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Summary

Disease 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. Typical (acquired) HUS is triggered by infectious agents such as strains of *E. coli* (Stx-*E. coli*) that produce powerful Shiga-like exotoxins, whereas atypical HUS (aHUS) can be genetic, acquired, or idiopathic (of unknown cause). Onset of atypical HUS ranges from prenatal to adulthood. Individuals with genetic atypical HUS frequently experience relapse even after complete recovery following the presenting episode. Sixty percent of genetic aHUS progresses to end-stage renal disease (ESRD).

Diagnosis/testing. Atypical HUS is considered genetic when two or more members of the same family are affected by the disease at least six months apart and exposure to a common triggering infectious agent has been excluded, or when a disease-causing mutation(s) is identified in one of the four genes known to be associated with aHUS, irrespective of familial history. The four genes known to be associated with aHUS are: *CFH* (encoding complement factor H), accounting for an estimated 30% of aHUS; *CD46 (MCP*) (encoding membrane cofactor protein) accounting for approximately 12% of aHUS; *CFI* (encoding complement factor I), accounting for an estimated 5%-10% of aHUS; and, rarely, *CFB* (encoding complement factor B).

Management. *Treatment of manifestations:* plasma manipulation (plasma infusion or exchange) to reduce mortality; however, plasma resistance or plasma dependence is possible. Bilateral nephrectomy when severe disease is not responsive to conventional therapies. *Surveillance:* serum concentration of hemoglobin, platelet count, and serum concentrations of creatinine, LDH, C3, C4, and haptoglobin: (1) 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 (2) in mutation-positive relatives following exposure to potential triggering events. *Agents/circumstances to avoid:* Those with known aHUS should avoid if possible pregnancy and the following drugs that are known precipitants of aHUS: anti-cancer molecules (including mitomycin C, cisplatin, daunorubimicin, cytosine arabinoside); immunotherapeutic agents (including cyclosporin and tacrolimus); and antiplatelet agents (including ticlopidine and clopidogrel). Plasma therapy is contraindicated in those with aHUS induced by *Streptococcus pneumoniae* because antibodies in adult plasma may exacerbate the disease. *Testing of relatives at risk:* While it is appropriate to offer molecular genetic testing to at-risk family members of patients in whom disease-associated mutations have been identified, predictive testing based on a predisposing factor (as opposed to a causative mutation) is problematic as it is one of only several risk factors required for disease causation. *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* mutations but not in those with *CFH*, *CFI*, or *CFB* mutations; however, simultaneous kidney and liver transplantation in young children with aHUS and *CFH* mutations may correct the genetic defect and prevent disease recurrence.

Genetic counseling. Predisposition to atypical HUS (aHUS) is inherited in an autosomal recessive or autosomal dominant manner with incomplete penetrance. Rarely digenic inheritance and uniparental isodisomy occur. Autosomal recessive inheritance: Heterozygotes (carriers) are usually asymptomatic; however, rarely carriers have developed aHUS in adulthood. At conception, each sib of an individual with autosomal recessive aHUS has a 25% chance of inheriting two disease-causing mutations, a 50% chance of inheriting one mutation and being a carrier, and a 25% chance of inheriting neither mutation. Autosomal dominant inheritance: Some individuals diagnosed with autosomal dominant aHUS have an affected parent or an affected close relative, but in the majority the family history is negative because of reduced penetrance of the disease-causing mutation in an asymptomatic parent, early death of a parent, late onset in a parent (or close relative), or a *de novo* mutation in the proband. Each child of an individual with autosomal dominant aHUS has a 50% chance of inheriting the mutation. In both genetic types, clinical severity and disease phenotype often differ among individuals with the same mutations; thus, age of onset and/or disease progression and outcome cannot be predicted.

Diagnosis

Clinical Diagnosis

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.

Typical (acquired) HUS is triggered by infectious agents such as strains of *E. coli* (Stx-*E. coli*) that produce powerful Shiga-like exotoxins and manifests with diarrhea (D^+HUS), often bloody. However, approximately 25% of children with typical HUS do not have diarrhea. Typical HUS may subside when the underlying condition has been treated or removed. Typical HUS is not known to be associated with any genetic predisposition.

Atypical HUS (aHUS) can be genetic, acquired, or idiopathic (of unknown cause). Individuals with aHUS frequently relapse even after complete recovery from the presenting episode; thus, aHUS is sometimes referred to as recurrent or relapsing HUS. Relapsing HUS is more likely to be genetic. The final outcome of aHUS is usually death or permanent renal or neurologic impairment.

Atypical HUS is considered genetic in the following situations:

- Two or more members of the same family are affected by the disease at least six months apart and exposure to a common triggering infectious agent has been excluded;
  or
- A disease-causing mutation(s) is identified in one of the four genes known to be associated with aHUS, irrespective of familial history.

Genetic atypical HUS can be multiplex (i.e., familial; two or more affected family members) or simplex (i.e., a single occurrence in a family).

Atypical HUS is considered acquired when an underlying environmental factor such as drugs, systemic disease, viral agents, or bacterial agents that do not result in Shiga-like exotoxins (Stx) can be identified.

Atypical HUS is considered idiopathic when no trigger (genetic or environmental) is evident.

Testing

Laboratory testing

Typical and atypical HUS. The following are laboratory hallmarks of both typical HUS and atypical HUS:

- **Thrombocytopenia** that is usually severe
  - Platelet count should be less than 150,000/mm^3 to establish the diagnosis. In most cases, platelet counts are below 60,000/mm^3.
  - Platelet survival time is reduced, reflecting enhanced platelet disruption in the circulation.
  - Giant platelets may be seen in the peripheral smear, a finding consistent with secondary activation of thrombocytopoiesis.
- **Microangiopathic hemolytic anemia** that is usually severe
  - Hemoglobin concentrations less than 10 mg/dL are reported in 99% of cases and less than 6.5 mg/dL in 40% of cases.
  - Serum lactate dehydrogenase (LDH) concentrations are increased (>460 U/L), often at very high levels, reflecting not only hemolysis, but also diffuse tissue ischemia.
  - Hyperbilirubinemia (mainly unconjugated), reticulocytosis, circulating free hemoglobin, and low or undetectable haptoglobin concentrations are additional nonspecific indicators of accelerated red cell disruption and production.
  - Detection of fragmented red blood cells (schistocytes) with the typical aspect of burr or helmet cells in the peripheral smear together with a negative Coombs test (with the exception of *Streptococcus pneumoniae*-associated HUS) are needed to confirm the microangiopathic nature of the hemolysis.
- **Acute renal insufficiency**
  - Serum concentration of creatinine greater than 97th centile for age
  - Serum concentration of urea (BUN) greater than 97th centile for age

Typical HUS. The following are characteristic findings **during acute illness** in typical but not in atypical HUS:

- 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 LPS (lipopolysaccharides) (O157, O26, O103, O111, and O145, by ELISA).

The detection of free fecal STEC (Shiga toxin-producing *E. coli*) can be made by commercial immunoassays and requires only a few hours [Gianviti et al 2003].

