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C3 Glomerulopathy

Synonyms: C3G, Glomerulonephritis with Dominant C3

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Summary

Clinical characteristics

C3 glomerulopathy (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) 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. Spontaneous remission of C3G is uncommon, and about half of affected individuals develop end-stage renal disease (ESRD) within ten years of diagnosis, occasionally developing the late comorbidity of impaired visual acuity.

Diagnosis/testing

The definitive diagnosis of C3G requires a renal biopsy with specialized immunofluorescence and electron microscopy studies both for diagnosis and to distinguish between the two major subtypes of C3G: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). Some individuals will have biallelic or heterozygous pathogenic variants identified by molecular genetic testing 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*).

Management

Treatment of manifestations: Nonspecific therapies used to treat numerous chronic glomerular diseases, including angiotensin-converting enzyme inhibitors, angiotensin II type-1 receptor blockers, and lipid-lowering agents (in particular hydroxymethylglutaryl coenzyme A reductase inhibitors). Complement inhibition with a terminal pathway blocker may alter disease course in some individuals. When ESRD develops, treatment options are limited to dialysis or transplantation. C3G recurs in nearly all grafts and is the predominant cause of graft failure in 50%-90% of transplant recipients.

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Prevention of primary manifestations: Plasma replacement therapy in individuals with pathogenic variants in *CFH* may be effective in controlling complement activation and slowing progression of ESRD.

Surveillance: Close monitoring of renal function by a nephrologist with familiarity with the C3G disease spectrum, complete biannual assessment of the complement pathway, periodic eye examinations to evaluate the fundus.

Evaluation of relatives at risk: If the family history is positive for renal disease, evaluation of apparently asymptomatic at-risk relatives can include molecular genetic testing (if the pathogenic variants in the family are known), urinalysis, and comprehensive analysis of the complement system.

Genetic counseling

C3G is a complex genetic disorder that is rarely inherited in a simple mendelian fashion. Multiple affected persons within a single nuclear family are reported only occasionally, with both dominant and recessive inheritance being described.

Diagnosis

C3 glomerulopathy (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); it is rarely inherited in a simple mendelian fashion.

Suggestive Findings

C3G **should be suspected** in individuals of all ages who present with one of the following:

- Hematuria
- Proteinuria
- Hematuria and proteinuria
- Acute nephritic syndrome
- Nephrotic syndrome
- Persistent hypocomplementemia (low serum levels of complement component C3)

Establishing the Diagnosis

The diagnosis of C3G **is established** in a proband with typical findings on **renal biopsy**. Some individuals will have biallelic or heterozygous pathogenic variants identified by **molecular genetic testing** in one or more of the genes listed in Table 1.

Note: Identification of a pathogenic variant may help to direct treatment of the individual.

Renal biopsy. The definitive diagnosis of C3G requires a renal biopsy with specialized studies (see Figure 1) both for diagnosis and to distinguish between C3 glomerulonephritis (C3GN) and dense deposit disease (DDD).

- Immunofluorescence (IF). The diagnosis of C3G can only be made with IF studies of a renal biopsy.
  - The predominant staining of C3 is key in delivering a C3G diagnosis.
  - IF should be predominantly positive for C3 with C3 intensity at least two orders of magnitude greater than any other immune reactant (i.e., IgA, IgG, IgM, and C1q) (Figure 1A).
- Electron microscopy (EM) is used to distinguish between C3GN and DDD, a clinically relevant distinction (Figure 1). EM should demonstrate dense transformation of the glomerulus.

- In C3GN there are light, hump-like and clustered deposits, which are found in the mesangium or in the subendothelial and/or subepithelial spaces.
- In DDD, the deposits are darker, denser, segmental, discontinuous, ribbon-like, or diffuse and are most frequently located in the lamina densa of the glomerular basement membrane (GBM) (Figure 1B-C).

- Light microscopy (LM) is necessary to quantitate changes associated with chronic kidney disease and risk for progression of ESRD.

  LM most commonly demonstrates mild mesangial cell hypercellularity (45% of cases), although membranoproliferative (25%), crescentic (18%), and acute proliferative and exudative (12%) patterns are also seen (Figure 1D).

Note: Timing of the biopsy is important. If the presentation suggests post-infectious glomerulonephritis (PIGN; see Figure 2), waiting for three months is typically recommended. During that interval, the hypocomplementemia, hematuria, and proteinuria that are characteristic of both PIGN and C3G should resolve in cases of PIGN [Walker et al 2007, Nester & Smith 2016, Goodship et al 2017].

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

- **A multigene panel** that includes *C3*, *CD46*, *CFB*, *CFH*, *CFHR1*, *CFHR5*, *CFI*, *DGKE*, and other genes of interest (see Differential Diagnosis) may 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.

  Note: Analysis of *CFH*-related genes is complicated by the high degree of sequence identity between *CFH* and the downstream *CFH*-related genes (*CFHR1-CFHR5*). This similarity results in susceptibility to nonallelic homologous recombination (NAHR) events, large-scale deletions or duplications (copy number variants), and generation of hybrid *CFH* genes. Molecular assays must be specifically designed to detect the spectrum of changes that can occur in this region.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

- **Serial single-gene testing.** Sequence analysis can be performed on a gene-by-gene basis, although this approach is generally not recommended because there are no phenotypic clues to inform the order of genes to be tested and because rare/novel variants can be present in multiple genes [Bu et al 2016]. If single-gene testing is performed, gene-targeted deletion/duplication testing over the *CFHR1-CFHR5* region should also be completed in all cases.

Table 1. Molecular Genetic Testing Used in C3G

Gene [1, 2]	Proportion of C3G Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
C3	~11% [6]	~100%	Unknown
CD46	0%~2% [7]	100%	Unknown
CFB	<1% [8]	100%	Unknown
CFH	~12% [9]	~98%	~2%
CFHR1 duplication [10]	2 individuals	NA	100% [11]
CFHR1/CFHR5 hybrid allele [10]	3 individuals	NA	100% [12]
CFHR3/CFHR1 hybrid allele [10]	5 individuals	NA	100% [13]
CFHR5	See footnote 14.	See footnote 15.	Unknown (general population); 100% (Cyprus) [14]
CFHR5/CFHR2 hybrid allele [10]	2 individuals	NA	100% [16]
CFI	~5% [17]	100%	Unknown
DGKE	13 individuals [18]	~100%	Unknown

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. 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.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Martínez-Barricarte et al [2010], Abrera-Abeleda et al [2011], Imamura et al [2015], Bu et al [2016], Iatropoulos et al [2016]
7. Servais et al [2012], Nester & Smith [2013a]
8. Imamura et al [2015]
9. Ault et al [1997], Dragon-Durey et al [2004], Licht et al [2006], Servais et al [2012], Sethi et al [2012b], Zhang et al [2012], Johnson et al [2014], Bu et al [2016], Iatropoulos et al [2016]
10. CFHR hybrid alleles are the gene fusion products of nonallelic homologous recombination between the highly homologous *CFHR* genes [Gale et al 2010, Malik et al 2012, Tortajada et al 2013, Chen et al 2014, Medjeral-Thomas et al 2014, Xiao et al 2016, Togarsimalemath et al 2017] (for details of exon arrangements see Figure 3).
11. Tortajada et al [2013]
12. Togarsimalemath et al [2017]
13. Malik et al [2012]
14. Four individuals of non-Cypriot origin; however, hundreds of affected individuals with a duplication of exons 2 and 3, presumably due to a founder effect, have been identified in Cyprus [Gale et al 2010, Athanasiou et al 2011, Deltas et al 2013].
15. Three patients of non-Cypriot origin have been reported with variants detectable by sequencing [Sethi et al 2012a, Vernon et al 2012, Besbas et al 2014].
16. Chen et al [2014], Medjeral-Thomas et al [2014], Xiao et al [2016]
17. Servais et al [2012], Nester & Smith [2016]
18. Ozaltin et al [2013], Westland et al [2014], Azukaitis et al [2017]

See Figure 3.

