



# Genetic Atypical Hemolytic-Uremic Syndrome

Synonym: Familial Atypical Hemolytic-Uremic Syndrome

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## Summary

### Clinical characteristics

Hemolytic-uremic syndrome (HUS) is characterized by hemolytic anemia, thrombocytopenia, and renal failure caused by platelet thrombi in the microcirculation of the kidney and other organs. The onset of atypical HUS (aHUS) ranges from the neonatal period to adulthood. Genetic aHUS accounts for an estimated 60% of all aHUS. Individuals with genetic aHUS frequently experience relapse even after complete recovery following the presenting episode; 60% of genetic aHUS progresses to end-stage renal disease (ESRD).

### Diagnosis/testing

The diagnosis of genetic aHUS is established in a proband with aHUS by identification of a pathogenic variant(s) in one or more of the genes known to be associated with genetic aHUS. The genes associated with genetic aHUS include *C3*, *CD46* (*MCP*), *CFB*, *CFH*, *CFHR1*, *CFHR3*, *CFHR4*, *CFHR5*, *CFI*, *DGKE*, *THBD*, and *VTN*.

### Management

*Treatment of manifestations:* Eculizumab (a human anti-C5 monoclonal antibody) to treat aHUS and to induce remission of aHUS refractory to plasma therapy; plasma manipulation (plasma infusion or exchange) to reduce mortality; however, plasma resistance or plasma dependence is possible. Eculizumab therapy may not be beneficial to those with aHUS caused by pathogenic variants in *DGKE*. Treatment with ACE inhibitors or angiotensin receptor antagonists helps to control blood pressure and reduce renal disease progression. Bilateral nephrectomy when extensive renal microvascular thrombosis, refractory hypertension, and signs of hypertensive encephalopathy are not responsive to conventional therapies, including plasma manipulation. Renal transplantation may be an option, although recurrence of disease in the graft limits its usefulness.

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*Prevention of primary manifestations:* Eculizumab prophylaxis may prevent disease recurrences in those with pathogenic variants in genes encoding circulating factors (*CFH*, *C3*, *CFB*, and *CFI*).

*Prevention of secondary complications:* Eculizumab therapy may prevent thrombotic microangiopathic events and prophylactic treatment may prevent post-transplantation aHUS recurrence; vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B is required prior to eculizumab therapy; prophylactic antibiotics may be needed if vaccination against *Neisseria meningitidis* is not possible at least two weeks prior to eculizumab therapy.

*Surveillance:* Serum concentration of hemoglobin, platelet count, and serum concentrations of creatinine, LDH, C3, C4, and haptoglobin:

- Every month in the first year after an aHUS episode, then every three to six months in the following years, particularly for those with normal renal function or chronic renal insufficiency as they are at risk for relapse; and
- In relatives with the pathogenic variant following exposure to potential triggering events.

*Agents/circumstances to avoid:* Plasma therapy is contraindicated in those with aHUS induced by *Streptococcus pneumoniae* because antibodies in the plasma of adults may exacerbate the disease. Individuals with known aHUS should avoid pregnancy if possible and the following drugs that are known precipitants of aHUS: chemotherapeutic agents (e.g., mitomycin, cisplatin, daunorubicin, bleomycin, cytosine arabinoside, gemcitabine); immunotherapeutic agents (e.g., cyclosporin, tacrolimus, muromonab-CD<sub>3</sub>, interferon, quinidine); antiplatelet agents (e.g., ticlopidine, clopidogrel); oral contraceptives, and anti-inflammatory agents.

*Evaluation of relatives at risk:* While it is appropriate to offer molecular genetic testing to at-risk relatives of persons in whom pathogenic variants have been identified, predictive testing based on a predisposing factor (as opposed to a pathogenic variant) is problematic as it is only one of several risk factors required for aHUS.

*Pregnancy management:* Women with a history of aHUS are at increased risk for an aHUS flare during pregnancy and even a greater risk in the postpartum period; the risk for pregnancy-associated aHUS (P-aHUS) is highest during the second pregnancy. Women with complement dysregulation should be informed of the 20% risk for P-aHUS, and any pregnancy in these women should be closely monitored.

*Other:* Live-related renal transplantation for individuals with aHUS should also be avoided in that disease onset can be precipitated in the healthy donor relative. Evidence suggests that kidney graft outcome is favorable in those with *CD46* and *DGKE* pathogenic variants but not in those with *C3*, *CFB*, *CFH*, *CFI*, or *THBD* pathogenic variants; however, simultaneous kidney and liver transplantation in young children with aHUS and *CFH* pathogenic variants may correct the genetic defect and prevent disease recurrence.

## Genetic counseling

Predisposition to aHUS associated with pathogenic variants in *C3*, *CD46*, *CFB*, *CFH* (including *CFH* hybrid genes), *CFHR5*, *CFI*, *THBD*, or *VTN* is typically inherited in an autosomal dominant manner with reduced penetrance. Atypical HUS associated with pathogenic variants in *DGKE* is typically inherited in an autosomal recessive manner. Deletions of *CFHR3/CFHR1* and *CFHR1/CFHR4* are inherited in an autosomal recessive manner. Polygenic inheritance is also reported in rare families.

- **Autosomal dominant inheritance.** Almost all individuals with autosomal dominant aHUS inherited an aHUS-related pathogenic variant from a heterozygous (typically unaffected) parent. Each child of an individual with autosomal dominant aHUS has a 50% chance of inheriting the pathogenic variant; offspring who inherit the pathogenic variant may or may not develop aHUS.
- **Autosomal recessive inheritance.** If both parents are known to be heterozygous for an autosomal recessive aHUS-related pathogenic variant, each sib of a proband has a 25% chance of inheriting two

pathogenic variants, a 50% chance of inheriting one pathogenic variant, and a 25% chance of inheriting neither pathogenic variant.

Once the aHUS-related pathogenic variant(s) have been identified in an affected family member, prenatal testing and preimplantation genetic testing for the familial pathogenic variant(s) are possible.

## Diagnosis

### Suggestive Findings

Genetic atypical hemolytic-uremic syndrome (aHUS) **should be suspected** in individuals with a diagnosis of aHUS in addition to ONE of the following criteria:

- One or more members of the same family have been diagnosed with aHUS at least six months apart and exposure to a common triggering infectious agent has been excluded.
- An individual has an HUS relapse even after complete recovery from the presenting episode.
- An underlying environmental factor such as drugs, systemic disease, viral agents, or bacterial agents that do not result in Shiga-like exotoxins can be identified.

For information about laboratory findings and renal histology related to typical and atypical HUS, click [here](#) (pdf).