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

Complement studies

- Serum C3 and C4 concentrations can be used to monitor complement activation or disregulation; however, these markers are not disease specific.
- CFH, CFI, and CFB serum concentrations should also be evaluated as they may give an indication of the underlying genetic background.

Renal histology (typical and atypical HUS). The common microvascular lesions of HUS consist of vessel (capillary and arteriole) wall thickening with endothelial swelling, which allows accumulation of proteins and cell debris in the subendothelial layer, creating a space between endothelial cells and the underlying basement membrane of affected microvessels. Both the widening of the subendothelial space and intraluminal platelet thrombi lead to a partial or complete obstruction of the vessel lumen. The partial occlusion of the lumen probably disrupts erythrocytes by

mechanical trauma, which explains the hemolysis and presence of fragmented and distorted erythrocytes in the blood smear.

In D^+HUS the glomeruli are large; the capillaries are distended by red cells and platelet fibrin thrombi that may extend proximally into the afferent arteriole, suggesting that the thrombus is initiated in the glomerular capillaries themselves. Arterial lesions and mesangial changes are not reported, even long after the initial episode of D^+HUS [Taylor et al 2004].

In D^-HUS glomerular thrombosis, intracapillary foamy cells, endocapillary swelling, endocapillary hypercellularity, mesangiolysis, and doubled basement membranes are observed. Arterioles have thrombosis, endothelial swelling, or fibrinoid necrosis. Arteries have intimal swelling with various amounts of hypercellularity and thrombosis [Taylor et al 2004].

Note: (1) In children younger than age two years the lesion is mainly confined to the glomerular tuft and is noted in an early phase of the disease. Glomerular capillary lumina are reduced or occluded. In patent glomerular capillaries packed with red blood cells and fibrin, thrombi occasionally are seen. (2) Examination of biopsies taken several months after disease onset shows that most glomeruli are normal; 20% eventually became sclerotic. (3) Arterial thrombosis does occur but is uncommon and appears to be a proximal extension of the glomerular lesion. (4) In the acute phase, tubular changes include foci of necrosis of proximal tubular cells and presence of red blood cells and eosinophilic casts in the lumina of distal tubules. Occasionally fragmented red blood cells can be detected in the distal tubular lumina. (5) In adults and older children, glomerular changes are different and more heterogeneous than in infants, and the classic pattern of thrombotic microangiopathy is less evident.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Genes. Evidence is emerging that 50%-60% of the atypical HUS (aHUS) is associated with genetically determined alterations of the complement system. Mutations have been found in the following genes:

- ***CFH*** (encoding complement factor H). Mutations in *CFH* account for 30% of aHUS.
- ***CD46****(MCP*) (encoding membrane cofactor protein). Mutations in *CD46* account for an estimated 12% of aHUS.
- ***CFI*** (encoding complement factor I). Mutations in *CFI* account for an estimated 5%-10% of aHUS.
- ***CFB*** (encoding complement factor B). Mutations in *CFB* have been reported in affected individuals from two Spanish families [Goicoechea de Jorge et al 2007].

Digenic inheritance. A few individuals have been described with variants in both *CFH* and *CD46* [Caprioli et al 2006, Richards et al 2007] and in both *CD46* and *CFI* [Caprioli et al 2006, Esparza-Gordillo et al 2006].

Uniparental disomy (UPD). In one child, complete paternal uniparental isodisomy of chromosome 1 resulted in severe deficiency of MCP expression. UPD was identified after homozygosity for a novel mutation (IVS10+2T>C) in the splice-donor of exon 10 was detected in an affected child and heterozygosity for the same mutation was found in her unaffected father, but not in her unaffected mother [Fremeaux-Bacchi et al 2007].

Gene conversion between *CFH* and *CFHL1*. A *CFH* mutant allele with two mutations in *cis*, p.[Ser1191Leu;Val1197Ala], has been occasionally reported in persons with aHUS. Gene conversion between *CFH* and *CFHL1* has been clearly demonstrated [Heinen et al 2006].

Clinical testing

- **Sequencing** of the entire coding regions, including all exons and adjacent intronic sequences of *CFH*, *CD46*, and *CFI*. Note: Although these tests are not routinely available around the world, they are of particular importance prior to transplantation [Bresin et al 2006] (see Management).
- **Deletion analysis** by multiplex ligation-dependent probe amplification (MLPA) for selected exons of *CFH*. A heterozygous hybrid allele derived from a crossing over between intron 21 of the gene *CFH* and intron 4 of the gene *CFHR1 (CFH*-related 1) was found in five persons with aHUS [Venables et al 2006]. The hybrid allele consists of the first 21 exons of *CFH* (encoding short consensus repeats [SCRs] 1-18 of *CFH*) and the last two exons of *CFHR1* (encoding SCR4 and SCR5 of *CFHR1*). The frequency of this heterozygous hybrid allele in aHUS is estimated to be approximately 6%.

  MLPA may be used to detect the hybrid *CFH/CFHR1* gene, as it is not detected by sequence analysis of *CFH*. Interestingly, the protein product of the hybrid *CFH/CFHR1* gene is identical to another *CFH* mutant allele with two mutations in *cis*, p.[Ser1191Leu;Val1197Ala], which arises by gene conversion between *CFH* and *CFHR1* and whose protein product lacks surface complement-regulatory activity.

- **Deletion/duplication analysis** of *CD46* and *CFI* genes is available clinically, but the mutation detection frequencies are unknown and may be quite low.
- **Sequencing** of the entire coding region of *CFB*, including all exons and adjacent intronic sequences of *CFB*. Two *CFB* mutations associated with aHUS have recently been reported. Both are gain-of-function mutations that result in either enhanced formation of C3bBb convertase or increased resistance to inactivation by complement regulators [Goicoechea de Jorge et al 2007].

Table 1 summarizes molecular genetic testing for this disorder.

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

Gene Symbol	Test Method	Mutations Detected	Proportion of aHUS Attributed to Mutations in This Gene	Mutation Detection Frequency by Gene and Test Method	Test Availability
CFH	Sequence analysis	Sequence variants [1]	30%	99% [2]	Clinical Testing
CFH/CFHR1 hybrid allele	Deletion analysis	*CFH/CFHR1* hybrid allele [3]	6%	100%	
	Sequence analysis	Sequence variants [1]	12%	99%	
CD46	Deletion/duplication analysis [4]	Deletion or duplication of partial or whole gene	Unknown [5]	Unknown [5]	Clinical Testing
CFI	Sequence analysis	Sequence variants [1]	5%-10%	99%	Clinical Testing
	Deletion/duplication analysis [4]	Deletion or duplication of partial or	Unknown [5]	Unknown [5]	

CFB	Sequence analysis	whole gene Sequence variants [1]	Unknown	99%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene and test method

1. Nonsense mutations, missense mutations, frameshift mutations, splicing mutations, small deletions or insertions.

2. Sequence analysis does not detect the *CFH/CFHR1* hybrid allele that accounts for approximately 6% of aHUS.

3. This hybrid allele, resulting from crossing over between intron 21 of *CFH* and intron 4 of *CFHR1*, consists of the first 21 exons of *CFH* and the last two exons of *CFHR1*. Deletion analysis detects the hybrid allele, which is not detected by sequence analysis of *CFH*.