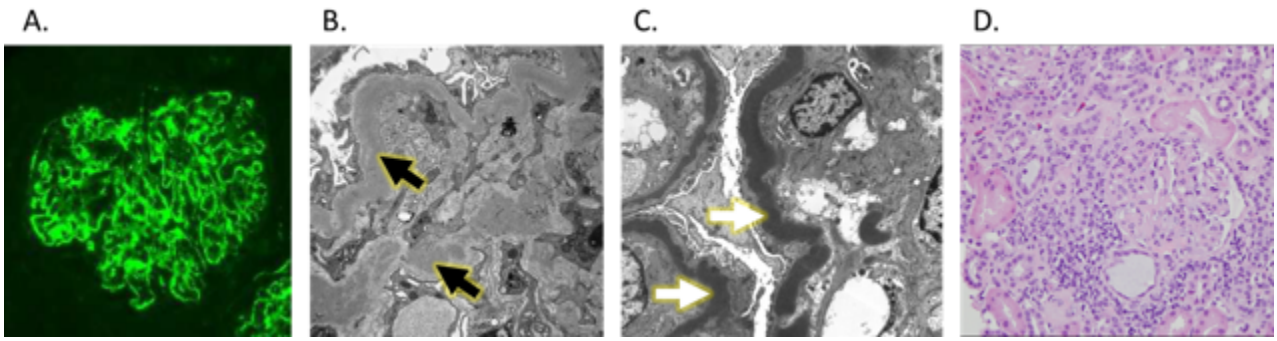

Figure 1. Disease-specific characteristic IF, EM, and LM biopsy images in C3 glomerulopathy (C3G)

A. Immunofluoresence (IF) shows bright staining for C3, which must be at least two orders of magnitude greater than any other immune reactant. Note the diffuse glomerular capillary C3 IF in this case.

B. EM of a glomerulus with C3GN (black arrows) showing light, hump-like, and clustered deposits in the mesangium and in the subendothelial and/or subepithelial spaces

C. EM of a glomerulus with DDD (white arrows). Note that the DDD deposits appear denser and more ribbon-like than the C3GN deposits.

D. LM showing mesangial proliferation with obliteration of glomerular capillaries and a robust inflammatory infiltrate

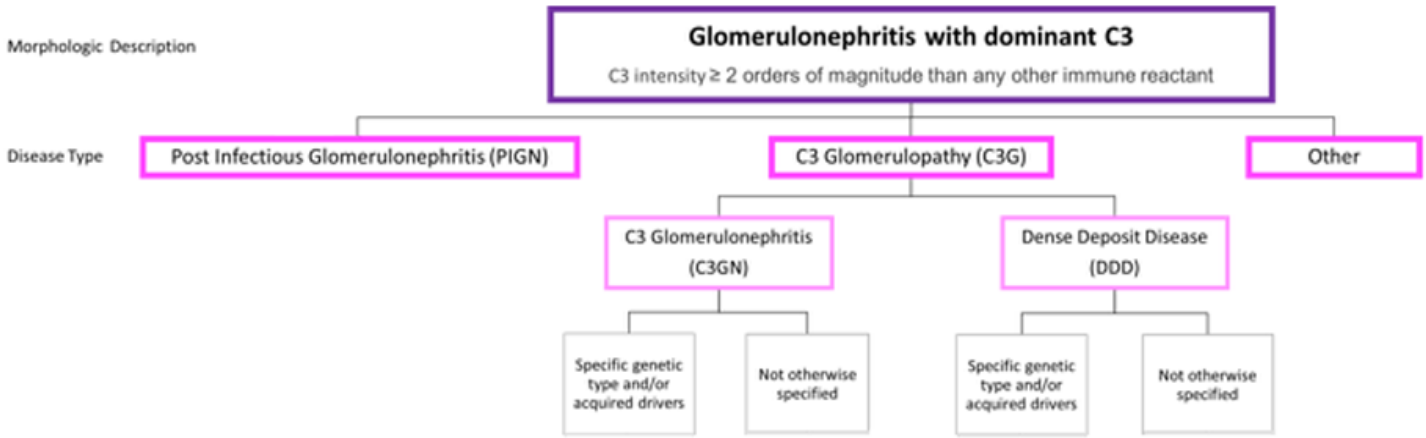

Figure 2. Schematic representation of disease types

Post-infectious glomerulonephritis (PIGN), C3 glomerulopathy (C3G), and other disease types fall under the classification "glomerular diseases with dominant C3" immunofluorescence (IF) staining, with the term "dominant" denoting an IF C3 intensity at least two orders of magnitude greater than any other immune reactant. C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) are subtypes of C3G.

Clinical Characteristics

Clinical Description

Age of onset. C3 glomerulopathy (C3G) affects individuals of all ages. Lu et al [2012] report a 1:1 female:male distribution and a median age at diagnosis of 23 years.

CFHR Hybrid Proteins associated with C3G phenotype: C3GN: C3 Glomerulonephritis; DDD: Dense Deposit Disease; C3G: C3 Glomerulopathy. CFHR1: ; CFHR2: ; CFHR3: ; CFHR5: .
The colored beads represent short consensus repeats (SCR) for the corresponding complement factor H related (CFHR) protein.

Report	Hybrid Proteins	Model	Diagnosis
Gale et al 2010	$CFHR5^{1\text{-}2,1\text{-}9}$		C3GN
Malik et al 2012	$CFHR3^{1\text{-}2}$—$CFHR1^{1\text{-}5}$		C3GN
Tortajada et al 2013	$CFHR1^{1\text{-}4}$—$CFHR1^{1\text{-}5}$		C3GN
Medjeral-Thomas et al 2014	$CFHR5^{1\text{-}2,1\text{-}9}$		C3GN
Chen et al 2014	$CFHR2^{1\text{-}2}$—$CFHR5^{1\text{-}9}$		DDD
Xiao et al 2016	$CFHR5^{1\text{-}2}$—$CFHR2^{1\text{-}4}$		C3GN
Togarsimalemath et al 2017	$CFHR1^{1\text{-}3}$—$CFHR5^{1\text{-}9}$		C3G

Figure 3. Complement factor H-related hybrid proteins and C3G
Adapted from Togarsimalemath et al [2017] and references therein

In comparing the two major subtypes, the median age at time of diagnosis in C3 glomerulonephritis (C3GN) is higher than in dense deposit disease (DDD). In childhood, DDD is more frequently diagnosed than C3GN [Nester & Smith 2016, Riedl et al 2017].