### Establishing the Diagnosis

The diagnosis of genetic aHUS is **established** in a proband with aHUS by identification of a pathogenic variant(s) in one or more of the genes associated with genetic aHUS (see Table 1). Genetic predisposition to aHUS is typically inherited in an autosomal dominant manner with reduced penetrance or in an autosomal recessive manner by a pathogenic variant(s) in a single gene; rarely, inheritance can be polygenic. To date, the reported mechanisms include the following:

- Heterozygous pathogenic variant in one or more of the following genes: *C3*, *CD46*, *CFB*, *CFH*, *CFHR5*, *CFI*, *THBD*, and/or *VTN*
- Homozygous or compound heterozygous pathogenic variants in *DGKE*

Modifiers that increase the penetrance and/or severity of aHUS but may not cause aHUS when present without one of the established molecular causes (see Molecular Genetics):

- *CFH*-H3 haplotype [Goodship et al 2017]
- *CD46* (*MCP*)-GGAAC haplotype [Esparza-Gordillo et al 2006]
- Homozygous deletion of *CFHR3/CFHR1*; often associated with the formation of anti-factor H autoantibodies causing autoimmune aHUS [Zipfel et al 2020]

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing** should be considered in individuals with aHUS presenting before age one year, particularly if the family history reveals consanguinity or evidence of autosomal recessive inheritance; consider sequence analysis of *DGKE* first. If sequence analysis of *DGKE* does not identify biallelic pathogenic variants, a multigene panel is indicated.
- **A multigene panel** that includes *C3*, *CD46*, *CFB*, *CFH*, *CFHR5*, *CFI*, *DGKE*, *THBD*, and *VTN* should be considered in individuals with aHUS presenting after age one year. Testing specifically designed to detect *CFH/CFHR1* and *CFHR1/CFH* hybrid alleles and deletions of *CFHR1/CFHR4* should also be considered.

Note: The high degree of sequence identity between *CFH* and its downstream *CFH*-related genes (*CFHR1*-*CFHR4*) results in susceptibility to nonallelic homologous recombination (NAHR) events, and consequently, in large-scale deletions or duplications (copy number variation) and generation of hybrid *CFH* genes. Molecular assays must be specifically designed to detect deletions resulting from gene conversion in this region.

Note: Molecular testing should include analysis of genetic modifiers including *CFHR3/CFHR1* deletion analysis and *CFH*-H3 and *CD46 (MCP)*-GGAAC haplotypes [Esparza-Gordillo et al 2006, Goodship et al 2017]. Homozygous deletion of *CFHR3/CFHR1* and complement gene haplotypes, mainly homozygous *CFH*-H3 and *CD46 (MCP)*-GGAAC – together with triggers (e.g., infection, pregnancy) – may increase penetrance of aHUS [Fakhouri & Frémeaux-Bacchi 2021].

- A multigene panel that includes other genes of interest (see Differential Diagnosis) may also be considered.

Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

- **More comprehensive genomic testing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of aHUS.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in Atypical Hemolytic-Uremic Syndrome

Gene <sup>1</sup>	Proportion of Genetic aHUS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants <sup>2</sup> Detected by Method	
		Sequence analysis <sup>3</sup>	Gene-targeted deletion/duplication analysis <sup>4</sup>
<i>C3</i>	6% <sup>5, 6</sup>	100%	None reported <sup>7</sup>
<i>CD46</i>	10% <sup>5, 6, 8</sup>	100%	None reported <sup>7</sup>
<i>CFB</i>	2% <sup>6</sup>	100%	None reported <sup>7</sup>
<i>CFH</i>	21%-25% <sup>5, 6</sup>	~95%-97%	~3%-5% <sup>9</sup>
<i>CFH/CFHR1</i> hybrid allele	~3%-5% <sup>9</sup>	NA	100%
<i>CFHR1/CFH</i> hybrid allele	3 individuals <sup>10</sup>	NA	100%
<i>CFHR1/CFHR4</i> deletion	3 individuals <sup>11</sup>	NA	100%
<i>CFHR3/CFHR1</i> deletion	26.5% <sup>11</sup>	NA	100%
<i>CFHR5</i>	6 individuals <sup>12</sup>	100%	None reported <sup>7</sup>
<i>CFI</i>	6% <sup>5, 6</sup>	100%	None reported <sup>7</sup>
<i>DGKE</i>	3% <sup>6, 13</sup>	100%	None reported <sup>7</sup>

Table 1. continued from previous page.

Gene <sup>1</sup>	Proportion of Genetic aHUS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants <sup>2</sup> Detected by Method	
		Sequence analysis <sup>3</sup>	Gene-targeted deletion/duplication analysis <sup>4</sup>
<i>THBD</i>	2%-5% <sup>6, 14</sup>	100%	None reported <sup>7</sup>
<i>VTN</i>	8 individuals <sup>6</sup>	100%	None reported <sup>7</sup>
Unknown	~40%	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

5. Nester et al [2015]

6. Bu et al [2018]

7. No large deletions or duplications involving *C3*, *CD46*, *CFB*, *CFHR5*, *CFI*, *DGKE*, *THBD*, or *VTN* have been reported to cause aHUS. Data are derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017].

8. In one child, complete paternal uniparental isodisomy of chromosome 1 with homozygosity for a splice defect of exon 10 resulted in severe deficiency of *CD46* expression [Frémeaux-Bacchi et al 2007].

9. Several *CFH/CFHR1* hybrid alleles have been identified (see Molecular Genetics). Sequence analysis does not detect the *CFH/CFHR1* hybrid allele that accounts for approximately 3%-5% of all aHUS [Venables et al 2006]. Other methods including MLPA analysis may be used to detect the hybrid gene [Venables et al 2006, Maga et al 2011].

10. Two *CFHR1/CFH* hybrid alleles have been identified by MLPA [Eyler et al 2013, Valoti et al 2015].

11. *CFHR3/CFHR1* deletion is often associated with the formation of anti-factor H autoantibodies causing autoimmune aHUS [Zipfel et al 2020].

12. Maga et al [2010], Westra et al [2012]

13. *DGKE* pathogenic variants are found in approximately 27% of individuals presenting with aHUS before age 1 year [Lemaire et al 2013].

14. Delvaeye et al [2009], Noris et al [2010]

## Clinical Characteristics

### Clinical Description

The onset of atypical hemolytic-uremic syndrome (aHUS) ranges from the neonatal period to adulthood. Collectively, aHUS is associated with poor outcome. Individuals with genetic aHUS frequently relapse even after complete recovery following the presenting episode. Sixty percent of genetic aHUS progresses to end-stage renal disease (ESRD) [Noris et al 2010].

Genetic aHUS accounts for an estimated 60% of all aHUS [Nester et al 2015]. It is likely that pathogenic variants in *C3*, *CD46*, *CFB*, *CFH*, *CFHR5*, *CFI*, *THBD*, and *VTN* confer a predisposition to developing aHUS, rather than directly causing the disease. Conditions that trigger complement activation may precipitate an acute event in those with the predisposing genetic background [Noris et al 2010].

**Triggers for aHUS** include nonenteric bacterial and viral infections, drugs, malignancies, transplantation, pregnancy, and other underlying medical conditions:

- **Infection** caused by *Streptococcus pneumoniae* accounts for 40% of aHUS. The clinical picture is usually severe, with respiratory distress, neurologic involvement, and coma; the mortality rate is 12.3% [Copelovitch & Kaplan 2008].