4. Testing that identifies deletions/duplications not detectable by sequence analysis of genomic DNA; a variety of methods including quantitative PCR, real-time PCR, multiplex ligation dependent probe amplification (MLPA), and array CGH (see Testing) may be used.

5. No deletions or duplications involving either the *CD46* or *CFI* gene as causative of aHUS disorder have been reported. Therefore, the mutation detection rate is unknown and may be very low. However, newly available deletion/duplication testing methods may identify mutations in affected individuals who tested negative by sequence analysis.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis of genetic aHUS in a proband

- Molecular genetic testing of *CFH*, *CD46*, *CFI*, and *CFB* in all individuals in whom clinical evaluation and laboratory testing supports the diagnosis of aHUS, because no one laboratory test is correlated with the presence or absence of a mutation in one of the genes encoding a complement factor.
- CFH and CFI circulating concentration measurement by ELISA methods and evaluation of CD46 protein expression on peripheral blood leukocytes by FACS are recommended in all affected individuals.
- Search for CFH autoantibodies in individuals in whom no *CFH*, *CD46*, and *CFI* mutation is identified as CFH autoantibodies have only been found in individuals who do not have an identifiable mutation in one of the genes encoding a complement factor.
- **Testing strategy may need to consider reports of digenic inheritance.** Complete sequencing of *CFH*, *CD46*, and *CFI* should be performed on all affected individuals.

Prognostication. Molecular genetic testing is particularly important prior to transplantation [Bresin et al 2006] as individuals with mutations in *CFH* or *CFI* tend to have recurrence of aHUS after renal transplantation (see Management, Other).

Predictive testing for at-risk asymptomatic family members requires prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Dense deposit disease / membranoproliferative glomerulonephritis type II (DDD/MPGN II). *CFH* mutations have been described in DDD/MPGN II:

- Ault et al [1997] reported a Native American boy with two heterozygous mutations in *CFH*.
- In four persons with MPGN II, Dragon-Durey et al [2004] identified three different homozygous mutations.
- Among 22 persons with biopsy-proven MPGN II, Abrera-Abeleda et al [2006] found an association between four SNPs in *CFH* and three SNPs in *CFHR5*.

See also Differential Diagnosis.

Glomerulonephritis with isolated C3 deposits (glomerulonephritis C3). *CFH* and *CFI* mutations have been described in glomerulonephritis C3 [Servais et al 2007]:

- Two persons had heterozygous mutations in *CFH*.
- One person had a heterozygous mutation in *CFI*.

Age-related macular degeneration (AMD). *CFH* normal variants have been described in association with AMD in different cohorts [Thakkinstian et al 2006].

Clinical Description

Natural History

Atypical HUS (aHUS) comprises genetic aHUS, acquired (sporadic) aHUS, and idiopathic (of unknown cause) aHUS.

Onset of atypical HUS ranges from prenatal to adulthood [Constantinescu et al 2004, Taylor et al 2004, Sellier-Leclerc et al 2007].

Collectively, aHUS is associated with poor outcome. Fifty percent of acquired aHUS and 60% of genetic aHUS progresses to ESRD [Ruggenenti et al 2001, Caprioli et al 2003, Caprioli et al 2006].

Genetic (multiplex and simplex) atypical HUS

Currently, genetic atypical HUS accounts for an estimated 50%-60% of all aHUS. Note: The remaining 40% may also be genetic; the causative genes have simply not yet been identified.

Genetic atypical HUS frequently relapses even after complete recovery following the presenting episode [Ruggenenti et al 2001, Taylor et al 2004], with death or permanent neurologic or renal sequelae being the final outcome in the majority of cases.

It is likely that *CFH*, *CD46*, and *CFI* mutations confer a predisposition to develop aHUS, rather than directly causing the disease, and that a second mutational event in the remaining normal allele is required for full-blown manifestation of the disease. Conditions that trigger complement activation either directly (bacterial and viral infections or sepsis) or indirectly by causing endothelial insult (drugs, certain systemic diseases) may precipitate an acute event in those with the predisposing genetic background [Caprioli et al 2006].

Multiplex aHUS (i.e., more than one affected individual in the family) accounts for approximately 10% of all aHUS. Both autosomal dominant and autosomal recessive forms of aHUS have been noted.

- In autosomal recessive aHUS the onset is usually early in childhood. The prognosis is poor, with a mortality rate of 60%-70%. Episodes of aHUS recur frequently.

- In autosomal dominant aHUS the onset is usually in adulthood. The prognosis is poor, with a cumulative incidence of death or ESRD of 50%-90%.

Sporadic (acquired) aHUS

Triggers for acquired aHUS include non-enteric bacterial infections, viruses, drugs, malignancies, transplantation, pregnancy, and other underlying medical conditions (scleroderma, anti-phospholipid syndrome, systemic lupus erythematosis). Triggering agents for acquired (sporadic) aHUS differ from those of typical HUS (see Differential Diagnosis, Distinguishing typical HUS from atypical HUS):

- **Infection** caused by *Streptococcus pneumoniae* accounts for 40% of aHUS and 5% of all causes of HUS in children in US. Neuroaminidase produced by *Streptococcus pneumoniae*, by removing sialic acids from the cell membranes, exposes Thomsen-Friedenreich antigen to preformed circulating IgM antibodies, which bind to this neoantigen on platelet and endothelial cells and cause platelet aggregation and endothelial damage. The clinical picture is usually severe, with respiratory distress, neurologic involvement, and coma; the mortality rate is 12.3% [Copelovitch & Kaplan 2008].
- **Drugs** that have been most frequently reported to induce aHUS include the following [Dlott et al 2004]:
    - Anti-cancer molecules (mitomycin, cisplatin, bleomycin, gemcitabine). The risk of developing aHUS after mitomycin is 2%-10%. The onset is delayed, occurring almost one year after starting treatment. The prognosis is poor, with up to 75% mortality at four months [Dlott et al 2004].
    - Immunotherapeutic agents (cyclosporine, tacrolimus, OKT3, interferon, and quinidine)
    - Antiplatelet agents (ticlopidine, clopidogrel)
    - A variety of common medications, including oral contraceptives and anti-inflammatory agents
- **Cancer-associated** aHUS complicates almost 6% of cases of metastatic carcinoma. Gastric cancer alone accounts for approximately half of such cases.
- **Post-transplantation** aHUS is being reported with increasing frequency [Ruggenenti et al 2001]. It may occur for the first time in individuals who have not experienced aHUS before (*de novo* post-transplantation aHUS) or may affect those whose primary cause of ESRD was aHUS (recurrent post-transplantation aHUS; see Management, Other). *De novo* post-transplantation aHUS may occur in individuals receiving renal transplants and other organs because of the use of calcineurin inhibitors or because of humoral (C4b-positive) rejection. Post-transplantation aHUS occurs in 5%-15% of renal transplantation patients receiving cyclosporine and in approximately 1% of those receiving tacrolimus.
- **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.
- **Post-partum** aHUS usually manifests in women within three months of delivery. The outcome is usually poor with 50%-60% mortality; residual renal dysfunction and hypertension are the rule in those who survive the acute episode.
- **Underlying medical conditions.** Autoimmune disease is one of the underlying medical conditions; autoantibodies to CFH are present in an estimated 6%-10% of individuals [Dragon-Durey et al 2005, Jozsi et al 2007].
  An ELISA assay uses purified human factor H-coated platelets to capture anti- *CFH* antibodies.