Renal disease. Individuals with C3G typically present with one of the following findings:

- Hematuria
- Proteinuria
- Hematuria and proteinuria
- Acute nephritic syndrome
- Nephrotic syndrome

Hypocomplementemia. Individuals with C3G have low levels of complement component C3. Complement dysregulation can be mediated by autoantibodies (see Pathophysiology).

Autoantibodies that may be detected in individuals with C3G:

- Serum C3 nephritic factor (C3NeFs). C3NeFs are present in up to ~50% of individuals with C3GN and ~80% of individuals with DDD [Salvadori & Bertoni 2016].
- Factor H autoantibodies (FHAAs). Blanc et al [2015] reported the prevalence of FHAAs in C3G individuals to be 11%.
- Factor B autoantibodies (FBAAs). FBAAs have been linked to C3G; their role in disease remains unclear [Pickering et al 2013].

Course and progression

- Spontaneous remission of C3G is uncommon [Habib et al 1975, Cameron et al 1983, Marks & Rees 2000, Thomas et al 2014]. While the disease can remain stable for years despite persistent proteinuria, in some individuals rapid fluctuations in proteinuria occur, with episodes of acute renal deterioration in the

absence of obvious triggering events. Efforts to move individuals to remission have not been successful [Daina et al 2012, McCaughan et al 2012]. Current data suggest that C3G remains a chronic disease subject to acute exacerbations, with constant activation of the complement alternative pathway (AP) [Goodship et al 2017].

- About half of affected individuals develop end-stage renal disease (ESRD) within ten years of diagnosis [Lu et al 2007, Servais et al 2012, Nester & Smith 2016, Goodship et al 2017], occasionally developing the late comorbidity of impaired visual acuity [Recalde et al 2016].
  - Progression to ESRD can be rapid [Smith et al 2007, Nester & Smith 2013b, Servais et al 2013].
  - Age and sex of an individual are not significant predictors of disease course.
  - Native kidney survival is comparable in C3GN and DDD [Servais et al 2013, Nester & Smith 2016].

Acquired partial lipodystrophy (APL). APL may develop as a direct aftermath of complement activation in 5%-17% of persons with C3G [Barbour et al 2013b, Goodship et al 2017]. The association between APL and C3G is related to the effects of AP dysregulation on both kidneys and adipose tissue [Goodship et al 2017]. The deposition of activated complement components in adipose tissue destroys adipocytes in areas where factor D (fD, also known as adipsin) is high; loss of subcutaneous fat in the upper half of the body typically precedes the onset of kidney disease by several years.

Eye findings. Individuals with C3G develop drusen as a result of complement activation, often in early adulthood [Barbour et al 2013b, Thomas et al 2014, Goodship et al 2017]. The whitish-yellow deposits, which lie within Bruch's membrane beneath the retinal pigment epithelium of the retina, are similar in composition and structure to the deposits observed in the kidney [D'Souza et al 2009, Lu et al 2012, Barbour et al 2013b]. The retinal distribution of drusen is variable [Thomas et al 2014, Goodship et al 2017] and initially has little impact on visual acuity or visual fields. However, vision loss can occur later in life [Cebeci et al 2016].

Recent investigations convey the importance of the complications that result from drusen [Cebeci et al 2016, Dalvin et al 2016, Savige et al 2016]. Tests of retinal function such as dark adaptation, electroretinography, and electrooculography can gradually become abnormal, and vision can deteriorate as subretinal neovascular membranes, macular detachment, and central serous retinopathy develop [Cebeci et al 2016, Dalvin et al 2016, Savige et al 2016].

The long-term risk for visual problems in individuals with C3G is approximately 10%. No correlation exists between disease severity in the kidney and in the eye.

Pathophysiology

See Figure 4. Fluid-phase dysregulation of the alternate pathway (AP) of the complement cascade is the triggering pathophysiologic event in C3G, and dysregulation of the C3 convertase alone is necessary and sufficient to result in C3G [Martínez-Barricarte et al 2010, Paixão-Cavalcante et al 2012, Zhang et al 2012].

During disease progression, activation of downstream complement proteins in the solid phase, in particular cleavage of C5 to C5a and C5b, can contribute to tissue injury in the micro-environment of the renal glomerulus [Appel et al 2005, Smith et al 2007]. Current consensus considers that in C3G, uncontrolled regulation of the AP may be due to both genetic and/or acquired drivers of disease [Servais et al 2012, Nester & Smith 2016, Goodship et al 2017].

Acquired drivers of disease include autoantibodies such as C3 nephritic factors (C3NeFs), C4 nephritic factors (C4NeFs), C5 nephritic factors (C5NeFs), factor H autoantibodies (FHAA), and factor B autoantibodies (FBAA).

C3NeFs and C5NeFs are most commonly detected and are autoantibodies that recognize neoantigenic epitopes on C3bBb, the C3 convertase of the AP, and on C3bBbC3b, the C5 convertase of the terminal pathway, respectively (see Figure 4) [Paixão-Cavalcante et al 2012, Zhang et al 2012, Nester & Smith 2013a, Nicolas et al

2014]. C3 convertases cleave C3 into C3b and C3a, while C5 convertases cleave C5 into C5a and C5b. In the presence of C3NeFs and C5NeFs, the half-lives of C3 convertase and C5 convertase are increased. Persistent cleavage of C3 drives down serum concentrations of C3 and increases serum concentrations of its cleavage products, C3c and C3d, while persistent cleavage of C5 increases serum concentrations of soluble C5b-9. C4NeFs are found in fewer than 5% of individuals with C3GN and stabilize the C3 convertase of the classic and lectin pathways (C4b2a) [Zhang et al 2017].

Nephritic factors may persist in serum throughout the disease course [Schwertz et al 2001, Paixão-Cavalcante et al 2012, Zhang et al 2012]. Serum concentrations of C3NeFs can vary over time [Appel et al 2005, Paixão-Cavalcante et al 2012, Zhang et al 2012, Servais et al 2013, Rabasco et al 2015]. Their presence is nearly always associated with evidence of complement activation such as decrease in serum concentration of C3 and increase in serum concentration of C3 cleavage products (e.g., C3c and C3d), but the relationship between nephritic factors, C3, and prognosis is not clear [Paixão-Cavalcante et al 2012, Zhang et al 2012, Rabasco et al 2015]. The observed differences may be reconciled by several observations relevant to C3NeFs, which have been most thoroughly studied. First, not all C3NeFs recognize the same epitope on C3bBb; second, the methods for their detection vary; third, many studies do not report titers; and fourth, there is good evidence that the triggering epitopes can change over time [Ohi et al 1992, Spitzer & Stitzel 1996, Paixão-Cavalcante et al 2012, Zhang et al 2012].

The consequence of AP dysregulation in C3G is kidney damage. As the degree of chronic damage increases, renal outcome ultimately becomes independent of the degree of complement dysregulation. With sufficient chronic damage, even if complement normalcy is restored, the likelihood of improving or stabilizing renal function becomes remote and ESRD ensues.

Factor H autoantibodies (FHAA) have been reported in individuals with C3G; epitope mapping shows that these autoantibodies bind the N-terminus of fH [Zhang et al 2012, Blanc et al 2015, Goodship et al 2017].