- **Drugs** most frequently reported to trigger aHUS include: chemotherapeutic agents (e.g., mitomycin, cisplatin, daunorubicin, bleomycin, cytosine arabinoside, gemcitabine), immunotherapeutic agents (e.g., cyclosporine, tacrolimus, muromonab-CD3, interferon, quinidine), antiplatelet agents (e.g., ticlopidine, clopidogrel), and a variety of common medications (e.g., oral contraceptives, anti-inflammatory agents).
- **Malignancy-associated** aHUS occurs in almost 6% of individuals with metastatic carcinoma. Gastric cancer accounts for approximately half of such cases.
- **Post-transplantation** aHUS may occur in individuals who have not had aHUS before or may affect those whose primary cause of ESRD was aHUS (post-transplant recurrence of aHUS).
- **Pregnancy-associated** aHUS may occasionally develop as a complication of preeclampsia. Some women progress to a life-threatening variant of preeclampsia with severe thrombocytopenia, microangiopathic hemolytic anemia, renal failure, and liver involvement (HELLP syndrome). Complete remission usually follows prompt delivery. Postpartum aHUS usually manifests in women within three months of delivery. The outcome is usually poor: ESRD or death in 50%-60%; residual renal dysfunction and hypertension are the rule in those who survive the acute episode.
- **Underlying medical conditions** include autoimmune disease (e.g., scleroderma, anti-phospholipid syndrome, systemic lupus erythematosus).

## Phenotype Correlations by Gene

The phenotype of aHUS ranges from mild (with complete recovery of renal function) to severe (resulting in ESRD or death). The course and outcome of the disease are influenced by the gene in which pathogenic variants occur:

- **C3.** Atypical HUS associated with *C3* pathogenic variants shows variable onset, presenting both in childhood and in adulthood [Noris et al 2010]. More than 60% of affected individuals will develop ESRD.
- **CD46.** Atypical HUS associated with *CD46* pathogenic variants typically presents in childhood with a milder acute episode. Eighty percent of individuals experience complete remission. Recurrences are frequent but have little effect on long-term outcome; 60%-70% of individuals remain dialysis free even after several recurrences. A subgroup of individuals, however, lose renal function either during the first episode or later in life.

**CD46 modifiers.** The *CD46* (*MCP*)-GGAAC haplotype (-547G, -261G, IVS9-78A, IVS12+638A, and c.2232C) was found to be associated with aHUS and increased disease severity [Esparza-Gordillo et al 2006].

- **CFB.** Atypical HUS associated with *CFB* pathogenic variants shows variable onset, presenting both in childhood and adulthood [Frémeaux-Bacchi et al 2013], and intrafamilial variability [Funato et al 2014]. Seventy percent of individuals eventually develop ESRD [Nester et al 2015].
- **CFH.** Atypical HUS associated with *CFH* pathogenic variants presents early in childhood in approximately 20% of affected individuals and in adulthood in approximately 30%. Irrespective of the pattern of inheritance, there is a high rate of relapse and a 60%-80% rate of ESRD or death.  
**CFH modifiers.** The *CFH-H3* haplotype (*CFH-tgtgt*; c.-332T, c.184G, c.1204T, c.2016G, and c.2808T) was found to be associated with aHUS and increased disease severity [Goodship et al 2017].
- **CFI.** Atypical HUS associated with *CFI* pathogenic variants is variable. The onset is in childhood in 50% of affected individuals [Noris et al 2010]. Fifty-eight percent develop ESRD.
- **DGKE.** Atypical HUS associated with biallelic pathogenic variants in *DGKE* presents typically before age one year in affected individuals [Lemaire et al 2013] but is not exclusively limited to infancy [Azukaitis et al 2017]. Affected individuals show persistent hypertension, hematuria, and proteinuria (sometimes in

nephrotic range). Relapsing episodes are reported before age five years. Chronic kidney disease occurs by the second decade of life.

- **THBD.** Atypical HUS associated with *THBD* pathogenic variants presents in childhood in about 90% of individuals [Noris et al 2010]. More than 50% of individuals will eventually develop ESRD.
- **Polygenic inheritance.** *CFH*, *CFI*, and *C3* pathogenic variants may have an additive effect and lead to a more severe aHUS phenotype in individuals with *CD46*-associated aHUS, including an increased incidence of ESRD and graft loss [Bresin et al 2013].

## Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

## Penetrance

**C3, CD46, CFH, CFI, and THBD.** Penetrance for pathogenic variants in these genes was reduced: *C3*: 56%; *CD46*: 53%; *CFH*: 48%; *CFI*: 50%; *THBD*: 64% [Caprioli et al 2006, Noris et al 2010].

**DGKE.** Penetrance was complete in kindreds with homozygous or compound heterozygous pathogenic variants in *DGKE* [Lemaire et al 2013, Azukaitis et al 2017].

## Nomenclature

Genetic aHUS is also referred to as hereditary HUS, familial aHUS, and complement mutation-associated HUS.

## Prevalence

Genetic aHUS accounts for an estimated 60% of all aHUS.

## Genetically Related (Allelic) Disorders

Biallelic or heterozygous pathogenic variants in *C3*, *CD46*, *CFB*, *CFH*, *CFHR1*, *CFHR5*, *CFI*, and *DGKE* have been implicated in the pathogenesis of [C3 glomerulopathy](#) (see Differential Diagnosis).

**THBD** pathogenic variants have been described in association with thrombophilia due to thrombomodulin defect (OMIM [614486](#)).

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *CFHR3*, *CFHR4*, and/or *VTN*.

## Differential Diagnosis

**Distinguishing typical HUS from atypical HUS (aHUS).** Typical HUS is triggered by infective agents such as certain strains of *Escherichia coli* that produce the Shiga-like powerful exotoxins (Stx-*E coli*).

Typical HUS triggered by Stx-*E coli* manifests as an acute disease with a prodrome of diarrhea (D<sup>+</sup>HUS), often bloody. However, approximately 25% of typical HUS is diarrhea negative. During an acute episode, identification of Shiga toxins in the stools (by the Vero cell assay) and/or serum antibodies against Shiga toxin (by enzyme-linked immunosorbent assay [ELISA]) and/or lipopolysaccharides (LPS) (O157, O26, O103, O111, and O145, by ELISA) distinguishes typical HUS (D<sup>+</sup>HUS or D<sup>-</sup>Stx<sup>+</sup>HUS) from aHUS (D<sup>-</sup>Stx<sup>-</sup>HUS). The detection of free fecal Shiga toxin-producing *E coli* (STEC) can be made by commercial immunoassays and requires only a few hours. Approximately 80%-90% of individuals recover without sequelae, either spontaneously (as in most cases

of childhood typical HUS) or after plasma infusion or exchange (as in adult or severe forms of typical HUS). Typical HUS usually subsides when the underlying condition is treated or removed [Imdad et al 2021].

