Review Article

Familial Atypical Hemolytic Uremic Syndrome: A Review of Its Genetic and Clinical Aspects

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Atypical hemolytic uremic syndrome (aHUS) is a rare renal disease (two per one million in the USA) characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Both sporadic (80% of cases) and familial (20% of cases) forms are recognized. The study of familial aHUS has implicated genetic variation in multiple genes in the complement system in disease pathogenesis, helping to define the mechanism whereby complement dysregulation at the cell surface level leads to both sporadic and familial disease. This understanding has culminated in the use of Eculizumab as first-line therapy in disease treatment, significantly changing the care and prognosis of affected patients. However, even with this bright outlook, major challenges remain to understand the complexity of aHUS at the genetic level. It is possible that a more detailed picture of aHUS can be translated to an improved understanding of disease penetrance, which is highly variable, and response to therapy, both in the short and long terms.

1. Introduction

Hemolytic uremic syndrome (HUS) is a rare disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. It is most frequently caused by infections of Shiga-like toxin producing bacteria, such as Escherichia coli strain O157:H7, O111:H8, O103:H2, O123, and O26 [1]. In approximately 10% of HUS cases, there is no association with Shiga-like toxin. These cases are classified as atypical HUS (aHUS) and occur with an incidence of about 2 per million in the USA [1, 2]. aHUS patients have a poorer prognosis than those with typical HUS, with acute phase aHUS mortality of about 8% [3, 4], and with 50%–80% of aHUS patients progressing to end-stage renal failure [1]. However, it is important to note that epidemiological outcomes data are relatively out of date because of the development of better diagnostic, treatment, and management strategies.

Atypical HUS can be classified as sporadic or familial. Familial aHUS is defined as the presence of aHUS in at least two members of the same family with diagnoses at least 6 months apart [1, 3, 5]. It accounts for less than 20% of aHUS cases [3]. In familial aHUS (and also sporadic aHUS), genetic (e.g., gene mutations, rare variants, and risk haplotypes) and acquired abnormalities (e.g., autoantibodies against factor H) are found in ~70% of patients [6]. Gene mutations are usually found in complement genes, such as factor H (CFH), factor I (CFI), factor B (CFB), complement component 3 (C3), and membrane cofactor protein (MCP or CD46). Evidence from familial studies indicates a high rate of incomplete penetrance, with about 50% of carriers of CFH or MCP aHUS-associated variants not developing disease [7]. The reasons underlying incomplete penetrance are unclear, although it is recognized that multiple predisposing genetic variants and risk haplotypes exist which may be relevant to disease onset in the face of environmental triggers such as pregnancy, viral infection, cancer, organ transplantation, and the use of certain drugs [8, 9].

In this paper, we focus on familial aHUS. Over the past 20 years, dozens of aHUS pedigrees have been reported, clarifying the underlying mechanisms of both familial and sporadic aHUS. In followed sections, we will discuss
the complement system and aHUS, genetic abnormalities identified in familial studies, factors associated with incomplete penetrance, and current methods of diagnosis and treatment.

2. The Complement System

The complement system is an essential component of the innate immunity (Figure 1). Its four major steps are: (1) the initiation of the complement cascade; (2) C3 convertase activation and amplification; (3) C5 convertase activation; (4) terminal pathway activation [10]. Initiation of the complement cascade occurs through three pathways: the classical pathway [11, 12], the lectin pathway [13, 14], and the alternative pathway [15, 16]. Once activated, C3 convertases are formed (the alternative pathway forms C3bBb, and the classical pathway or the lectin pathway forms C4bC2a), which cleave C3 to C3a and C3b. C3b can indiscriminately bind to surfaces of microbes and host cells [17, 18]. On the surface of microbes or modified host cells, C3b and factor B form more C3 convertases, which produce more C3b. This amplification process exponentially increases the amount of C3b and C3 convertases.

On the surface of intact host cells, in contrast, C3b deposition and C3 convertase amplification are prevented by complement regulators. Regulators distribute in the fluid phase (CFH, CFHR1, CFP, etc.) and on cell surfaces (CR1, MCP, DAF, etc.) to control complement activity through two major mechanisms: decay acceleration activity and cofactor activity [10]. CFH, for example, acts as a cofactor with CFI to cleave C3b to an inactive form, iC3b; has the decay acceleration activity, which promotes the decay of the C3 convertase [19, 20] and competes with CFB for binding to C3b. If C3 convertase amplification is allowed to proceed unchecked, additional C3b binds to C3 convertases to generate C5 convertases (C3bBbC3b or C4bC2aC3b) [21]. C5 convertases cleave C5 to C5a and C5b to initiate the terminal pathway and form terminal complement complexes with C6, C7, C8, and C9 to lyse target cells [22, 23].