Factor B autoantibodies (FBAA) have been linked to C3G; however, their role in disease remains unclear [Pickering et al 2013]. FBAAs were identified in a person with DDD without serum C3NeFs. FBAAs bind to and stabilize C3 convertase, targeting both fB and C3b, enhancing the consumption of C3. C5 convertase formation from C3 convertase is prevented, thus interfering with activation of the terminal complement cascade [Strobel et al 2010]. Additional studies have identified FBAAs targeting fB and C3b in two individuals with DDD; C3 convertase activity was increased although no C3NeFs were identified [Chen et al 2011].

As a general rule, C3Nefs, FHAAs, and FBAAs extend the half-life and stabilize C3 convertase, which leads to persistent AP activation in the fluid phase [Noris & Remuzzi 2015].

Genotype-Phenotype Correlations

To date, the most striking genotype-phenotype correlation has been with *CFHR* fusion genes and the C3GN phenotype (as opposed to the DDD phenotype) (see Figure 3).

Nomenclature

C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). Prior to adopting the C3G classification [Pickering et al 2013], dense deposit disease (DDD) was also described as membranoproliferative glomerulonephritis type 2 (MPGN2). C3 glomerulonephritis (C3GN) was recognized as atypical MPGN1 (Burkholder variant of MPGN1) and atypical MPGN3 (Strife and Anders variant of MPGN3) [D'Agati & Bomback 2012, Sethi et al 2016].

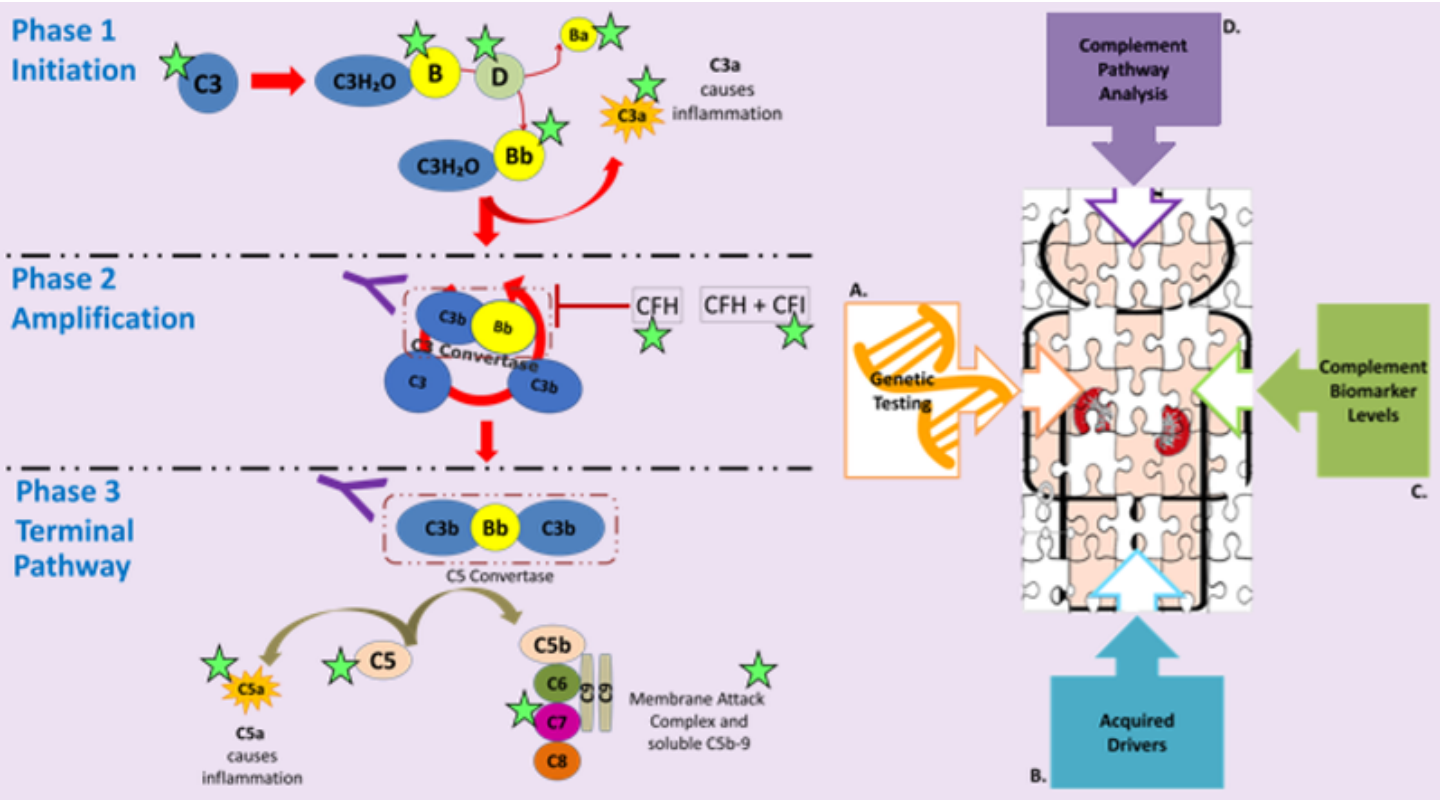

Figure 4. Complement alternative pathway (AP)

Left. Three phases of complement activity are illustrated:

Phase 1. Initiation of a "tick-over," or the spontaneous activation of the AP, occurs through the hydrolysis of C3 to C3(H_2O), which associates with factor B (fB). Cleavage by factor D (fD) results in the generation of a pro-C3 convertase, C3(H2O)Bb. This proconvertase cleaves C3 into C3a and C3b, setting the stage for the amplification phase of the complement cascade.

Phase 2. Amplification of cleavage of C3 into C3a and C3b provides a source of C3b, from which additional C3 convertase is generated in a robust amplification process. Complement factor H (fH) and complement factor I (fI) are important regulators of complement activity, while properdin (fP) potentiates complement activity. Persistent amplification ultimately leads to generation of C5 convertase and triggering of the terminal pathway of complement.

Phase 3. Effector in further pathway continues unchecked; C5 convertase is formed. This serine protease cleaves C5 into C5a and C5b. C5b associates with C6, C7, C8, and C9 to generate the membrane attack complex (MAC). Multiple different levels of investigation are required to evaluate the complement system. Simply measuring C3 and C4 serum levels is not adequate. Obtaining detailed data on complement is comparable to adding pieces to a puzzle, and allows for a more complete picture of complement activity in the individual with C3G.

Right. A comprehensive analysis includes the following:

A. Genetic testing

B. Screening for autoantibodies (acquired drivers of disease)

C. Measuring complement biomarkers (complement proteins and their breakdown products)

D. Quantitating complement pathway activity

Prevalence

The rarity of C3G makes it difficult to estimate prevalence, although from epidemiologic studies, its prevalence in the USA is estimated at 2-3 per 1,000,000 [Smith et al 2007].

Genetically Related (Allelic) Disorders

Table 2 includes other phenotypes caused by pathogenic variants in the gene(s) associated with C3G.