Genotype-Phenotype Correlations

The phenotype of aHUS is variable ranging from mild forms, with complete recovery of renal function, to severe forms, with end-stage renal failure (ESRD) or death being the final outcome [Noris & Remuzzi 2005]. Although genotype-phenotype correlations are not always straightforward, analysis of published reports [Caprioli et al 2003, Neumann et al 2003, Noris & Remuzzi 2005, Caprioli et al 2006, Sellier-Leclerc et al 2007] reveals that the course and outcome of the disease are influenced by the gene involved.

CFH. Atypical HUS associated with *CFH* mutations presents early in childhood in approximately 70% of cases and in adulthood in approximately 30% of cases. Irrespective of the pattern of inheritance and location of the mutations, the clinical course is characterized by a high rate of relapse and a 60%-80% rate death or ESRD following the presenting episode or as a consequence of relapse.

CD46. Atypical HUS associated with *CD46* mutations presents mostly in childhood; the acute episode is in general milder than that associated with *CFH* mutations. Eighty percent of affected individuals experience complete remission. Recurrences are frequent but have little effect on long-term outcome; an estimated 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.

CFI. Atypical HUS associated with *CFI* mutations is variable in phenotype. The onset is in childhood in 50% of affected individuals. Fifty-eight percent develop ESRD over the long term.

CFB. Atypical HUS associated with *CFB* mutations is poorly understood, as few affected individuals with *CFB* mutations have been reported.

Digenic inheritance

CFH* and *CD46* or *CD46* and *CFI. A few individuals have been identified with variants in both *CFH* and *CD46* [Caprioli et al 2006, Richards et al 2007] and in both *CD46* and *CFI* [Caprioli et al 2006, Esparza-Gordillo et al 2006] indicating that *CFH*, *CD46*, and *CFI* genetic variants could have an additive effect in determining the aHUS phenotype, since the proteins encoded by *CFH*, *CD46*, and *CFI* interact with each other to control complement activation on host cells.

Moreover, a number of common polymorphic variants described in the RCA (regulator of complement activation) cluster (see Molecular Genetic Pathogenesis) may predispose to aHUS both in individuals with *CFH/CD46/CFI* mutations and in those without identifiable mutations [Caprioli et al 2003, Esparza-Gordillo et al 2005, FH aHUS Mutation Database].

Genotype-phenotype correlations could potentially optimize treatment (see Management, Other).

Penetrance

The incomplete penetrance of HUS often found in those with *CFH* and *CD46* mutations indicates that such mutations confer a predisposition to develop aHUS, rather than directly causing the syndrome and that multiple genetic and/or environmental hits are required for full-blown disease manifestation.

CFH. A substantial number of individuals with *CFH* mutations never develop aHUS. Overall the penetrance of the disease in those with *CFH* mutations is 59%. Conditions that trigger complement activation, either directly (bacterial and viral infections) or indirectly by causing endothelial insult (drugs, systemic diseases, pregnancy), precipitate the acute event in approximately 60% of those with *CFH* mutations [Caprioli et al 2006]. The reasoning is that in these individuals suboptimal *CFH* activity is sufficient to protect the host from the effects of complement activation in physiologic conditions; however, suboptimal *CFH* activity is not sufficient to prevent C3b from being deposited on vascular endothelial cells when exposure to an agent that activates complement results in production of higher than normal amounts of C3b.

CD46. For those with *CD46* mutations penetrance is 54% [Caprioli et al 2006].

Nomenclature

Typical HUS is also referred to as Shiga-like toxin associated HUS (Stx-HUS) and D^+HUS (diarrhea-positive HUS), although 25% of cases do not manifest diarrhea. Thus, at a minimum a search for free-fecal Shiga toxin (by commercial immunoassays) is recommended even in D^-HUS.

Atypical HUS (aHUS) is also referred to as non-Shiga-like toxin-associated HUS (non-Stx-HUS) and D^-HUS (diarrhea-negative HUS). However, the term diarrhea-negative HUS to refer to aHUS is not completley accurate, as 25% of typical HUS does not manifest diarrhea.

Prevalence

Atypical HUS is less common than typical HUS and accounts for only 5%-10% of individuals presenting with findings of HUS [Ruggenenti et al 2001].

According to a recent US study the incidence of aHUS in children is approximately one tenth that of typical HUS, corresponding to an estimated annual incidence of 2:1,000,000 population.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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

Typical HUS triggered by Stx-*E. coli* manifests with a prodrome of diarrhea (D^+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 LPS (O157, O26, O103, O111, and O145, by ELISA) distinguishes typical HUS (D^+HUS or D^- Stx^+HUS) from aHUS (D^-Stx^-HUS).

In its most common presentation, typical HUS manifests as an acute disease and 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) [Ruggenenti et al 2001].

Typical HUS usually subsides when the underlying condition is treated or removed.

Distinguishing atypical HUS from thrombotic thrombocytopenic purpura (TTP). Atypical HUS and TTP 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, probably reflecting the systemic nature of the underlying defect. 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, a plasma metalloprotease that cleaves von Willebrand factor (VWF) multimers soon after their secretion by endothelial cells. ADAMTS13 deficiency can be constitutive, as a result of homozygous or compound heterozygous mutations in the gene *ADAMTS13*, or acquired, as a result of the presence of an inhibitory antibody. Evaluation of ADAMTS13 activity in serum or plasma is performed by several specialized laboratories using different tests based on the capability of the protease to cleave standard VWF multimers in vitro. One such test is the collagen binding assay. In large clinical studies, deficiency of ADAMTS13 activity was found in individuals with TTP but not in those with either typical or atypical HUS [Galbusera et al 2006]. This observation generated the hypothesis that TTP is caused by a deficiency of ADAMTS13 activity, whereas atypical HUS is unrelated to ADAMTS13 defects.

The exception to the above hypothesis occurs when *ADAMTS13* and *CFH* mutations are observed in the same individual.

- In a recent report of two sisters with thrombotic microangiopathy, one presented with neurologic symptoms only and the other with superimposed severe renal impairment [Noris et al 2005]. Both sisters had complete ADAMTS13 deficiency resulting from two heterozygous *ADAMTS13* mutations; however, the sister who developed chronic renal failure also had a heterozygous *CFH* mutation that was not present in her sister, who had neurologic symptoms only. Thus, it was hypothesized that *CFH* haploinsufficiency had a role in

determining the renal complications superimposed on the systemic disease caused by ADAMTS13 deficiency.

