85] Martinez-Barricarte et al identified a gain-of-function *C3* mutation in a familial case of C3G.[86] The authors demonstrated that the *C3* mutation conferred resistance to AP regulation. Abrera-Abeleda et al have identified complement gene mutations in 66 patients with biopsy-proven DDD.[87] In addition, in this cohort, the authors identified four novel sequence variants in *ADAMTS-19* (another member of the disintegrin and metalloprotease family), *C3aR1* (complement component 3a receptor), *CR1* (complement receptor type 1), and *C3*. The functional significance of the latter gene findings is unknown.

As in aHUS, the FHR proteins play a role in the pathogenesis of DDD.[43] A familial mutation in *CFHR1* was found to result in the duplication of the N-terminus SCR domains. The result was a mutant FHR1 protein, capable of forming unusually large multimeric complexes. These complexes exhibited competition with FH and led to dysregulation of the AP.[43] Similarly, Chen et al described a chromosomal deletion in the *CFHR* gene cluster in familial DDD which resulted in a FHR2–FHR5 hybrid protein capable of stabilizing the C3 convertase, and reducing FH-mediated decay.[88] *CFHR5* polymorphisms have been described in DDD, however, the functional significance of these polymorphisms remains unclear.[89]

Similar gene abnormalities are also present in the C3GN form of C3G. In the Servais et al study, 7 of 56 patients with C3GN diagnosed by biopsy were identified to have *CFH* mutations.[4] Additionally, three of the C3GN patients were found to have mutations in *CFI*, all of which had been previously described in aHUS and one patient with a mutation in *MCP*.[4]

The *CFHR* genes also play a role in C3GN. Gale et al were the first to report on CFHR5 nephropathy, an autosomal dominant familial C3G in patients of Cypriot descent. The authors identified an internal duplication of exons 2 and 3 of *CFHR5* which segregated with a C3-dominant glomerulonephritis on biopsy.[90,91] A familial C3GN involving CFHR5 in families of non-Cypriot descent has also been identified.[92]

The homology in the *CFHR* region plays a role in the C3GN setting.[93] A familial case of C3G highlighted a rearrangement within the *CFHR* locus resulting in a hybrid *CFHR3–CFHR1* gene whose product appeared to have a competitive function with FH.[94] Another case study identified a CFHR1 duplication, capable of forming multimers with enhanced binding of CFHR1 to C3b, iC3b and C3 dg, thus altering normal AP activity.[43]

In the absence of overt genetic mutation in some (particularly DDD patients), the data support the presence of a "complotype."[87,95–97] The complotype is an inherited set of common polymorphisms in complement proteins that predict susceptibility to inflammatory or infectious diseases. These are not mutations but are rather risk factors for the development of the disease. There is evidence that they have an impact on susceptibility to inflammatory and infectious disease.

Conclusion

Here, we provide a comprehensive review of the contribution of genetics to our understanding of complement-mediated renal disease. Additional genetic discoveries are sure to follow, however, it is clear that the genetics of complement are becoming the key to both accurate diagnosis and targeted therapy for these rare, previously untreatable diseases. This set of diseases provides a clear example of the power of genetics in improving the outcome of patients with rare disease.

Note

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Conflict of Interest

None.

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