Table 2. Allelic Disorders

Gene	Phenotype [1]
CD46	Atypical hemolytic-uremic syndrome
CFB	Atypical hemolytic-uremic syndrome
CFH	Factor H deficiency (OMIM 609814); atypical hemolytic-uremic syndrome; basal laminar drusen (OMIM 126700)
CFHR1	Atypical hemolytic uremic syndrome
CFHR5	CFHR5 deficiency (OMIM 614809)
CFI	Factor I deficiency (OMIM 610984); atypical hemolytic-uremic syndrome; age-related macular degeneration (OMIM 615439)
DGKE	Nephrotic syndrome type 7 (OMIM 615008); atypical hemolytic-uremic syndrome

1. See hyperlinked *GeneReview* or OMIM phenotype entry for more information.

Differential Diagnosis

Table 3. Disorders to Consider in the Differential Diagnosis of C3G

Disorder	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping w/C3G	Distinguishing from C3G
Post-infectious glomerulonephritis [1]	NA	Acquired	Hematuria, proteinuria, nephritic syndrome, edema, ↓ serum C3, C3 glomerular deposition, subepithelial hump-like deposits	Post-infection (throat or skin) often due to Group A hemolytic *streptococcus* bacterium; ↓ levels of C3 resolve w/in 3 mos; glomerular codeposition of C3 & IgG
Immune-complex MPGN [2]	NA	Acquired	Hematuria, proteinuria, C3 deposits, subendothelial & subepithelial deposits, progressive disease	Immune complex-mediated, often low complement C4 levels; codeposition of C3 & IgG/IgM/C1q/C4 on IF
Juvenile acute non-proliferative glomerulonephritis [3]	NA	Acquired	Mesangial cell proliferation, subepithelial deposits on EM	C3 levels typically remaining in lower limits of nl
Familial lecithin-cholesterol acyltransferase deficiency [4]	*LCAT*	AR	ESRD, glomerular pattern of IF similar to dense deposit disease	Abnl lipoprotein (lipoprotein X); corneal opacities; normochromic anemia; capillary endothelial damage; cross-striated & vacuole structures
Partial lipodystrophy [5]	Several genes	AD/AR	Loss of subcutaneous fat in upper half of the body	No renal disease; no dysregulation of complement alternative pathway
Age-related macular degeneration [6]	Many genes	AD	Drusen	No renal disease

Table 3. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping w/C3G	Distinguishing from C3G
Malattia Leventinese & Doyne honeycomb retinal dystrophy [7]	*EFEMP1*	AD	Drusen	No renal disease

abnl = abnormal; AD = autosomal dominant; AR = autosomal recessive; EM = electron microscopy; IF = immunofluorescence; MOI = mode of inheritance; MPGN = membranoproliferative glomerulonephritis; nl = normal

1. Sotsiou [2001], Kambham [2012], Sethi et al [2013], Khalighi et al [2016]

2. Sethi & Fervenza [2011], Noris & Remuzzi [2015], Nester & Smith [2016]

3. West et al [2000], Fujita et al [2007]

4. Sessa et al [2001], Ossoli et al [2015]

5. Eisinger et al [1972], Mathieson & Peters [1997], Licht & Mengel [2008], Licht & Fremeaux-Bacchi [2009], Gale & Owen-Casey [2014]

6. Hageman et al [2005] , Licht & Mengel [2008], Licht & Fremeaux-Bacchi [2009], Gale & Owen-Casey [2014]

7. Stone et al [1999], Mullins et al [2001], Sohn et al [2015], Hulleman [2016], Vaclavik & Munier [2016]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with C3G, the following evaluations are recommended if they have not already been completed:

- Evaluate the complement system by measuring serum/plasma concentrations of C3, C3c, C3d, C4, C5, fB, Ba, Bb, fH, fI, properdin, and s(C5b-9).
- Quantitate the degree of complement function by measuring CH50 and APH50.
- Measure autoantibodies including C3NeFs, C4NeFs, C5NeFs, FHAA, and FBAA.
- Establish the extent of renal disease by measuring serum creatinine concentration, and monitor creatinine clearance, proteinuria, and hematuria.
- Quantitate the degree of chronic renal damage by renal biopsy.
- Obtain a baseline ophthalmologic examination.
- Consult with a clinical geneticist and/or genetic counselor.

Treatment of Manifestations

Currently, there are no therapeutic agents specifically designed to target the underlying complement dysregulation that occurs in individuals with C3G. Nonspecific therapies are most commonly used.

Nonspecific therapies have been shown to be effective in numerous chronic glomerular diseases. The judicious use of these agents along with optimal blood pressure control is of benefit in individuals with C3G.

- **Angiotensin-converting enzyme inhibitors and angiotensin II type-1 receptor blockers** decrease proteinuria in many glomerular diseases and slow the progression to renal failure [Licht et al 2006, Lu et al 2012, Nester & Smith 2016, Riedl et al 2017]. A retrospective study found that the combination of angiotensin blockers and immunosuppressants (steroids) is more effective than each therapy alone in preventing the development of renal failure [Nasr et al 2009, Nester & Smith 2013b, Thomas et al 2014, Cook 2017].
- **Lipid-lowering agents,** and in particular hydroxymethylglutaryl coenzyme A reductase inhibitors, may delay progression of renal disease as well as correct endothelial cell dysfunction and alter long-term atherosclerotic risks in the presence of hyperlipidemia [Nester & Smith 2013b, Thomas et al 2014]. These agents are not widely used in children.

- **Complement inhibition** with a terminal pathway blocker may alter disease course. Eculizumab is a recombinant humanized monoclonal antibody that targets C5. It blocks cleavage of C5 by C5 convertase, thereby having two effects: (1) an anti-inflammatory effect caused by preventing the release of C5a, a potent anaphylatoxin; and (2) an anticomplement effect caused by preventing formation of the terminal complement complex (see Figure 4). Reports of its use in individuals with C3G have demonstrated limited success [ClinicalTrials.gov NCT00838513, Bomback et al 2012].
  - Individuals with C3G treated with eculizumab have not produced a uniform response [Noris & Remuzzi 2015].
  - Early administration of eculizumab prior to sclerotic tissue formation provides better results, reduces proteinuria, and improves kidney health [Vivarelli & Emma 2014]; however, success of this therapeutic is limited in C3G because proximal complement control is not restored (see Figure 4).

Renal allografts. When end-stage renal disease (ESRD) develops, treatment options are limited to dialysis or transplantation. When an individual with C3G elects to undergo a renal transplant, it is important to recognize that C3G recurs in nearly all grafts and is the predominant cause of graft failure in 50%-90% of transplant recipients [Appel et al 2005, Angelo et al 2011, Lu et al 2012, Servais et al 2012, Zand et al 2014, Salvadori & Bertoni 2016, Goodship et al 2017]. Data suggesting that any therapeutic interventions reverse this course are limited, although isolated reports have described the use of plasmapheresis, which appears to be of equivocal benefit [Fremeaux-Bacchi et al 1994, Kurtz & Schlueter 2002]. A thorough complement and genetic evaluation of the transplant recipient is recommended pre-transplantation as results may inform post-transplant care. In addition, a genetic assessment is recommended for relatives being considered as kidney donors.