Mutations of complement genes can either change expression level or disrupt protein function. Figure 2 shows a model of dysregulation of complement regulators inducing aHUS. Mutations in complement genes impair the regulation of C3b on host cells, leading to formation of membrane attack complex and host cell damage. Most genetic abnormalities in aHUS patients are found in complement membrane regulators and C3 convertases. Multiple genetic and environmental risk factors are believed necessary to develop disease; however, relatively little is known about how environmental triggers affect homeostasis of complement system in the face of predisposing genetic variants in complement genes [8]. It is also unclear whether genetic variants in complement gene increase susceptibility to typical HUS [24, 25].

3. Genetic Abnormality in Family Cases

The term “familial aHUS” is used to describe families in which two or more persons develop aHUS at different times without exposure to common triggering infectious agents, or when disease-causing mutations are identified in one of
Figure 2: Regulation and dysregulation of complement activity on host cells. C3b is generated by the classical, lectin, or alternative pathways. (a) To protect normal host cells, C3b is inactivated by membrane regulators, such as factor H (CFH) and membrane cofactor protein (MCP). Factor I (CFI) cleaves C3b into iC3b and other C3 degradation products with the activity of cofactor regulators. (b) If genetic and/or environmental risk factors reduce the efficiency of membrane complement regulators, C3 convertase (C3bBb) can accumulate on cell surfaces, creating a C3b amplification loop. Formation of C5 convertase (C3bBbC3b) triggers C5 cleavage into C5b, which interacts with C6, C7, C8, and C9 to generate membrane attack complex (MAC) leading to cell damage.

3.1. CFH and CFHR Mutations. Complement factor H, encoded by CFH gene, is an essential inhibitor of C3 convertase and a central regulator of the complement alternative pathway. It is produced by liver as a soluble protein but can attach to and act on cell surfaces. CFH protein contains 20 repetitive units of about 60 amino acids named short consensus repeats (SCRs; also known as complement control protein (CCP) repeats or Sushi domains) [27]. N-terminal SCRs regulate binding to C3b, while C-terminal SCRs facilitate cell-surface binding and regulation. CFH regulates the complement system through three mechanisms: (1) inhibiting the assembly of C3 convertase by competitive binding to C3b, (2) accelerating the decay of C3 convertase, and (3) acting as a cofactor in the cleavage and degradation of C3b by CFI [27].

CFH is the most thoroughly studied gene in aHUS. Mutations associated with aHUS were first identified in CFH by a familial genetic study in 1998 when Warwicker and colleagues conducted linkage analysis in three aHUS families and mapped the aHUS risk region to a 26-cM interval on chr 1q32 with a lod score of 3.94. The linked region includes the CFH and CFHR genes, and in sequencing CFH, a heterozygous c.3716C>G variant changing an arginine to glycine was found to cosegregate with disease in family 2. In family 3, a CFH deletion, c.145_148delAGAA, was found [28].