Note: STEC isolation and detection of LPS antibodies are not routinely available and require a few days to complete.

**Distinguishing aHUS from thrombotic thrombocytopenic purpura (TTP).** Atypical HUS and TTP (OMIM 274150) share a common pathologic lesion (thrombotic microangiopathy) but have different clinical manifestations. In aHUS the lesions and clinical symptoms are mainly localized in the kidney, whereas the pathologic changes of TTP are more extensively distributed. Clinically, TTP manifests mainly with central nervous system symptoms, but renal insufficiency has been reported.

Approximately 80% of TTP is triggered by deficient activity of ADAMTS13. ADAMTS13 deficiency can be constitutive, as a result of biallelic *ADAMTS13* pathogenic variants; or acquired, as a result of an inhibitory antibody. Evaluation of ADAMTS13 activity is performed using tests based on the capability of the protease to cleave standard VWF multimers in vitro (e.g., collagen binding assay). Deficiency of ADAMTS13 activity is typically not found in individuals with HUS [Barbour et al 2012]. The exception occurs when *ADAMTS13* and *CFH* pathogenic variants are observed in the same individual. Affected individuals with both *ADAMTS13* and *CFH* pathogenic variants have been reported [Noris et al 2005, Zimmerhackl et al 2007].

**Distinguishing aHUS from C3 glomerulopathy (C3G).** C3G is a complex ultra-rare complement-mediated renal disease caused by uncontrolled activation of the complement alternative pathway (AP) in the fluid phase (as opposed to cell surface in aHUS) that is rarely inherited in a simple mendelian fashion. C3G affects individuals of all ages, with a median age at diagnosis of 23 years. Individuals with C3G typically present with hematuria, proteinuria, hematuria and proteinuria, acute nephritic syndrome or nephrotic syndrome, and low levels of the complement component C3. Some affected individuals have biallelic or heterozygous pathogenic variants in one or more of the genes that have been implicated in the pathogenesis of C3G (i.e., *C3*, *CD46*, *CFB*, *CFH*, *CFHR1*, *CFHR5*, *CFI*, and *DGKE*).

Individuals with aHUS associated with homozygous pathogenic variants in *CFH* and very low levels of circulating CFH protein can blur the distinction between HUS and C3G. This overlap in phenotypes is evident in those few individuals who have a mixed diagnosis of aHUS and C3G in the same biopsy or in biopsies taken at different points in time [Gnappi et al 2012]. See [C3 Glomerulopathy](#).

**Distinguishing aHUS from disorders of intracellular cobalamin metabolism.** Disorders of intracellular cobalamin metabolism have a variable phenotype and age of onset. The prototype and best understood phenotype is *cb1C*; it is also the most common of these disorders. The age of initial presentation of *cb1C* spans a wide range. In infants, the presentation can include poor feeding and slow growth, neurologic abnormality, and, rarely, HUS. The *cb1C* phenotype is caused by biallelic pathogenic variants in *MMACHC*. HUS may also be observed in *cb1E* (caused by biallelic pathogenic variants in *MTRR*) and *cb1G* (caused by biallelic pathogenic variants in *MTR*). See [Disorders of Intracellular Cobalamin Metabolism](#).

## Management

Guidelines for the initial assessment and early management of children with aHUS have been published [Loirat et al 2016].

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with genetic atypical hemolytic-uremic syndrome (aHUS), the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.



**Table 2.** Recommended Evaluations Following Initial Diagnosis in Individuals with Genetic Atypical Hemolytic-Uremic Syndrome

System/Concern	Evaluation	Comment
<b>Renal</b>	<ul style="list-style-type: none"> <li>• Creatinine clearance (i.e., GFR)</li> <li>• Serum concentration of creatinine resources</li> <li>• Urinalysis</li> </ul>	To assess renal function
<b>Hematologic</b>	<ul style="list-style-type: none"> <li>• Platelet count</li> <li>• Erythrocyte count</li> <li>• Histologic eval of blood smear for schistocytes</li> <li>• Leukocyte count</li> <li>• Serum LDH concentration</li> <li>• Haptoglobin</li> </ul>	To evaluate hematologic status & assess severity of hemolysis
<b>Immunologic</b>	<ul style="list-style-type: none"> <li>• Serum C3 &amp; C4 concentrations</li> <li>• Plasma concentrations of Bb &amp; sC5b-9</li> <li>• Serum concentrations of CFH &amp; CFI</li> <li>• CD46 expression on leukocytes</li> </ul>	To assess complement system
	Testing for CFH autoantibodies	Affected persons who have autoantibodies could benefit from an immunosuppressive therapy (see Treatment of Manifestations).
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	To inform patients & families re nature, MOI, & implications of genetic aHUS to facilitate medical & personal decision making

GFR = glomerular filtration rate; LDH = lactate dehydrogenase; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

**Eculizumab** (a human anti-C5 monoclonal antibody) has been shown to induce remission of acute episodes of aHUS refractory to plasma therapy and is now widely used as a first-line therapy to treat aHUS. Eculizumab should be considered first-line therapy when the diagnosis of aHUS is unequivocal, as this treatment has the potential to rescue renal function when administered early after onset of the disease [Zuber et al 2012a, Fakhouri et al 2013, Goodship et al 2017].

**Plasma infusion or exchange** guidelines have been published for children [Loirat et al 2016] and adults [Taylor et al 2010]. Cohort data show that response to plasma therapy was in part related to the genetic background of the treated individual [Noris et al 2010]. Despite the variability in response to therapy, plasma therapy is the only therapy with near-complete global availability and therefore it remains an important treatment for aHUS. Plasma therapy should be started as soon as aHUS is suspected and continued until resolution of thrombotic microangiopathy. In individuals who respond, plasma exchange can be gradually withdrawn, although a significant proportion will require continued plasma exchange to maintain remission. There is minimal evidence to suggest the superiority of either plasma exchange or plasma infusion, and instead the selected option should be based on individual tolerance, local expertise, and resources (e.g., a neonatal benefit from infusion vs exchange) [Nester et al 2015].

- Plasma exchange usually involves exchanging 1-2 plasma volumes (40 mL/kg) per session in adults and 50-100 mL/kg in children. Typically, plasma exchange is initially undertaken daily; the duration and frequency of treatment is then determined by the clinical response.

Treatment can be intensified by increasing the volume of plasma replaced. Twice-daily exchange of one plasma volume is probably the treatment of choice for those with refractory disease in order to minimize the recycling of infused plasma.

- Plasma infusion is the first-line therapy when plasma exchange or eculizumab therapies are not available. In plasma infusion 30-40 mL/kg of plasma is administered initially, followed by 10-20 mL/kg/day. Plasma infusion should be used to treat or prevent recurrent episodes.