Prevention of Primary Manifestations

Most treatments for C3G are ineffective; however, plasma replacement therapy in individuals with pathogenic variants in *CFH* has been reported by some authors to be effective in controlling complement activation and slowing progression of ESRD [Licht et al 2006]. Other authors report that the benefit of plasma exchange is inconsistent in reducing progression to ESRD [Kurtz & Schlueter 2002, McCaughan et al 2012, Servais et al 2013, Thomas et al 2014].

Surveillance

The following are appropriate:

- Close monitoring of renal function by a nephrologist with familiarity with the C3G disease spectrum

  Note: Frequency of follow up and testing required is determined by the degree of renal dysfunction.
- Complete biannual assessment of the complement pathway
- Periodic eye examinations to evaluate the fundus

Evaluation of Relatives at Risk

There are very few familial cases of C3G. However, if the family history is positive for renal disease, it is appropriate to evaluate apparently asymptomatic sibs of a proband and at-risk relatives to identify those who would benefit from periodic observation and continued follow up for management of renal disease.

Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known. Penetrance rates, however, are not known.
- Urinalysis
- Comprehensive analysis of the complement system if the pathogenic variants in the family are not known.

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

Pregnancy Management

Chronic kidney disease does not preclude pregnancy, but any pregnancy in a woman with C3G should be followed by a nephrologist and obstetrician with expertise in caring for pregnant women with chronic kidney disease [Nava et al 2017, Piccoli et al 2018].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Numerous anti-complement therapies are entering clinical trials for individuals with C3G. These trials are registered under ClinicalTrials.gov.

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.

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

C3G is a complex genetic disorder that is rarely inherited in a simple mendelian fashion. In most persons with C3G, inheritance is complex and incompletely understood. For these reasons, recurrence risk to family members is not known but likely very low.

- In persons with C3G in whom two pathogenic variants can be identified, inheritance is autosomal recessive.
- Multiple affected persons within a single nuclear family are only reported occasionally; in these instances, parental consanguinity is common [Licht et al 2006].
- Autosomal dominant cases of C3G are reported in association with CFHR hybrid fusion proteins (see Figure 3).

Autosomal Recessive C3G – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive C3G are obligate heterozygotes (carriers) for a pathogenic variant.

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

Carrier Detection

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

Autosomal Dominant C3G – Risk to Family Members

Parents of a proband

- Few individuals (<1%) diagnosed with C3G have an affected parent.
- Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the pathogenic variant occurred *de novo*, the proportion of C3G caused by a *de novo* pathogenic variant is unknown.
    - Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
    - If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- The family history of some individuals diagnosed with C3G may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of 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 affected, the risk to the sibs of inheriting the genetic variant is 50%. However, there is reduced penetrance in families [Xiao et al 2014].
- If the parents have been tested for the pathogenic variant identified in the proband and:
    - A parent of the proband has the pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
    - If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.
- If the parents have not been tested for the pathogenic variant but are clinically unaffected, the risk to the sibs of a proband is extremely low. The sibs of a proband with clinically unaffected parents are still at increased risk for C3G because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant C3G has a 50% chance of inheriting the pathogenic variant; however, penetrance is extremely variable [Xiao et al 2014].

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, his or her family members may be at risk.

Other Etiologies – Risk to Family Members

Parents, sibs, and offspring of a proband. The risk to the family members of a proband who does not have identified pathogenic variants or a family history consistent with autosomal recessive or dominant inheritance is low.

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.

Other autoimmune diseases, in particular diabetes mellitus type 1 and celiac disease, are diagnosed more frequently in families with C3G (16% of families) than would be expected based on estimates in the general population [Smith et al 2007, Lu et al 2012, Barbour et al 2013a, Thomas et al 2014].

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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, pathogenic mechanisms, 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 pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing 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.

- **Kidneeds**
  Dedicated to the study of C3 glomerulopathy
  Cedar Rapids IA
  Email: kidneedsMPGN@yahoo.com
  kidneeds.lab.uiowa.edu

- **Kidney Foundation of Canada**
  Canada
  Phone: 514-369-4806; 800-361-7494
  Email: info@kidney.ca
  www.kidney.ca

- **Medline Plus**
  Glomerulonephritis
- **National Kidney Foundation**
  Phone: 855-NKF-CARES; 855-653-2273
  Email: nkfcares@kidney.org
  kidney.org

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. C3 Glomerulopathy: 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
CFHR5	1q31.3	Complement factor H-related protein 5		CFHR5	CFHR5
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

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 C3 Glomerulopathy (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
217030	COMPLEMENT FACTOR I; CFI
601440	DIACYLGLYCEROL KINASE, EPSILON, 64-KD; DGKE

Table B. continued from previous page.

608593	COMPLEMENT FACTOR H-RELATED 5; CFHR5
609814	COMPLEMENT FACTOR H DEFICIENCY; CFHD
610984	COMPLEMENT FACTOR I DEFICIENCY; CFID
613779	COMPLEMENT COMPONENT 3 DEFICIENCY, AUTOSOMAL RECESSIVE; C3D
615008	NEPHROTIC SYNDROME, TYPE 7; NPHS7

Molecular Pathogenesis

The complement system, composed of the classic pathway and the alternate pathway, is a component of the immune system that enhances the function of antibodies and phagocytes. C3 glomerulopathy (C3G) is caused by uncontrolled activation of the complement alternative pathway.

With the exception of *DGKE*, all the genes discussed in association with C3G encode proteins in the complement system. C3 and CFB are integral to complement activation and together form C3bBb, a C3 convertase that amplifies the initial complement response, and C3bBbC3b, a C5 convertase that cleaves C5 into C5a and C5b to trigger the terminal pathway. CD46, CFH, CFHR1, CFHR5, and CFI are complement regulators. The role of *DGKE* in complement activation, although minimal, is believed to be essential in normal podocyte function.

Familial cases of C3G are uncommon and when identified are most often highly penetrant heterozygous copy number variants involving the *CFHR1-5* genes (see Figure 3), homozygous variants that lead to *CFH* deficiency, or heterozygous gain-of-function variants in *C3*. Common to all of these variants is an impact on the regulation of the AP in the fluid phase [Noris & Remuzzi 2017].

Since C3G is rarely inherited in a simple mendelian fashion, the study of rare variants and haplotypes associated with disease is important.

Several studies have shown that some common variants in complement genes are also associated with C3G and increase the odds ratio of developing disease [Abrera-Abeleda et al 2011, Kobayashi et al 2017]. While the identification of common variants that are C3G "risk alleles" *cannot* be used to direct clinical care, the identification of rare variants in complement genes does affect patient care, especially in the context of a comprehensive assessment of complement function, which includes plasma levels of complement proteins and their split products, assays for autoantibodies, and tests of overall complement activity. For more detailed information, see Osborne et al [2018].

C3

Gene structure. *C3* comprises 41 exons that encode complement C3, which has a molecular weight of 176 kd. The mature protein forms a beta chain and an alpha chain. For a detailed summary of gene and protein information, see Table A.

Benign variants. Several *C3* variants (some of which are common in the population) are associated with C3G and define an at-risk haplotype [Hageman et al 2005, Smith et al 2007, Fremeaux-Bacchi et al 2008, Abrera-Abeleda et al 2011, Iatropoulos et al 2016, Riedl et al 2017, Osborne et al 2018].