Numerous missense transversion and transition variants in CFH have now been associated with aHUS through familial studies [29–34]. Typically, affected patients are heterozygous for these changes, which predominantly occur in the C-terminal SCRs 19 and 20. Since these SCRs are essential for
| Author                | Year | Population       | Size/carrier/affected | Gene: variant or haplotype | Risk genotype | Penetrance rate | SNP rs ID       | MAF        |
|-----------------------|------|------------------|-----------------------|----------------------------|---------------|-----------------|----------------|------------|
| Warwicker et al. [28] | 1998 | 51/3/11          |                       | CFH: c.3716C>G (p.R1197G) | C/G           |                 | rs121913051    |            |
|                       |      |                  |                       | CFH: c.143_148delAGAA    | het           |                 |                |            |
| Ying et al. [31]      | 1999 | Bedouin-Arab     | 55/11                 | CFH: c.3645C>T (p.S1191L) | T/T           |                 | rs460897       | 29.35%     |
| Richards et al. [40]  | 2003 | Belgian          | 8/0/3                 | MCP: p.237_288delDS      | het           | 100.0%          | rs121909589    |            |
|                        |      | German           | 4/1/2                 | MCP: c.822T>C (p.S206P)  | T/C           | 66.7%           |                |            |
|                        |      | Turkish          | 4/2/2                 | MCP: c.822T>C (p.S206P)  | C/C           | 50.0%           |                |            |
| Caprioli et al. [30]  | 2003 | 13/1/2           |                       | CFH: c.1494_1496delAAA   | het           | 66.7%           |                |            |
|                        |      |                  |                       | CFH: c.3620T>A (p.Y1183R)| T/A           | 66.7%           |                |            |
|                        |      |                  |                       | CFH: c.3701C>T (p.R1210C)| C/T           | 75.0%           | rs121913059    | 0.02%      |
|                        |      |                  |                       | CFH: c.3579A>T           | A/T           |                 |                |            |
| Noris et al. [41]     | 2003 | White            | 4/1/2                 | MCP: c.843_844delAC      | het           | 66.7%           |                |            |
|                        |      |                  |                       | CFH: c.3717G>A (p.R1215Q)| G/A           | 60.0%           |                |            |
| Frémeaux-Bacchi et al. [42] | 2006 | White            | 5/0/3                 | MCP: p.G162R             | het           | 100.0%          |                |            |
|                        |      |                  |                       | MCP: p.Y155D             | het           | 100.0%          |                |            |
|                        |      |                  |                       | MCP: c.IVS7-7A>G         | het           | 100.0%          |                |            |
| Esparza-Gordillo et al. [43] | 2006 | Spanish          | 24/11/2              | MCP: c.598C>T (p.P1655)  | C/T           | 28.6%           |                |            |
|                        |      |                  |                       | MCP: c.218C>T            | C/T           | 85.7%           |                |            |
|                        |      |                  |                       | MCP: c.147G>A            | G/A           | 85.7%           |                |            |
| Caprioli et al. [7]   | 2006 | Sardinian        | 8/4/3*                | MCP: D1S2735, D1S2796,   | 2.1,+A,T8     | 42.9%           |                |            |
|                        |      |                  |                       | IVS1-1G>C, ExVSCR3, ExXII, D1S2692 |            |                |                |            |
|                      |      |                  |                       | MCP: c.IVS1-1G>C         | G/C           | 42.9%           |                |            |
| Goicoechea de Jorge et al. [53] | 2007 | Spanish          | 32/4/7*               | CFB: c.858C>G (p.F286L)  | C/G           | 64.0%           |                |            |
|                        |      |                  |                       | MCP: c.768T>G            | T/G           | 28.6%           |                |            |
|                        |      |                  |                       | MCP: c.843_844delAC      | het           | 50.0%           |                |            |
|                        |      |                  |                       | MCP: c.1775G>A           | G/A           | 10.0%           | rs121909583    |            |
|                        |      |                  |                       | MCP: c.1775G>A           | G/A           | 10.0%           | rs121909583    |            |
|                        |      |                  |                       | MCP: c.3767_3771delTATA | hom          | 37.5%           |                |            |
|                        |      |                  |                       | MCP: c.3007G>T (p.W978C) | G/T           | 40.0%           |                |            |
|                        |      |                  |                       | MCP: c.218C>T            | C/T           | 85.7%           |                |            |
|                        |      |                  |                       | MCP: c.147G>A            | G/A           | 85.7%           |                |            |
| Author                  | Year | Population | Size/carrier/affected | Gene: variant or haplotype | Risk genotype | Penetrance rate | SNP rs ID | MAF     |
|-------------------------|------|------------|-----------------------|----------------------------|---------------|----------------|-----------|---------|
| Hakobyan et al. [32]    | 2010 | 15/3/4     | CFH: p.C853R, H402    | het+H                      | 33.3%         |                |           |         |
| Provaznikova et al. [44]| 2012 | 3/0/2      | MCP: c.1148C>T        | C/T                        |               |                |           |         |
|                         |      | 2/0/2      | MCP: c.404G>A         | G/A                        |               |                |           |         |
|                         |      | 2/0/2      | MCP: c.350insA        | het                        |               |                |           |         |
|                         |      | 1/7/2      | MCP: c.2T>A           | T/A                        | 50.0%         |                |           |         |
| Sartz et al. [52]       | 2012 | 20/2/4     | C3: c.4973T>C (p.V1636A) | T/C                        | 100.0%        |                |           |         |
|                         |      |            | CFH: c.IVS12+5G>T     | G/T                        | 100.0%        |                |           |         |
|                         |      |            | MCP: c.1058C>T (p.A304V) | C/T                        | 50.0%         |                |           |         |
|                         |      |            | CFH: c.2850G>T (p.Q950H) | G/T                        | 50.0%         |                |           |         |
| Francis et al. [38]     | 2012 | 35/4/3     | CFH/CFHR3 hybrid      | het                        | 42.9%         |                |           |         |