Platelet count and serum LDH concentration are the most sensitive markers for monitoring response to plasma therapy. Plasma treatment should be continued until platelet count and serum LDH concentration remain normal after therapy is discontinued. Discontinuation of plasma therapy is the only way to know if complete remission has been achieved. Immediate exacerbation of disease activity (principally manifested by falling platelet count that requires the resumption of daily plasma therapy) occurs in 29%-82% of individuals after treatment is discontinued. Thus, many cycles of stopping and resuming plasma therapy may occur, in which case therapy with eculizumab should be considered.

**Genetic characterization** of persons with aHUS has the potential to optimize the treatment:

- **C3.** Response to plasma treatment in persons with C3 pathogenic variants was comparable (57%) to that in persons with *CFH* pathogenic variants [Noris et al 2010]. It is hypothesized that plasma exchange could remove mutated hyperactive C3 and also provide regulatory plasma proteins to counteract complement activation induced by mutated C3.
- **CFB.** Limited data are available on response of individuals with *CFB* pathogenic variants to treatment with plasma. Remission with plasma exchange or infusion has been reported [Funato et al 2014].
- **CD46.** The rationale for using plasma in individuals with *CD46* pathogenic variants is not so clear, since the CD46 protein (also known as MCP) is a transmembrane protein and, theoretically, plasma infusion or plasma exchange would not compensate for the MCP defect. Published data indicate that the majority (80%-90%) of individuals undergo remission following plasma infusion or exchange [Richards et al 2003, Caprioli et al 2006]; however, complete recovery from the acute episode was also observed in 100% of individuals not treated with plasma [Noris et al 2010]. The decision whether to treat with plasma should be based on the clinical severity of the acute episode.
- **CFH**
  - Plasma infusion or exchange has been used in individuals with aHUS and *CFH* pathogenic variants with the rationale of providing normal CFH to compensate for the genetic deficiency, as CFH is a circulating plasma protein. In published studies, some individuals with *CFH* pathogenic variants did not respond to plasma therapy and died or developed ESRD. Others required infusion of plasma at weekly intervals in order to raise CFH plasma levels enough to maintain remission [Landau et al 2001].
  - Stratton and Warwicker [2002] were able to induce sustained remission in an individual with a *CFH* pathogenic variant with three months of weekly plasma exchange in conjunction with intravenous immunoglobulins. One year after discontinuation of plasma therapy, the individual remained disease free and dialysis independent.
  - A dozen case reports showed that early plasma therapy, generally consisting of daily plasma exchange followed by maintenance plasma exchange/infusion, could prevent relapses and preserve renal function at follow up for up to six years [Loirat et al 2016].
  - In the authors' series [Noris et al 2010], approximately 60% of individuals with *CFH* pathogenic variants treated with plasma underwent either complete or partial remission (hematologic normalization with renal sequelae). However, the remaining individuals did not respond to plasma and 20% died during the acute episode.
  - In the French cohort [Frémeaux-Bacchi et al 2013], progression to ESRD during the first episode of aHUS was similar in children and adults with *CFH* pathogenic variants who received high-intensity plasma therapy compared to those who did not.
  - In individuals with **anti-CFH autoantibodies**, plasma treatment induced complete or partial remission (normalization of hematologic parameters with renal sequelae) of 75% of episodes [Noris

et al 2010]. Persons with anti-CFH autoantibodies benefit from treatment with steroids or other immunosuppressants in conjunction with plasma exchange.

- **CFI.** Theoretically one should expect a good response to plasma therapy in individuals with *CFI* pathogenic variants because CFI (like CFH) is a circulating protein; the results, however, suggest that a larger quantity of plasma is required to provide sufficient wild type CFH or CFI to compensate for the genetic deficiency [Caprioli et al 2006]. Indeed, remission was achieved in only 25% of episodes treated with plasma in persons with *CFI* pathogenic variants [Noris et al 2010].
- **DGKE.** Absence of evidence linking DGKE deficiency to the complement cascade and relapses of acute aHUS in affected individuals with pathogenic variants in *DGKE* receiving plasma therapy suggest that this treatment may not benefit individuals with *DGKE* pathogenic variants [Lemaire et al 2013].
- **THBD.** Plasma treatment induced disease remission in about 80% of acute episodes in persons with *THBD* pathogenic variants [Noris et al 2010].

**Treatment with ACE inhibitors or angiotensin receptor antagonists** helps to reduce renal disease progression to end-stage renal failure, while at the same time controlling blood pressure levels.

**Bilateral nephrectomy** may serve as rescue therapy in selected individuals with extensive microvascular thrombosis at renal biopsy, refractory hypertension, and signs of hypertensive encephalopathy, in whom conventional therapies including plasma manipulation are not adequate to control the disease (i.e., persistent severe thrombocytopenia and hemolytic anemia). Results have been excellent in some individuals [Ruggenti et al 2001].

**Renal transplantation** outcome is determined largely by the underlying genetic abnormality. An important advance has been the development of transplant protocols integrating eculizumab treatment [Nester et al 2011]. Eculizumab therapy may be used to treat post-transplantation aHUS recurrence, as reported in individuals with pathogenic variants in *C3*, *CFH*, and *CFI* [Zuber et al 2012b]. Eculizumab prophylactic therapy may also prevent post-transplantation aHUS recurrence [Goodship et al 2017] (see Prevention of Secondary Complications).

Molecular genetic testing can help to define graft prognosis; thus, all affected individuals should undergo such testing prior to transplantation.

- **C3, CFB, and CFI.** Graft failures secondary to recurrences occurred in one individual with a *CFB* pathogenic variant and in 70% of individuals with *CFI* pathogenic variants. The percentage of graft failure was slightly lower (50%) in individuals with *C3* pathogenic variants [Noris et al 2010].
- **CD46.** Four individuals with isolated *CD46* pathogenic variants have undergone renal transplantation with no disease recurrence [Noris et al 2010]. The strong theoretic rationale is that because the CD46 protein (MCP) is a transmembrane protein that is highly expressed in the kidney, transplantation of a kidney expressing normal MCP corrects the defect. However, in a French cohort, post-transplant recurrence was seen in two of three individuals with an isolated *CD46* pathogenic variant [Le Quintrec et al 2013].
- **CFH.** In individuals with *CFH* pathogenic variants the graft outcome is poor. Recurrence ranges from 30% to 100% and is significantly higher than in individuals without *CFH* pathogenic variants [Noris & Remuzzi 2010, Le Quintrec et al 2013]. As CFH is mainly produced by the liver, kidney transplantation does not correct the *CFH* genetic defect in these individuals.

Simultaneous kidney and liver transplantation has been performed in two young children with aHUS and *CFH* pathogenic variants [Noris & Remuzzi 2005]. However, following transplantation both children experienced premature irreversible liver failure. The first child recovered after a second uneventful liver transplantation. This child, who had had monthly recurrences of aHUS before transplantation, had no

symptoms of aHUS for more than two years following transplantation. The second child expired after primary nonfunction of the liver graft followed by multiorgan failure.