Pathogenic variants. Pathogenic variants and their location are shown in Table 4.

Table 4. *C3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Affected Domain	Reference Sequences
c.443G>A	p.Arg148Gln	C3β chain	NM_000064.3 NP_000055.2
c.1855G>A	p.Val619Met	Linker	
c.3125G>A	p.Arg1042Gln	TED	
c.3908G>A	p.Arg1303His	CUBf	
c.3959G>A	p.Arg1320Gln	CUBf	
c.4552T>C	p.Cys1518Arg	C345C	
c.4873T>C	p.Asp1625His	C345C	

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). See Quick Reference for an explanation of nomenclature.

Normal gene product. *C3* encodes complement component C3, the central activating protein of the AP. This 1,663-amino-acid protein has 15 domains, including the anaphylatoxin (ANA), αNT, CUB (C1r/C1s, Uegf, Bmp1), C345C, thioester (TED), linker (LNK), and anchor domains and eight macroglobulin (MG) domains (see Figure 5). C3 is mainly synthesized in the liver, and it is the central protein of the complement system. Spontaneous or proteolytic cleavage of C3 generates the anaphylatoxin C3a (inflammatory effector cells) and the C3b fragment that deposits on cell surfaces triggering the complement cascade activation.

Abnormal gene product. Most pathogenic variants listed in Table 4 affect proper cleavage of C3 protein by affecting recognition sites for the binding of CFH and CFI, two regulators of complement activation. Pathogenic variants may also produce reduced quantities of C3 protein (i.e., truncating variants or frameshifts that lead to premature stop variants) [Martínez-Barricarte et al 2010].

CD46

Gene structure. *CD46* (cluster differentiation 46) has 14 exons that encode the 43.7-kd membrane cofactor protein (MCP).

Benign variants. Several variants in *CD46* have been associated with C3G and define an at-risk haplotype [Servais et al 2007, Fang et al 2008, Servais et al 2012, Osborne et al 2018].

Normal gene product. *CD46* encodes MCP, a complement regulatory protein of 392 amino acids that is highly expressed in the kidney. It is a transmembrane protein and a member of the regulators of complement activation (RCA), and has eight domains: four short consensus repeat (SCRs 1-4-sushi) domains, which contain ligand-binding domains for decay and cofactor activity; an O-linked-glycosylation site, rich in serine, threonine, and proline (STP) domain, which can be alternately spliced; a helical transmembrane domain; and two cytoplasmic topological domains. Its major role in controlling complement activity is to inactivate C3b and C4b by functioning as a cofactor for factor I [Servais et al 2012, Liszewski & Atkinson 2015].

Abnormal gene product. Pathogenic variants in *CD46* typically lead to reduced surface expression of MCP, which contributes to defective surface regulation of complement [Servais et al 2012].

CFB

Gene structure. *CFB* comprises 18 exons that encode complement factor B, which has a molecular weight of 93 kd. For a detailed summary of gene and protein information, see Table A.

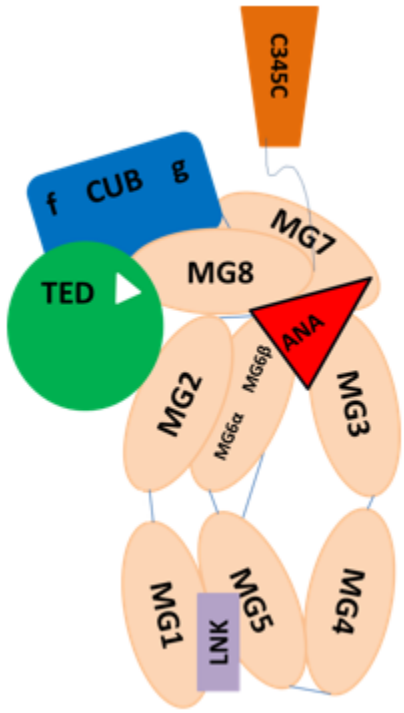

Figure 5. Schematic representation of complement component C3

The structural organization of C3 contains eight macroglobulins, anaphylatoxin (ANA), αNT, CUB (C1r/C1s, Uegf, Bmp1), C345C, linker, and thioester (TED) domains.

Benign variants. Benign variants in *CFB* associated with complement regulation have been described [Gold et al 2006].

Pathogenic variants. The p.Ser367Arg pathogenic variant is in the von Willebrand factor A (VWFa) domain, the catalytic unit of Bb, and is a gain-of-function variant that contributes to AP dysregulation [Imamura et al 2015].

Table 5. *CFB* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1099A>C	p.Ser367Arg	NM_001710.5 NP_001701.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff has not independently verified the classification of variants.
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Normal gene product. *CFB* is composed of 764 amino acids and has five domains: three complement component protein (sushi) domains; a VWFa domain; and a peptidase S1 (serine protease) domain. Factor B (fB) is a component of the AP. It binds to C3b and is then cleaved by fD into Ba, a non-catalytic fragment that is released, and Bb, a catalytic subunit that remains bound to C3b to form C3 convertase (C3bBb). The fB cleavage site is near the N-terminus of the VWFa domain.

Abnormal gene product. Pathogenic variants in *CFB* may lead to gain-of-function properties that contribute to the dysregulation of the complement cascade [Alberts et al 2002, Imamura et al 2015].

CFH

Gene structure. *CFH* has 23 exons that encode complement factor H, a protein of 1,231 amino acids. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Several variants of *CFH* (some of which are common in the population) define an at-risk haplotype that has been associated with C3G [Hageman et al 2005, Servais et al 2007, Smith et al 2007, Zhang et al 2012, Johnson et al 2014, Xiao et al 2014, Merinero et al 2018, Riedl et al 2017, Osborne et al 2018].

Pathogenic variants. *CFH* pathogenic variants in C3G occur in heterozygous, homozygous, and compound heterozygous states. *CFH* has been implicated in C3G by the following:

- A report of two sisters with DDD who were homozygous for the c.670_672delAAG (p.Lys224del) pathogenic variant in *CFH* [Licht et al 2006, Zipfel et al 2006]. Factor H (fH) carrying this pathogenic variant is present in the serum at normal concentrations but is nonfunctional [Zipfel et al 2006]. The normal N-terminal activities of fH (C3b binding and complement regulation) are defective, indicating that dysfunctional fH is associated with the development of DDD [Licht et al 2006].
- Studies of skin fibroblasts from a child with fH deficiency and chronic hypocomplementemic renal disease and abnormal fH localization. One copy of a p.Cys536Arg missense variant and one copy of a p.Cys959Tyr missense variant were detected in *CFH*. Both pathogenic variants affect conserved cysteine residues characteristic of the short consensus-repeat (SCR) modules of fH and therefore predict profound changes in the higher-order structure of the 155-kd protein [Ault et al 1997].
- Two brothers with MPGN were reportedly homozygous for a p.Arg127Leu amino acid change in *CFH* [Dragon-Durey et al 2004]. Homozygosity for this missense variant is associated with absence of fH in the serum, suggesting that this variant results in sequestration of the protein in the endoplasmic reticulum.