* Pedigrees are included if at least two family members were diagnosed with aHUS at least 6 months apart.
* More than one mutation identified within the family.
* * presents undetermined number.
* ***The risk haplotype MCP ggaac is formed by rs2796267, rs2796268, rs1962149, rs859705, and rs7144.
cell-surface attachment, this finding suggests that membrane
dysregulation of the complement system is critical to the
pathogenesis of aHUS.

Based on available studies, we estimate that penetrance
of CFH mutations ranges from 12.5% to 100% (Table 1).
It is remarkable that one CFH rare variant, rs121913059
(c.3701C>T or p.R1210C), has been reported in five families
from three familial studies [29, 30, 32]. This variant decreases
CFH binding to C3b, heparin, and endothelial cells, and leads
to a positive sheep erythrocyte hemolytic assay [35]. The
Y402H variant (rs1061170, c.1204T>C) of CFH, notable for
its association with age-related macular degeneration [36],
dense deposit disease, and C3 glomerulonephritis [37], has
not been associated with aHUS. However, Hakobyan et al.
have reported low expression of the CFH-H402 allele in
association with other known aHUS variants in two aHUS
families, suggesting that in some instances the CFH-H402
allele may contribute to the aHUS phenotype [32].

In addition to CFH, CFHR3 has been linked with familial
aHUS. The CFH-related genes (CFHR1, CFHR2, CFHR3,
CFHR4, and CFHR5) localize next to CFH and share many
of the functional properties of CFH. A recent study has reported
a hybrid CFH/CFHR3 gene caused by a microhomology-
mediated deletion that is associated with familial aHUS. The
transcript product of the hybrid gene contains 24 SCRs with
SCRs 1–19 deriving from CFH and SCRs 20–24 deriving
from CFHR3. The hybrid protein shows normal fluid-phase
activity but loses complement regulation on cell surfaces
[38].

3.2. MCP Mutations. MCP (CD46) encodes membrane
cofactor protein, which acts as a cofactor for CFI to regulate
complement activity by cleaving C3b and C4b deposited
on the surface of host cells. MCP is a transmembrane
protein with four N-terminal extracellular Sushi domains, a
transmembrane domain, and a C-terminal cytoplasmic tail.
Sushi domains 3 and 4 are responsible for complement regu-
lation [39].

MCP is well studied in aHUS. In 2003, Richards et al.
[40] first reported mutations of MCP in aHUS families.
Two mutations were found in three families—a 6 bp deletion
(p.237_238delDS) and c.822T>C (p.S206P, rs121909589).
The c.822T>C mutation causes an amino acid change of
serine to proline and leads to a significant reduction of
C3b binding. Soon afterwards, Noris et al. reported another
aHUS family carrying a 5 bp deletion in MCP gene, which
causes a premature stop codon in the fourth Sushi domain
[41]. Expression analysis showed around 50% reduction in
MCP as compared to healthy controls. Subsequently, several
more MCP mutations have been identified in aHUS families
[7, 33, 42–44].

Studies indicate that MCP mutations account for up to
15% of aHUS patients [7, 33, 42]. Although the majority of
MCP mutations are heterozygous (~75%), some homozy-
gous or compound heterozygous mutations in MCP have
been reported [45]. MCP mutations are defined as (a) type
I (~75%) if they reduce expression on cell surface and (b)
type II (~25%) if expression is normal but complement
regulatory activity is impaired [46, 47].

The MCP ggaac haplotype formed by c.−652A>G
(rs2796267), c.−366A>G (rs2796268), c.IVS9−78G>A
(rs1962149), c.IVS12+638G>A (rs859705), and c.4070T>C
(rs7144), is associated with aHUS in both sporadic and fami-
iliar cases [43, 48, 49]. Further studies are needed to determine
the functional or expression differences between MCP ggaac
and normal haplotypes.