- Other affected individuals with both *ADAMTS13* and *CFH* mutations have been reported by a French group [Zimmerhackl et al 2007].

Distinguishing aHUS from dense deposit disease / membranoproliferative glomerulonephritis type II (DDD/MPGN II). DDD/MPGN II typically occurs in children age five to 15 years who present with one of the following: hematuria, proteinuria, hematuria and proteinuria, acute nephritic syndrome, or nephrotic syndrome. DDD/MPGN II is associated with alternative pathway complement activation usually caused by C3 nephritic factors, IgG autoantibodies that stabilize the alternative C3 convertase (C3bBb). Diagnosis of DDD/MPGN II requires electron microscopy and immunofluorescence studies of a renal biopsy [Walker et al 2007]. Electron microscopy demonstrates dense transformation of the glomerular basement membrane (GBM) that occurs in a segmental, discontinuous, or diffuse pattern in the lamina densa. The precise composition of these altered areas remains unknown. Immunofluorescence should be positive for C3, usually in the absence of immunoglobulin deposition.

Spontaneous remissions are uncommon in DDD/MPGN II. Approximately half of affected individuals develop ESRD within ten years of diagnosis. Other findings can include visual impairment late in the disease, acquired partial lipodystrophy, and other autoimmune diseases including diabetes mellitus type 1 and celiac disease. Mutations in *CFH*, *FHR5*, *C3*, and *LMNA* have been implicated in the pathogenesis of DDD/MPGN II.

DDD/MPGN II has been reported in individuals with CFH deficiency. In contrast to individuals with aHUS, persons with DDD/MPGN II generally have homozygous or compound heterozygous *CFH* mutations that cause severely reduced CFH levels [Dragon-Durey et al 2004]. However, the rare cases of aHUS associated with homozygous mutations in *CFH* and very low levels of circulating protein can blur the distinction between HUS and DDD/MPGN. Furthermore, this overlap in phenotypes is evident in those few individuals who have a mixed diagnosis of aHUS and DDD/MPGN in the same biopsy or in biopsies taken at different points in time [Bresin et al 2007].

Distinguishing aHUS from cobalamin C (cblC) disease. Cobalamin C (cblC), caused by mutations in *MMACHC*, is characterized by abnormal vitamin B12 metabolism, manifest as metabolic acidosis, methylmalonic aciduria, homocystinuria, hematologic abnormalities, and, on occasion, aHUS [Geraghty et al 1992, Van Hove et al 2002]. Inheritance is autosomal recessive [OMIM 277400].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with atypical hemolytic-uremic syndrome (aHUS), the following evaluations are recommended:

- Renal function
  - Creatinine clearance (i.e., glomerular filtration rate [GFR])
  - Serum concentration of creatinine
  - Urinalysis
- Hematologic status
  - Platelet count
  - Erythrocyte count
  - Search for schistocytes in the blood smear
  - Leukocyte count
- Other
  - Serum LDH concentration
  - Haptoglobin
  - Serum C3 and C4 concentrations
- Molecular genetic testing of *CFH*, *CD46*, and *CFI*
- Measure serum concentrations of CFH and CFI
- Assessment of CD46 expression on leukocytes
- Testing for CFH autoantibodies in individuals in whom no *CFH*, *CD46*, and *CFI* mutations have been identified

Treatment of Manifestations

Plasma infusion or exchange. The mortality rate for aHUS dropped from 50% to 25% after plasma manipulation (plasma infusion or exchange) was introduced [Lara et al 1999]. A consistent number of patients with aHUS respond to plasma treatment [Lara et al 1999, Caprioli et al 2006]. Debate continues as to whether plasma infusion and/or plasma exchange is effective in the treatment of acute episodes.

It has been proposed that plasma exchange is more effective than plasma infusion because it removes potentially toxic substances from the blood; the efficacy of plasma exchange was shown in one study to be superior to that of plasma infusion [Ruggenenti et al 2001]. However, patients treated with plasma exchange were given larger amounts of plasma than those treated with plasma infusion alone; when equivalent volumes of plasma were given, the two treatments appeared to be equally effective. In situations (e.g., renal insufficiency, heart failure) that limit the amount of plasma that can be provided with infusion alone, plasma exchange should be considered the therapy of choice [Ruggenenti et al 2001].

In plasma exchange, usually one plasma volume (40 mL/kg) is exchanged per session. 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 patients with refractory disease in order to minimize the recycling of infused plasma.

Plasma infusion is the first-line therapy when plasma exchange is 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 whether 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 after treatment discontinuation in 29%-82% of patients. Thus, many cycles of stopping and resuming plasma therapy may be required.

Plasma infusion or exchange has been used in patients with aHUS caused by *CFH* mutations with the rationale of providing normal CFH to compensate for the genetic deficiency (see Genotype-Phenotype Correlations).

Plasma infusion or plasma exchange was used to treat acute episodes in patients with *CD46 (MCP)* mutations; however, remission generally occurred in both plasma-treated episodes and non-treated episodes, suggesting that plasma infusion or exchange does not have a great impact on the outcome of aHUS in persons with *CD46* mutations [Caprioli et al 2006]. These findings can be explained with the reasoning that the protein encoded by *CD46* is membrane-bound and theoretically plasma infusion or exchange would not correct the defect.

Bilateral nephrectomy has been performed in a small number of rare 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); follow-up has been excellent in some patients [Remuzzi et al 1996].

Surveillance

Individual with known aHUS. Measure serum concentration of hemoglobin, platelet count, and serum concentrations of creatinine, LDH, C3, and 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 patients with normal renal function or chronic renal insufficiency as they are at risk for relapse (Patients with ESRD usually do not relapse.)
- Every two weeks for those rare individuals with homozygous *CFH* mutations 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 (based on the Authors' experience); each center may follow different guidelines, deriving from their own experience.

At-risk relative of an individual with aHUS

- Offer molecular genetic testing to at-risk family members of patients in whom disease-associated mutations have been identified.
    - For relatives who are mutation-positive (i.e., have the family-specific mutation), monitoring of hemoglobin, platelet count, and serum concentrations of creatinine, LDH, C3 and C4, and haptoglobin) when exposed to potential triggering events such as severe infections, inflammation, and pregnancy.
    - For relatives who are mutation-negative (i.e., do not have the family-specific mutation), no monitoring is needed.
- For family members of patients in whom disease-associated mutations have NOT been identified, no monitoring is needed.

Agents/Circumstances to Avoid

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

Individual with known aHUS. An individual with known aHUS should avoid if possible the following known precipitants of aHUS, especially any that are known to have triggered aHUS (see Clinical Description, Sporadic (acquired) aHUS).

- **Drugs**
    - Some anti-cancer molecules, including mitomycin C, cisplatin, daunorubimicin, cytosine arabinoside
    - Immunotherapeutic agents, including cyclosporin and tacrolimus
    - Antiplatelet agents, including ticlopidine and clopidogrel
    - Some common medications such as oral contraceptives, anti-inflammatory agents
- **Pregnancy**

Unaffected mutation-positive relatives of an individual with aHUS should avoid known precipitants of aHUS (see Clinical Description, Sporadic (acquired) aHUS (acquired) aHUS).