In six other individuals with *CFH* pathogenic variants and in one child heterozygous for pathogenic variants in two genes (*CFH* and *CFI*) who received simultaneous kidney and liver transplantation [Saland et al 2006, Saland et al 2009, Noris et al 2010], good renal and liver function were recorded at two-year follow up. In these individuals, extensive plasma exchange was given prior to surgery to provide enough normal CFH to prevent damage to the liver graft.

- **DGKE.** Three individuals with aHUS caused by pathogenic variants in *DGKE* received cadaveric renal transplantation at ages two, 19, and 21 years [Lemaire et al 2013]. Two allografts have survived two years and four years, at last observation, whereas the other failed after six years due to chronic rejection. Importantly, there were no aHUS recurrences after transplantation. Another five individuals have received renal allografts, with no post-transplant recurrence reported [Azukaitis et al 2017]. On the basis of these findings, it appears that renal transplantation can be efficacious and safe in individuals with aHUS caused by pathogenic variants in *DGKE*.
- **THBD.** Three individuals with *THBD* pathogenic variants had disease recurrence in the kidney graft, an unexpected occurrence as thrombomodulin (like CD46) is an endothelial transmembrane protein. However, a soluble thrombomodulin form circulates in plasma and has functional activities similar to those of membrane-bound thrombomodulin. It is possible that the grafts were not sufficiently protected against complement activation because of dysfunctional soluble thrombomodulin in persons with *THBD* pathogenic variants [Noris et al 2010, Caroti et al 2015]. However, in two individuals, successful kidney transplantation was reported, without recurrence of the disease 12 and seven months, respectively, after transplantation [Caroti et al 2015, Milan Manani et al 2017].

## Prevention of Primary Manifestations

Eculizumab prophylaxis may prevent disease recurrences in individuals with pathogenic variants affecting circulating factors (*CFH*, *C3*, *CFB*, and *CFI*).

## Prevention of Secondary Complications

**Eculizumab** has a greater efficacy than plasma therapy in the prevention of thrombotic microangiopathic events, with earlier intervention associated with a greater clinical benefit [Legendre et al 2013]. Eculizumab can be used as a prophylactic treatment to prevent post-transplantation aHUS recurrence in individuals at moderate to high risk of recurrence, as defined below [Nester et al 2011, Weitz et al 2011, Krid et al 2012, Zuber et al 2012b]:

- Individuals with pathogenic variants in *C3*, *CFB*, and *CFH* or those who have the *CFH/CFHR1* hybrid allele are at high risk for disease recurrence [Zuber et al 2012b].
- Individuals with anti-*CFH* antibodies, pathogenic variants in *CFI*, variants of uncertain significance, and/or no identified pathogenic variants are at moderate risk for disease recurrence [Zuber et al 2012b].

The major adverse effect of eculizumab is the increased risk for meningococcal infection [Rother et al 2007].

- Vaccination against *Neisseria meningitides* (tetraivalent vaccine A, C, Y, W135) is mandatory two weeks before administration of eculizumab.
- In those who are not vaccinated two weeks prior to therapy with eculizumab, daily prophylactic antibiotics (e.g., oral penicillin or a macrolide) should be administered for two weeks following vaccination.
- Since currently available vaccines do not cover all *Neisseria meningitidis* strains, a few countries require continuous antibiotic prophylaxis throughout eculizumab treatment.

In children treated with eculizumab, vaccination against *Streptococcus pneumonia* and *Haemophilus influenza* type B infections is also required.

## Surveillance

**Individuals with known aHUS.** Measure serum concentration of hemoglobin, platelet count, and serum concentrations of creatinine, LDH, C3, C4, and haptoglobin with the following frequency:

- Every month in the first year after an aHUS episode, then every three to six months in the following years, particularly for persons with normal renal function or chronic renal insufficiency, as they are at risk for relapse

Note: Individuals with ESRD usually do not relapse.

- Every two weeks for those rare individuals with homozygous *CFH* pathogenic variants that result in very low or undetectable levels of the CFH protein

Note: The proposed time intervals for checking hemoglobin, platelet count, and serum concentrations of creatinine, LDH, C3, C4, and haptoglobin are suggestions [Authors, personal observation]; each center may follow different guidelines based on their own experience.

## Agents/Circumstances to Avoid

Discontinue cyclosporine or tacrolimus when aHUS develops following challenge with the medication.

Fresh frozen plasma should be avoided (i.e., plasma therapy is contraindicated) in persons with aHUS induced by *Streptococcus pneumoniae* because plasma from an adult contains antibodies against the Thomsen-Friedenreich antigen, which may exacerbate the disease. It is preferable to transfuse washed red blood cells or platelets. There is no evidence that plasmapheresis is of value [Copelovitch & Kaplan 2008].

Avoid potential precipitants of aHUS, including the following known triggers:

- Pregnancy
- Medications: some chemotherapeutic agents (e.g., mitomycin, cisplatin, daunorubicin, bleomycin, cytosine arabinoside, gemcitabine), immunotherapeutic agents (e.g., cyclosporin, tacrolimus, muromonab-CD<sub>3</sub>, interferon, quinidine), antiplatelet agents (e.g., ticlopidine, clopidogrel), oral contraceptives, and anti-inflammatory agents

## Evaluation of Relatives at Risk

**For early diagnosis and treatment.** Molecular genetic testing should be offered to at-risk family members of a person with a molecular diagnosis of genetic aHUS.

Note: Testing of family members needs to be done with caution because presence of the family-specific pathogenic variant(s) is predisposing rather than causative, and thus is only one of several risk factors required for development of aHUS. Predictions based on a single risk factor in unaffected individuals are unreliable; thus, risk cannot be quantified for a given individual.

The following are appropriate for relatives in whom the family-specific pathogenic variant(s) have been identified:

- Monitoring of hemoglobin, platelet count, and serum concentrations of creatinine, LDH, C3, C4, and haptoglobin, when exposed to potential triggering events such as severe infections, inflammation, and pregnancy (See Surveillance.)
- Avoidance of known precipitants of aHUS (See Clinical Description.)



Note: No monitoring is needed for the relatives of individuals with typical HUS (i.e., individuals with HUS triggered by an infective agent such as certain strains of *E coli* that produce the Shiga-like powerful exotoxins [Stx-*E coli*]) and for the relatives of individuals in whom no aHUS-related pathogenic variant has been identified.

**For kidney donation.** Any relative who is a potential kidney donor should undergo molecular genetic testing to clarify his/her genetic status so that only those who do not have the familial aHUS-related pathogenic variant(s) are evaluated further.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

Women with a history of aHUS are at increased risk for aHUS flare during pregnancy and an even greater risk in the postpartum period. Pregnancy-associated aHUS (P-aHUS) occurred in 21 of 100 adult women with aHUS, with 79% presenting postpartum [Fakhouri et al 2010]. Treatment consisted mainly of plasma exchange, and outcomes were poor: 62% developed ESRD by one month after presentation and 76% by last follow up. The risk for P-aHUS was highest during a second pregnancy. Complement abnormalities were found in 18 of the 21 adult women with P-aHUS. Pregnancies in affected women with complement abnormalities were complicated by fetal loss (in 4.8%) and preeclampsia (7.7%).