3.3. C3 Mutations. Complement component C3 is the key-
stone in the complement system. It undergoes spontaneous
hydrolysis and is also cleaved by C3 convertase to C3b and
C3a. C3b interacts with CFB to form C3bB, which is then
cleaved to C3bBb by CFD forming the C3 convertase.
Additional C3b leads to the formation of C5 convertase,
which activates the terminal pathway. C3 products are key ligands
for multiple complement regulators, including CFH and
MCP. Theoretically, mutations influencing C3 binding ability
or other functions could disrupt complement regulation and
contribute to the development of aHUS.

Reported C3 mutations are heterozygous and localized
on both the beta and alpha chains. In 2008, Frémeaux-Bacchi
et al. first reported nine mutations of C3 in 14 patients
from 11 families, including a p.R570W mutation in a very
large family. Five of the nine identified mutations (p.R570Q,
p.R570W, p.A1072V, p.D1093N, and p.Q1139K) reduce lig-
and binding to MCP, making the mutant convertase resistant
to cleavage by CFI thus impairing complement regulation of
C3 convertase amplification on cell membranes [50]. Lhotta
et al. have also reported a large Austrian family carrying the
p.R570Q C3 mutation. In their study, they showed reduced or
borderline C3 levels in mutation carriers [51]. Recently,
another familial C3 mutation, V1636A, has been identified
to cause increased affinity of CFB for C3b [52].

3.4. CFB Mutations. Complement factor B, a key component
of C3 convertase (C3bBb), contains three Sushi domains, a
WFA domain, and a peptidease S1 domain. It is cleaved by
CFD into Ba and Bb. Bb is a serine protease, which binds to
C3b to generate the C3 convertase.

In 2007, Goicoechea de Jorge et al. reported a CFB
gene mutation in an aHUS family with seven patients
[53]. Sequence analysis and functional studies indicated that
the missense mutation, c.858C>G (p.F286L), in the WFA
domain, caused more rapid formation and a higher level of
C3 convertase. Penetration was incomplete with seven of 11
mutation carriers developing aHUS. Interestingly, the MCP
ggaac risk haplotype was found only in patients and one
young carrier who is probably still at risk for disease, suggest-
ing that the effects of the CFB variant are modulated by var-
ients in other complement gene.

3.5. CFI Mutations. Complement factor I is an inhibitory
regulator of complement system. It cleaves C3b or C4b with
the presence of cofactors, such as CFH and MCP, to iC3b,
which is cleaved to smaller C3 degradation products. Defects
in CFI cause multiple complement-related diseases, includ-
ing aHUS and CFI deficiency (OMIM: 610984), a disease
characterized by recurrent infections and glomerulonephritis
in some patients [54].
Most CFI mutations have been found in sporadic aHUS cases. These mutations either interrupt cofactor activity or impact the expression level of CFI [55]. In familial aHUS studies, CFI mutations have been reported in three pedigrees (Table 1) [33, 43, 52]. In a Spanish family, a heterozygous 2 bp insertion within the coding region of CFI has been identified to cause a premature stop codon, p.T538X, which reduces plasma levels of CFI by 50%. A missense mutation in MCP (c.598C>T) and the MCP ggaac risk haplotype were also identified in this family, with all patients carrying all three genetic risk factors. Nine unaffected persons carry only one or two genetic risk factors, suggesting that it is the combination of mutations and the risk haplotype that are critical to the development of aHUS [43].

3.6. Combined Mutations and Incomplete Penetrance of Familial aHUS. Multiple familial studies have reported that it is the combination of complement gene mutations that contributes to aHUS [29, 30, 32, 42, 43, 52, 53]. For instance, in a study by Sartz et al., four mutations, one each in C3, MCP, CFI, and CFH, were found in two patients from a single family [52]. The C3 mutation, p.V1636A, increases the affinity for CFB and C3 convertase; the MCP mutation, p.A304V, increases the activation of the alternative pathway on cell surfaces; and although the functional significance of the CFI mutation (c.IVS12-5) and the CFH mutation (p.Q950H) is unknown, they have been reported in other aHUS cases [52]. The aggregate data suggest that accumulated dysregulation by combined mutations impairs the complement system and leads to disease [29, 30, 32, 42, 43, 52, 53]. It is unknown whether other complement factors, such as THBD, CR1, C5-C9, and DAF, contain risk variants that contribute to the mutation/variant load in aHUS.