Testing of Relatives at Risk

Molecular genetic testing should be offered to at-risk family members of patients in whom disease-associated mutations have been identified.

Note: Testing for predisposing mutations is a challenging issue. The problem with predictive testing based on a predisposing factor (as opposed to a causative mutation) is that it is one of only several risk factors required for disease causation. Predictions based on a single risk factor in unaffected individuals are unreliable. From currently available data, the penetrance of disease for all mutations is approximately 50%. The degree of penetrance is thought to be determined by: (1) common polymorphic variants of *CFH* and *CD46* [Caprioli et al 2003] (2) risk haplotypes in RCA (see Molecular Genetic Pathogenesis) cluster [Esparza-Gordillo et al 2005] and (3) exposure to environmental triggers (e.g., infection and drugs); therefore, the risk cannot be quantified for a given individual.

For relatives who are mutation-positive (i.e., who have the family-specific mutation), the following are appropriate:

- Monitoring when exposed to potential triggering events such as severe infections, inflammation, and pregnancy (see Surveillance)
- Avoiding known precipitants of aHUS (see Clinical Description, Sporadic (acquired) aHUS)

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

Therapies Under Investigation

Research efforts are aimed at identifying more specific approaches that may interfere with the primary cause of microangiopathy in the different forms of aHUS.

- For aHUS associated with *CFH* mutations, specific replacement therapies with recombinant CFH could become a viable alternative to plasma treatment. Efforts are also ongoing to isolate plasma fractions enriched in CFH that could provide the patient with sufficient active molecules while minimizing the risk of allergy and fluid overload associated with standard plasma infusion therapy.
- The discovery of mutations in three different complement-regulatory genes provides sufficient evidence to undertake clinical trials using complement inhibitors that block the activation of C3 [Kirschfink 2001]. Studies on other complement-regulatory genes would help to fully clarify the molecular determinants underlying the pathogenesis of aHUS and potentially improve management and therapy.

Advances in vector safety and transfection efficiency may eventually make gene therapy a realistic option.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Patients with *Streptococcus pneumoniae*-induced aHUS. Fresh frozen plasma should be avoided (i.e., plasma therapy is contraindicated) in patients with aHUS induced by *Streptococcus pneumoniae* because adult plasma 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].

Plasma-resistant/plasma-dependent patients. Some patients 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 induces remission in some plasma-resistant cases, but is ineffective and actually increased 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-resistant and plasma-dependent patients with no consistent benefit [Ruggenenti et al 2001].

Renal transplantation is not necessarily an option for aHUS in contrast to typical HUS. An estimated 50% of individuals with aHUS who underwent renal transplantation had a recurrence of the disease in the grafted organ [Artz et al 2003]. Recurrences occur at a median time of 30 days after transplantation (range 0 days to 16 years). There is no effective treatment of recurrences and cases reported so far invariably ended with loss of the kidney [Ruggenenti et al 2001, Artz et al 2003].

Precipitation of aHUS in renal donors. Renal transplantation for individuals with aHUS from a live related donor has been shown to precipitate disease onset in the healthy donor relative in two families [Donne et al 2002]. Subsequent molecular genetic testing revealed that one of the donors had a *CFH* mutation that put him at risk for aHUS. Thus, molecular genetic testing should be particularly recommended before live related donation to avoid the risk of triggering disease in the donors.

Influence of genotype in determining treatment. Genetic characterization of patients has the potential to optimize the treatment of aHUS:

- **Plasma therapy**
  CFH. Plasma infusion or exchange has been used in patients with aHUS and *CFH* mutations with the rationale of providing normal CFH to compensate for the genetic deficiency. In published studies, some patients with *CFH* mutations did not respond at all 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 a patient with a *CFH* mutation, by three months of weekly plasma exchange in conjunction with intravenous immunoglobulins. One year after discontinuation of plasma therapy, the patient remained disease free and dialysis independent. In the authors' series [Caprioli et al 2006] and unpublished data, approximately 50% of patients with *CFH* mutations treated with plasma underwent either complete or partial remission (hematologic normalization with renal sequelae). However, the remaining patients did not respond at all to plasma and 20% died during the acute episode.

Similar results were observed in patients with *CFI* mutations [Caprioli et al 2006]. Theoretically one should expect a good response to plasma therapy in patients with *CFH* and *CFI* mutations because CFH and CFI are circulating proteins; 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].

CD46. The rationale for using plasma in patients with *CD46* mutations 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 [Richards et al 2003, Caprioli et al 2006] indicate that the majority (70%-80%) of patients undergo remission following plasma infusion or exchange; however, complete recovery from the acute episode was also observed in 70%-80% of patients not treated with plasma. The decision whether or not to treat with plasma should be based on the clinical severity of the acute episode.

- **Kidney transplantation.** Whether kidney transplantation is an appropriate treatment in patients with aHUS who have progressed to ESRD is debatable. An estimated 50% of patients who undergo renal transplantation have a recurrence of the disease in the grafted organ [Noris & Remuzzi 2005]. Molecular genetic tests could help to define graft prognosis; thus, all patients should undergo such testing prior to transplantation.

  CFH. In patients with *CFH* mutations the graft outcome is poor. Recurrence rate ranges from 30% to 100% (depending on the survey) and is significantly higher than in patients without *CFH* mutations [Neumann et al 2003, Noris & Remuzzi 2005, Bresin et al 2006]. As CFH is mainly produced by the liver, kidney transplantation will not correct the *CFH* genetic defect in these patients.

  Simultaneous kidney and liver transplantation has been performed in two young children with aHUS and *CFH* mutations with the objective of correcting the genetic defect and preventing disease recurrence [Noris & Remuzzi 2005]. However, both cases treated with this procedure were complicated by premature irreversible liver failure. The first patient recovered after a second uneventful liver transplantation. The child, who before transplantation had monthly recurrences before transplantation, has had no symptoms of aHUS for more than two years' follow-up. The second case had a fatal, primary nonfunction of the liver graft followed by multi-organ failure and death.

  In two other patients with *CFH* mutations with combined kidney and liver transplantation [Saland et al 2006], good renal and liver function were recorded at two-year follow-up. In those two cases extensive plasma exchange was given prior to surgery to provide enough normal CFH to prevent liver graft damage.

  CFI* and *CFB. As CFI and CFB are plasma proteins, one could speculate that aHUS recurrence may take place in the transplanted kidney, resulting in graft failure. The few data available support this hypothesis as graft failures secondary to recurrences occurred in 15 of 18 patients with *CFI* mutations and in one patient with a *CFB* mutation.

  CD46. Kidney graft outcome is favorable in patients with *CD46* mutations; four patients have been successfully transplanted with no disease recurrence [Noris & Remuzzi 2005]. The strong theoretical rationale is that because the CD46 protein (MCP) is a transmembrane protein highly expressed in the kidney, transplantation of a kidney expressing normal MCP corrects the defect.