On the basis of these results, women with complement dysregulation should be informed of the 20% risk for P-aHUS, and pregnancy in these women should be closely monitored.

**Eculizumab.** The experience gained from pregnant women with paroxysmal nocturnal hemoglobinuria who had been treated with eculizumab suggest a risk-benefit balance in favor of eculizumab use [Kelly et al 2010]. Similarly, data showed that eculizumab can be successfully used for the treatment of aHUS during pregnancy [Ardissino et al 2013, Cañigral et al 2014, De Sousa Amorim et al 2015].

## Therapies Under Investigation

A clinical trial is currently evaluating the efficacy and safety of [crovalimab](#) in adult and adolescent participants with aHUS.

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## Other

**Plasma-resistant/plasma-dependent disease.** Some individuals with aHUS are plasma resistant (i.e., they do not achieve remission despite plasma therapy); some become plasma dependent, experiencing disease relapse as soon as plasma infusion or exchange is stopped.

- Splenectomy, while inducing remission in some persons with plasma resistance, is ineffective and actually increases morbidity and mortality in others.
- Other treatments, including antiplatelet agents, prostacyclin, heparin or fibrinolytic agents, steroids, and intravenous immunoglobulins, have been attempted in both plasma resistance and plasma dependence with no consistent benefit [Ruggenti et al 2001].

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The*

following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

## Mode of Inheritance

Predisposition to atypical HUS (aHUS) associated with pathogenic variants in *C3*, *CD46*, *CFB*, *CFH* (including *CFH* hybrid genes), *CFHR5*, *CFI*, *THBD*, or *VTN* is typically inherited in an autosomal dominant manner with reduced penetrance [Noris et al 2010, Bu et al 2018].

Atypical HUS associated with pathogenic variants in *DGKE* is typically inherited in an autosomal recessive manner [Lemaire et al 2013]. Deletions of *CFHR1/CFHR4* and *CFHR3/CFHR1* are inherited in an autosomal recessive manner [Zipfel et al 2007, Moore et al 2010].

Rare polygenic inheritance occurs [Esparza-Gordillo et al 2006, Bresin et al 2013, Bu et al 2018].

## Autosomal Dominant Inheritance – Risk to Family Members

### Parents of a proband

- Almost all individuals with autosomal dominant aHUS inherited an aHUS-related pathogenic variant from a heterozygous parent. Some parents who are heterozygous for an aHUS-related pathogenic variant are affected; however, the majority of heterozygous parents are unaffected and their child is the only family member known to have aHUS [Noris et al 2010, Loirat & Frémeaux-Bacchi 2011].
- Rarely, individuals diagnosed with autosomal dominant aHUS have the disorder as the result of a *de novo* pathogenic variant [Pérez-Caballero et al 2001, Neumann et al 2003, Noris et al 2010].
- If both parents of a proband with a known pathogenic variant are unaffected, molecular genetic testing is recommended for the parents of the proband. If a pathogenic variant is identified in a parent, the parent is at risk of developing aHUS and of transmitting the pathogenic variant to other offspring.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of individuals with autosomal dominant aHUS may appear to be negative because of reduced penetrance in an asymptomatic parent, early death of a parent, or late onset in a parent (or close relative). Therefore, an apparently negative family history cannot be confirmed without molecular genetic testing to establish that neither parent is heterozygous for the pathogenic variant identified in the proband.

**Sibs of a proband.** The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Because of reduced penetrance, sibs who inherit the pathogenic variant may or may not develop aHUS (see Penetrance).
- Clinical severity and disease phenotype often differ among individuals with the same pathogenic variants. Although age of onset and/or disease progression and outcome cannot be predicted in sibs who inherit a familial pathogenic variant, the penetrance and/or severity of aHUS are known to be increased in individuals who inherit both a familial aHUS-related pathogenic variant and a genetic modifier (modifiers increase the penetrance and/or severity of aHUS but may not cause aHUS when present without one of the established molecular causes [see Molecular Genetics]).

- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% based on the theoretic possibility of parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with autosomal dominant aHUS has a 50% chance of inheriting the pathogenic variant; because of reduced penetrance, offspring who inherit the pathogenic variant may or may not develop aHUS.

**Other family members.** The risk to other family members depends on the genetic status of the proband's parents: if a parent is heterozygous for an aHUS-related pathogenic variant, his or her family members may be at risk.

## Autosomal Recessive Inheritance – Risk to Family Members

### Parents of a proband

- The parents of a child with autosomal recessive aHUS are obligate heterozygotes (i.e., presumed to be carriers of one pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an aHUS-related pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband; uniparental isodisomy has been reported in two probands [Frémeaux-Bacchi et al 2007, Wilson et al 2013].
- Heterozygotes are usually asymptomatic. Rare instances of heterozygotes developing aHUS in adulthood have been reported [Caprioli et al 2006].

### Sibs of a proband

- If both parents are known to be heterozygous for an autosomal recessive aHUS-related pathogenic variant, each sib of a proband has a 25% chance of inheriting two pathogenic variants, a 50% chance of inheriting one pathogenic variant, and a 25% chance of inheriting neither pathogenic variant.
  - Sibs who inherit biallelic *DGKE* pathogenic variants typically have clinical features of aHUS before age one year.
  - Age of onset and/or disease progression and outcome cannot be predicted in sibs who inherit biallelic pathogenic variants in other aHUS-related genes, as clinical severity and disease phenotype often differ among individuals with the same pathogenic variants because of the role of environmental triggers and/or genetic modifiers.
- Heterozygotes are usually asymptomatic. Rare instances of heterozygotes developing aHUS in adulthood have been reported [Caprioli et al 2006].

**Offspring of a proband.** The offspring of an individual with autosomal recessive aHUS are obligate heterozygotes for a pathogenic variant and will usually be asymptomatic.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an aHUS-related pathogenic variant.

### Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

## Polygenic Inheritance – Risk to Family Members

Polygenic aHUS is caused by the simultaneous presence of two pathogenic variants: one pathogenic variant in one complement-regulatory gene and another pathogenic variant in a different complement-regulatory gene.

### Parents of a proband

- Typically, one parent has a pathogenic variant in one complement-regulatory gene and the other parent has a pathogenic variant in a different complement-regulatory gene. However, both parents should undergo confirmatory genetic testing because it is possible that one parent has both pathogenic variants and is asymptomatic.
- In the families reported to date with polygenic inheritance, heterozygotes have usually been asymptomatic.

**Sibs of a proband.** Assuming that each parent has one pathogenic variant, at conception each sib has a 75% chance of inheriting one or two pathogenic variants (and being at increased risk of developing aHUS) and a 25% chance of not inheriting a pathogenic variant (and being unaffected).

**Offspring of a proband.** The risk to offspring of inheriting one or two pathogenic variants is 75%.

**Other family members.** Other family members may be at risk and molecular genetic testing should be offered.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Predictive testing** for at-risk asymptomatic adult family members requires prior identification of the pathogenic variant(s) in the family.