Incomplete penetrance is widely observed, with the estimated penetrance of aHUS in mutation carriers being about 50–60% [7, 8]. Within families, affected persons may also show different symptoms and onset ages [56]. These findings strongly suggest that most aHUS-associated genetic variants predispose to rather than cause the disease. However, the genetic picture is incomplete as most studies have focused on only the common complement genes in a disease where rare genetic variants in other complement genes and genes in other pathways are likely to be contributory to the phenotype. Importantly, the effect of common variants is probably marginal as demonstrated by Ermini and colleagues who tested 501 SNPs in 47 complement genes in 220 aHUS patients and 549 controls and found disease associations for only CFH, MCP, and the CFHRs [49]. However, until a comprehensive rare variant screen is completed, it will remain very difficult to calculate disease risk for persons in aHUS families.

4. Diagnosis and Treatment

aHUS is clinically characterized by microangiopathic haemolytic anaemia (low hemoglobin, high lactic acid dehydrogenase, undetectable or low haptoglobin, presence of schistocytes in the peripheral blood smear, and negative Coombs test), thrombocytopenia (platelets < 150000/mm³ or a documented rapid decrease), and acute kidney injury (AKI) (hematuria, proteinuria, and/or reduced renal function). However, as a systemic disease, aHUS can affect the endothelia of any organ, and extrarenal manifestations including involvement of the central nervous system, liver, heart, pancreas, and skin, are observed in as many as 20% of patients [3, 4]. These additional sites of involvement can blur the distinction between aHUS and other primary thrombotic microangiopathies (TMAs), such as STEC-associated HUS, thrombotic thrombocytopenic purpura (TTP), HELLP syndrome (hemolytic anemia, elevated liver enzymes, and low platelets), and transcyanocobalamin deficiency, or TMAs secondary to malignant hypertension, catastrophic antiphospholipid syndrome, or disseminated intravascular coagulation.

The treatment of aHUS is based on two main strategies: supportive treatment and cause-specific treatment. The former is focused on careful fluid, electrolyte, acid-base, and nutritional management, with the use of blood transfusion, antihypertensive medications, and/or dialysis, as needed. Cause-specific treatment includes plasma therapy provided by either plasma infusion (fresh frozen plasma, 20–40 mL/kg/day if the patient is not volume overloaded) or by high volume plasma exchange with fresh frozen plasma (150% of plasma volume daily or every other day until clinical remission). A recent impressive improvement in the management of aHUS has been reported with the use of the anti-C5 monoclonal antibody, Eculizumab, which binds to C5 thereby preventing activation of the terminal complement cascade. This relatively new (since 2009) treatment is continued until stable clinical remission. Whether life-long or recurrence-specific treatment is necessary and how genetics may or may not impact care of persons on Eculizumab have not been determined.

5. Transplantation

Only recently has renal transplantation become the treatment of choice for patients in end stage renal disease on chronic dialysis for aHUS. Until the availability of Eculizumab, transplantation was associated with a 40%–80% risk for disease recurrence [3, 57–59]. The notable exception was aHUS patients with MCP mutations since MCP is expressed on the renal endothelia and not in the fluid phase. Eculizumab has become a key resource for preventing recurrence following kidney transplantation and for rescue therapy in case of disease recurrence. Combined liver-kidney transplant with preemptive and perioperative plasma therapy [60], although successfully used in the very recent past, in the Eculizumab era no longer appears to be first-line treatment. Transplantation with a living-related donor is not recommended given our current incomplete understanding of the genetics of aHUS.

6. Conclusion

Over the past two decades, studies of familial aHUS have greatly increased our understanding of this disease. The identification of genetic variants in complement genes has
defined the mechanism whereby complement dysregulation at the cell surface level leads to disease. This understanding has culminated in the use of Eculizumab as first-line therapy in disease treatment, significantly changing the care and prognosis of affected patients. However, even with this bright outlook, major challenges remain to understand the complexity of aHUS at the genetic level. It is possible that a more detailed picture of aHUS can be translated into patient-specific short- and long-term therapy with Eculizumab and/or other anticomplement drugs in the developmental pipeline.

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