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Predisposition to atypical HUS (aHUS) is inherited in an autosomal recessive manner or in an autosomal dominant manner with incomplete penetrance [Caprioli et al 2006].

Rare digenic inheritance occurs [Esparza-Gordillo et al 2006] and one case of uniparental isodisomy has been reported [Fremeaux-Bacchi et al 2007].

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of a child with autosomal recessive aHUS are obligate heterozygotes and therefore carry a single copy of a disease-causing mutation.
- Heterozygotes (carriers) are usually asymptomatic. Rare cases of carriers who have developed aHUS in adulthood have also been reported [Caprioli et al 2006].

Sibs of a proband

- At conception, each sib of an individual with autosomal recessive aHUS has a 25% chance of inheriting two disease-causing mutations, a 50% chance of inheriting one mutation and being a carrier, and a 25% chance of inheriting neither mutation.
- Heterozygotes (carriers) are usually asymptomatic.
- Clinical severity and disease phenotype often differ among individuals with the same mutations; thus, age of onset and/or disease progression and outcome cannot be predicted.

Offspring of a proband. The offspring of an individual with autosomal recessive aHUS are obligate heterozygotes (carriers) for a disease-causing mutation and will likely be asymptomatic.

Note: Because individuals known to be homozygous have not yet reached reproductive age, whether offspring of these individuals will be affected is currently unknown.

Carrier Detection

Carrier testing for family members at risk for autosomal recessive aHUS is available on a clinical basis once the disease-causing mutations have been identified in the proband.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Some individuals diagnosed with autosomal dominant aHUS have an affected parent or other close relative, but the majority of cases are simplex (i.e., a single occurrence in a family).

- In simplex forms of aHUS the *CFH* mutation was either inherited from a healthy parent or, more rarely (only 4 cases reported) occurred as a *de novo* mutation in the proband [Perez-Caballero et al 2001, Neumann et al 2003].
- Family history may be negative because of reduced penetrance of the disease-causing mutation in an asymptomatic parent, early death of a parent, late onset in a parent (or close relative), or a *de novo* mutation in the proband.
- If both parents are unaffected and a disease-causing mutation is identified in the proband, molecular genetic testing should be offered to both parents. If a disease-causing mutation is identified in a parent, the parent is at risk of developing aHUS and of transmitting the disease-causing mutation to other offspring.
- Clinical severity and disease phenotype often differ among individuals with the same mutations; thus, age of onset and/or disease progression and outcome cannot be predicted.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the parents.
- If a parent of the proband is affected, has a positive family history, or is found to have a disease-causing mutation, the risk to the sibs of inheriting the mutation is 50%.
- Clinical severity and disease phenotype often differ among individuals with the same mutations; thus, age of onset and/or disease progression and outcome cannot be predicted.
- If the disease-causing mutation found in the proband cannot be detected in DNA extracted from the leukocytes of either parent, the risk to the sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband

- Each child of an individual with autosomal dominant aHUS has a 50% chance of inheriting the mutation.
- Clinical severity and disease phenotype often differ among individuals with the same mutations; thus, age of onset and/or disease progression and outcome cannot be predicted.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is found to be affected or is a carrier of a disease-causing mutation, his or her family members may be at risk and molecular genetic testing should be offered.

Risk to Family Members — Digenic Inheritance

Digenic aHUS is caused by the simultaneous presence of one mutation in each of two complement-regulatory genes. Individuals with mutations in *CFH* and *CD46* [Caprioli et al 2006, Richards et al 2007] and individuals with mutations in *CD46* and *CFI* [Caprioli et al 2006, Esparza-Gordillo et al 2006] have been reported.

Parents of a proband

- The parents are obligate heterozygotes.
- Heterozygotes (carriers) are usually asymptomatic.

Sibs of a proband

- At conception, each sib has a 25% chance of inheriting both mutations, a 50% chance of inheriting one mutation and being a carrier, and a 25% chance of inheriting neither mutation.
- Heterozygotes (carriers) are usually asymptomatic.

Offspring of a proband. All offspring are obligate carriers of one of the mutations.

Other family members of a proband. Other family members may be at risk and molecular genetic testing should be offered.

Carrier Detection

Carrier testing for family members at risk for digenic aHUS is available on a clinical basis once the disease-causing mutations have been identified in the family.

Related Genetic Counseling Issues

See Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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 or at risk.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

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. Atypical Hemolytic-Uremic Syndrome: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific HGMD
CFH	1q32	Complement factor H	CFH
CD46	1q32	Membrane cofactor protein	CD46
CFI	4q25	Complement factor I	CFI
CFB	6p21.3	Complement factor B	CFB
THBD	20p11.2	Thrombomodulin	THBD

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click here.

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

120920 MEMBRANE COFACTOR PROTEIN; MCP
134370 COMPLEMENT FACTOR H; CFH
138470 COMPLEMENT FACTOR B; CFB
188040 THROMBOMODULIN; THBD
217030 COMPLEMENT FACTOR I; CFI

235400 HEMOLYTIC UREMIC SYNDROME, ATYPICAL, SUSCEPTIBILITY TO, 1; AHUS1

612926 HEMOLYTIC UREMIC SYNDROME, ATYPICAL, SUSCEPTIBILITY TO, 6; AHUS6

Molecular Genetic Pathogenesis

In 1998 Warwicker et al studied three families with aHUS and established linkage in the affected individuals to the regulator of complement activation (RCA) gene cluster on human chromosome 1q32, which encodes for several complement-regulatory proteins [Warwicker et al 1998].

Because an association between familial HUS and CFH abnormalities had been reported previously, the first examined candidate gene in this region was factor H *(CFH)*. CFH is a plasma glycoprotein that plays an important role in the regulation of the alternative pathway of complement. It serves as a cofactor for the C3b-cleaving enzyme, factor I (encoded by *CFI*) in the degradation of newly formed C3b molecules and controls decay, formation, and stability of the C3b convertase C3bBb. The CFH glycoprotein consists of 20 homologous short consensus repeats (SCRs). The complement-regulatory domains needed to prevent fluid phase alternative pathway amplification have been localized within the N-terminal SCR1-4 [Rodriguez de Cordoba et al 2004].

The inactivation of surface-bound C3b is dependent on the binding of the C-terminal domain of CFH protein to polyanionic molecules that increases CFH protein affinity for C3b and exposes its complement-regulatory N-terminal domain. The C-terminal domain contains two C3b-binding sites, located in SCR12-14 and SCR19-20, and three polyanion-binding sites, located in SCR7, SCR13, and SCR19-20 [Jozsi et al 2004]. However, the C3b- and the polyanion-binding sites located in SCR19-20 are required for CFH to inactivate surface-bound C3b, since deletion of this portion of the molecule renders CFH protein incapable of blocking complement activation on sheep erythrocytes.