**Precipitation of aHUS in renal donors.** In two families, renal transplantation precipitated disease onset in the previously healthy donor [Donne et al 2002]. Subsequent molecular genetic testing revealed that one of the donors had a *CFH* pathogenic variant that put him at risk for aHUS. Since that time, molecular genetic testing is recommended before live-related donation to avoid the risk of triggering disease in the donor.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

## Prenatal Testing and Preimplantation Genetic Testing

Once the aHUS-related pathogenic variant(s) have been identified in an affected family member, prenatal testing and preimplantation genetic testing for the familial pathogenic variant(s) are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **MedlinePlus**  
[Hemolytic-uremic syndrome \(HUS\)](#)
- **National Kidney and Urologic Diseases Information Clearinghouse (NKUKIC)**  
3 Information Way  
Bethesda MD 20892-3580  
**Phone:** 800-860-8747 (toll-free); 866-569-1162 (toll-free TTY)  
**Email:** [healthinfo@niddk.nih.gov](mailto:healthinfo@niddk.nih.gov)  
[Hemolytic Uremic Syndrome](#)
- **A.R.M.R. Foundation (Fondazione Aiuti per la Ricerca sulle Malattie Rare)**  
Italy  
**Email:** [segretariapresidenza@armr.it](mailto:segretariapresidenza@armr.it); [presidenza@armr.it](mailto:presidenza@armr.it)  
[www.armr.it](http://www.armr.it)
- **American Kidney Fund**  
**Phone:** 800-638-8299  
[www.kidneyfund.org](http://www.kidneyfund.org)
- **National Kidney Foundation (NKF)**  
**Phone:** 855-NKF-CARES; 855-653-2273  
**Email:** [nkfcare@kidney.org](mailto:nkfcare@kidney.org)  
[www.kidney.org](http://www.kidney.org)
- **International Registry of Recurrent and Familial HUS/TTP**  
Mario Negri Institute for Pharmacological Research  
Clinical Research Center for Rare Diseases "Aldo e Cele Daccò"  
Villa Camozzi - Via Camozzi, 3  
Ranica 24020  
Italy  
**Phone:** +39 35 4535304  
**Fax:** +39 35 4535373  
**Email:** [raredis@marionegri.it](mailto:raredis@marionegri.it)  
[International Registry of Recurrent and Familial Hemolytic Uremic Syndrome \(HUS\) and Thrombotic Thrombocytopenic Purpura \(TTP\)](#)



## Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

**Table A.** Genetic Atypical Hemolytic-Uremic Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
C3	19p13.3	Complement C3	C3 database C3base: Mutation registry for C3 deficiency	C3	C3
CD46	1q32.2	Membrane cofactor protein	CD46 database	CD46	CD46
CFB	6p21.33	Complement factor B	CFB database	CFB	CFB
CFH	1q31.3	Complement factor H	CFHbase: Mutation registry for Factor H deficiency (previously known as HF1base)	CFH	CFH
CFHR1	1q31.3	Complement factor H-related protein 1	CFHR1 database	CFHR1	CFHR1
CFHR3	1q31.3	Complement factor H-related protein 3	CFHR3 database	CFHR3	CFHR3
CFHR4	1q31.3	Complement factor H-related protein 4		CFHR4	CFHR4
CFI	4q25	Complement factor I	CFI database CFIbase: Mutation registry for Factor I deficiency (previously known as IFbase)	CFI	CFI
DGKE	17q22	Diacylglycerol kinase epsilon		DGKE	DGKE
THBD	20p11.21	Thrombomodulin	THBD database	THBD	THBD
VTN	17q11.2	Vitronectin		VTN	VTN

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for Genetic Atypical Hemolytic-Uremic Syndrome (View All in OMIM)

120700	COMPLEMENT COMPONENT 3; C3
120920	CD46 ANTIGEN; CD46
134370	COMPLEMENT FACTOR H; CFH
134371	COMPLEMENT FACTOR H-RELATED 1; CFHR1
138470	COMPLEMENT FACTOR B; CFB
188040	THROMBOMODULIN; THBD
193190	VITRONECTIN; VTN
217030	COMPLEMENT FACTOR I; CFI
235400	HEMOLYTIC UREMIC SYNDROME, ATYPICAL, SUSCEPTIBILITY TO, 1; AHUS1
601440	DIACYLGLYCEROL KINASE, EPSILON, 64-KD; DGKE

Table B. continued from previous page.

605336	COMPLEMENT FACTOR H-RELATED 3; CFHR3
605337	COMPLEMENT FACTOR H-RELATED 4; CFHR4
612922	HEMOLYTIC UREMIC SYNDROME, ATYPICAL, SUSCEPTIBILITY TO, 2; AHUS2
612923	HEMOLYTIC UREMIC SYNDROME, ATYPICAL, SUSCEPTIBILITY TO, 3; AHUS3
612924	HEMOLYTIC UREMIC SYNDROME, ATYPICAL, SUSCEPTIBILITY TO, 4; AHUS4
612925	HEMOLYTIC UREMIC SYNDROME, ATYPICAL, SUSCEPTIBILITY TO, 5; AHUS5
612926	HEMOLYTIC UREMIC SYNDROME, ATYPICAL, SUSCEPTIBILITY TO, 6; AHUS6

## Molecular Pathogenesis

Hyperactivation of the complement system is the pathogenetic mechanism leading to the endothelial damage and the microvascular thrombosis in aHUS [Noris & Remuzzi 2017]. Genetic dysregulation of the alternative pathway of complement system is the main cause of aHUS.

Table 3. Genetic Atypical Hemolytic-Uremic Syndrome: Mechanism of Disease Causation by Gene

Gene <sup>1</sup>	Mechanism of Disease Causation
<i>C3</i>	Gain of abnormal function
<i>CD46</i>	Loss of function
<i>CFB</i>	Gain of abnormal function
<i>CFH</i>	Loss of function
<i>CFHR1</i>	Unknown
<i>CFHR3</i>	
<i>CFHR4</i>	
<i>CFHR5</i>	Loss of function
<i>CFI</i>	
<i>DGKE</i>	
<i>THBD</i>	
<i>VTN</i>	Unknown

**Gene-specific laboratory technical considerations.** Several hybrid alleles derived by nonallelic homologous recombination of *CFH* and *CFHR1* have been reported in individuals with aHUS [Venables et al 2006].

Table 4. Genetic Atypical Hemolytic-Uremic Syndrome: *CFH* Notable Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000186.4 NP_000177.2	c.3628C>T	p.Arg1210Cys	Common pathogenic variant [Martinez-Barricarte et al 2008]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

## Chapter Notes

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### Revision History

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- 20 November 2008 (cd) Revision: deletion/duplication testing for *CFI* and *CD46* available clinically
- 17 December 2007 (cd) Revision: sequence analysis available for *CFB*
- 16 November 2007 (me) Review posted live
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