Abnormalities in two additional genes encoding for complement-regulatory proteins have been recently involved in predisposition to aHUS. Two independent reports described mutations in *CD46*, encoding membrane cofactor protein (MCP), in affected individuals of four families [Noris et al 2003, Richards et al 2003]. MCP is a widely expressed transmembrane glycoprotein that serves as a cofactor for CFI protein to cleave C3b and C4b deposited on the host cell surface [Goodship et al 2004]. MCP has four extracellular N-terminal SCRs important for their inhibitory activity, followed by a serine-threonine-proline rich domain, a transmembrane domain, and a cytoplasmic tail. To date, 43 *CD46* mutations in aHUS have been reported, with a mutation frequency of 10%-15% [FH aHUS Mutation Database]. Evaluation of mutant protein expression and function showed either severely reduced protein expression on the cell surface or reduced C3b-binding capability and/or capacity to block complement activation [Caprioli et al 2006].

Twenty-four mutations in *CFI*, which encodes a plasma serine protease that cleaves and inactivates C3b and C4b, have been reported in individuals with aHUS, with a frequency of 5%-12% in different studies [Fremeaux-Bacchi et al 2004, Kavanagh et al 2005, Caprioli et al 2006]. All are heterozygous mutations, 80% cluster in the serine-protease domain and may either cause reduced protein secretion or result in mutant proteins with decreased cofactor activity. However, studies on the p.Gly261Asp mutation revealed no alteration of CFI serum concentration or functional defect in CFI [Nilsson et al 2007].

More recently, two gain-of-function mutations in the gene encoding complement factor B (CFB), a zymogen that carries the catalytic site of the complement alternative pathway convertase, have been found in two families from a Spanish HUS cohort [Goicoechea de Jorge et al 2007].

The protein product of a *CFH* familial mutation has complement-inhibitory activity, and similar to normal CFH protein, binds surface proteoglycans. Genetic variants of *CFHR5* that have been identified may play a secondary role in the pathogenesis of HUS [Monteferrante et al 2007].

Complete absence of both CFHR1 and CFHR3 proteins was detected in aHUS [Zipfel et al 2007]. CHR1/CFHR3 plasma deficiency may contribute to defective regulation of complement activation on cell and tissue surfaces.

CFH

Normal allelic variants. *CFH* is approximately 100 kb long. It comprises 23 exons.

Pathologic allelic variants. See Table 2.

Table 2. *CFH* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.3572C>T	p.Ser1191Leu	
c.3590T>C	p.Val1197Ala	NM_000186.2NP_000177.2
CFH/CFHR1 hybrid allele 1		

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

1. See Molecular Genetic Testing.

The list of published and unpublished mutations within *CFH* is continuously updated in the FH aHUS Mutation Database.

Since the first report by Warwicker et al [1998], a number of studies have been performed, describing more than 100 different *CFH* mutations in individuals with aHUS [Saunders et al 2006].

The vast majority of *CFH* mutations in aHUS are heterozygous and cause either single amino acid changes or premature translation terminations that primarily cluster in the C-terminus domains and are commonly associated with normal CFH protein plasma levels. A minority of the mutations result in the production of a truncated protein or impaired secretion of protein [Perez-Caballero et al 2001, Richards et al 2001, Caprioli et al 2006].

Normal gene product. Mainly synthesized by the liver, the complement factor H (CFH) protein is a 150-kd single-chain plasma glycoprotein and consists of 20 homologous structural domains called SCRs (short consensus repeats), each comprising approximately 60 amino acids.

Abnormal gene product. Expression and functional studies demonstrated that CFH proteins carrying HUS-associated mutations (deriving from point mutations, gene conversion, and a hybrid allele) have a severely reduced ability to interact with polyanions and with surface-bound C3b [Jozsi et al 2004], resulting in a lower density of mutant CFH molecules bound to endothelial cell surface and a diminished complement-regulatory activity on the cell membrane [Jozsi et al 2004]. In contrast these mutants have a normal capacity to control activation of the complement in plasma, as indicated by their retention of normal cofactor activity in the proteolysis of fluid-phase C3b.

The majority of *CFH* mutations are heterozygous and cluster in the exons that encode for the C-terminal portion of the protein. A minority of the mutations result in the production of a truncated protein or impaired secretion of protein [Perez-Caballero et al 2001, Richards et al 2001, Caprioli et al 2006].

See Molecular Genetic Pathogenesis.

CD46

Normal allelic variants. *CD46* is an estimated 43 kb long. It comprises 14 exons.

Pathologic allelic variants. The majority of *CD46* mutations are heterozygous and cluster in the exons encoding the four N-terminal extracellular short consensus repeats (SCRs).

The list of published and unpublished mutations within *CD46* is continuously updated in the FH aHUS Mutation Database.

Normal gene product. The *CD46* gene encodes the membrane cofactor protein (MCP), with is a widely expressed transmembrane glycoprotein composed of four extracellular SCRs followed by a serine-threonine-proline rich region, a transmembrane domain, and a cytoplasmatic tail.

Abnormal gene product. *CD46* mutations generally result in either reduced MCP expression or impaired C3b binding capability [Noris et al 2003, Richards et al 2003, Caprioli et al 2006]. See Molecular Genetic Pathogenesis.

CFI

Normal allelic variants. *CFI* is approximately 63 kb long. It comprises 13 exons.

Pathologic allelic variants. See Table 3. The majority of *CFI* mutations cluster in the exons that encode the serine-protease domain.

Table 3. ***CFI* Pathologic Allelic Variants Discussed in This *GeneReview***

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.782G>A	p.Gly261Asp	NM_000204.2NP_000195.2

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

The list of published and unpublished mutations within *CFI* is continuously updated in the FH aHUS Mutation Database.

Normal gene product. Mainly produced by the liver, complement factor I (CFI) protein is a 88-kd plasma serine-protease with a modular structure. It is a heterodimer and consists of a non-catalytic 50-kd heavy chain linked to a catalytic 38-kd light chain by a disulphide bond.

Abnormal gene product. Approximately 40% of the mutations result in partial CFI deficiency, the functional significance of the others remains to be determined [Fremeaux-Bacchi et al 2004, Caprioli et al 2006]. See Molecular Genetic Pathogenesis.

CFB

Normal allelic variants. *CFB* is an estimated 6 kb long. It comprises 18 exons.

Pathologic allelic variants. See Table 4.

Table 4. *CFB* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.858C>G	p.Phe286Leu	NM_001701.2NP_001701.2

c.967A>G p.Lys323Glu

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

Two heterozygous mutations in affected members of two Spanish pedigrees, resulting in c.858C>G and c.967A>G changes in *CFB* have been reported [Goicoechea de Jorge et al 2007].

Normal gene product. *CFB* encodes complement factor B, a 90-kd protein consisting of three domains: a three-module complement control protein, a von Willebrand factor A domain, and a C-terminal serine protease domain that adopts a default inactive (zymogen) conformation.

Abnormal gene product. In affected members of two Spanish pedigrees, two gain-of-function heterozygous mutations, p.Phe286Leu and p.Lys323Glu, were found to result in enhanced formation of the C3bBb convertase and increased resistance to inactivation by complement regulators, respectively [Goicoechea de Jorge et al 2007].

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Chapter Notes

Author Notes

Web site: http://www.marionegri.it/

Revision History

- 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 to live Web site
- 27 March 2007 (mn) Original submission