Table 6. *CFH* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.380G>T	p.Arg127Leu	NM_000186.3 NP_000177.2
c.670_672delAAG	p.Lys224del (ΔLys224)	
c.1606T>C (1679T>C)	p.Cys536Arg (Cys518Arg)	
c.2655del	p.Arg885SerfsTer13	
c.2876G>A (2949G>A)	p.Cys959Tyr (Cys991Tyr)	

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). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. Complement factor H (fH) protein is the key regulator of the alternative pathway of complement and is composed of 1,231 amino acids. Its structural organization is based on 20 homologous repeat domains (short consensus repeats [SCRs] or sushi domains). Each SCR has 60 amino acids. The first four SCRs (1-4) at the N-terminus are essential for fluid-phase complement regulation, binding of fH to C3b, decay acceleration activity of C3bBb, and fI cofactor activity in mediating the cleavage of C3b to iCb3. The last two SCRs (19-20) at the C terminus bind to cell surfaces to regulate C3 convertase in that microenvironment. See Figure 6.

Abnormal gene product. *CFH* pathogenic variants associated with C3G are more frequently found in the N-terminal short consensus repeats (SCRs 1-4), a region essential for fluid-phase complement control. In contrast, in atypical hemolytic uremic syndrome (aHUS), pathogenic variants are more frequently located in the carboxy terminus (SCRs 18-20), a region involved in cell surface regulation.

CFHR1

Gene structure. *CFHR1* comprises six exons that encode complement factor H-related protein 1. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. A duplication of exons 2 through 5 results in an abnormal fusion protein (Figure 3). The duplication alters the complex oligomerization of the FHR proteins, leading to increased FHR deregulation likely due to increased binding to C3b, iC3b, and C3dg, with decreased fH binding and decreased AP control (see Figure 3) [Tortajada et al 2013].

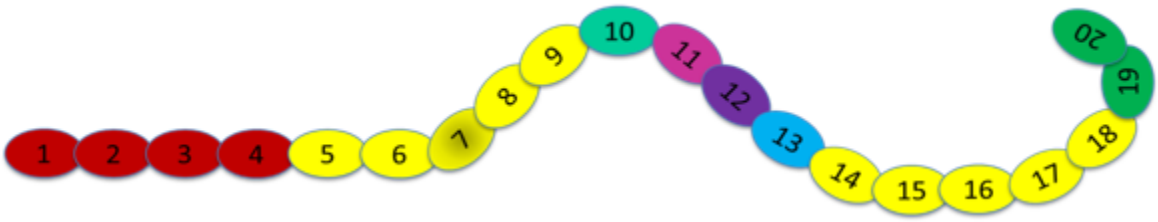

Figure 6. Schematic representation of factor H

The 20 bead-like homologous short consensus repeats (SCRs) each have 60 amino acids. The first four SCRs (1-4) (red beads) regulate activation in the fluid phase, binding to C3b, decay acceleration activity, and fI cofactor activity. The last two SCRs (19-20) (green beads) bind to cell surfaces and regulate complement activity on cells.

Table 7. *CFHR1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Dup exons 1-4	Duplication of all amino acids in SCR 1-4 of protein	NM_002113.2 NP_002104.2

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). See Quick Reference for an explanation of nomenclature.

Normal gene product. *CFHR1* encodes complement factor H-related 1 (FHR1), a protein of 330 amino acids and a member of the regulators of complement activation (RCA) family. Its structural organization is highly homologous to fH, although FHR1 has only five SCRs. The last two SCRs (SCRs 4 and 5) share 96%-100% homology to SCRs 19 and 20 of fH. FHR1 homodimerizes through its first two SCRs and also forms heterodimers with FHR2 and FHR5.

Abnormal gene product. Fusion proteins of FHR1 lead to the formation of complex multimers with FHR1, FHR2, and FHR5 that alter complement regulation by outcompeting fH, which results in reduced convertase regulation (see Figure 3) [Xiao et al 2016].

CFHR5

Gene structure. *CFHR5* has ten exons that encode complement factor H-related 5 (FHR5), a protein of 551 amino acids organized into nine SCRs. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Several *CFHR5* variants (some of which are common in the population) are associated with C3G and define an at-risk haplotype [Abrera-Abeleda et al 2006, Zipfel et al 2015, Osborne et al 2018].

Pathogenic variants. Pathogenic variants are more frequently associated with C3GN than with DDD (CFHR5 nephropathy is a type of C3GN) [Goicoechea de Jorge et al 2009].

Normal gene product. The normal gene product encoded by *CFHR5* is complement factor H-related protein 5 (FHR5), a plasma protein organized like fH in repetitive SCRs. FHR5 has nine SCRs and possesses fI-dependent cofactor activity that leads to inactivation of C3b [McRae et al 2001, Rodríguez de Córdoba et al 2004, McRae et al 2005]. In 92 renal biopsies from patients with different glomerular diseases, FHR5 was present in all complement-containing glomerular immune deposits [Murphy et al 2002], suggesting that FHR5 plays an important role in protecting the glomerulus from complement activation. The precise role of FHR5 in the physiopathology of C3G remains to be determined.

Abnormal gene product. Several abnormal gene products of *CFHR5* have been reported in association with C3G. These products usually arise as a consequence of nonallelic homologous recombination, which results in hybrid gene formation (see Figure 3).

The presence of *CFHR5* pathogenic variants in C3G is consistent with the hypothesis that FHRs play an important role in the complement regulation and disease pathogenesis [Abrera-Abeleda et al 2006, Zhang et al 2013].

CFI

Gene structure. *CFI* comprises 13 exons that encode complement factor I (fI), which has a molecular weight of 33 kd. For a detailed summary of gene and protein information, see Table A.

Benign variants. Several *CFI* variants (some of which are common in the population) are associated with C3G and define an at-risk haplotype [Fremeaux-Bacchi et al 2013, Imamura et al 2015, Chauvet et al 2017, Osborne et al 2018].

Pathogenic variants

- c-4C>T – in the Kozac sequence. This noncoding variant is associated with DDD [Iatropoulos et al 2016].
- p.Gly57Asp – in FIMAC domain, a region for fI-C3b degradation [Iatropoulos et al 2016]
- c.Ala240Gly – in LDL receptor class A 1 and associated with C3G, aHUS, and AMD. The variant results in partial reduction in secretion [Nilsson et al 2010].

Table 8. *CFI* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.719C>G	p.Ala240Gly (Ala222Gly)	NM_000204.3 NP_000195.2
c.-4C>T		
c.170G>A	p.Gly57Asp	

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). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. *CFI* encodes complement fI, a protein of 583 amino acids synthesized in the liver. The fI protein cleaves fluid-phase and cell-bound C3b and C4b, inhibiting their activity in the complement cascade. Factor H and several other RCA proteins are obligatory cofactors for fI activity.

Abnormal gene product. Abnormal fI may lead to a partial reduction in secreted fI, thus compromising its cofactor activity with fH [Servais et al 2012]. Deficiency in fI can lead to complement dysregulation and consequently low serum levels of other complement proteins.

DGKE

Gene structure. *DGKE* comprises 11 exons that encode diacylglycerol kinase epsilon, which has a molecular weight of 64 kd. For a detailed summary of gene and protein information, see Table A.

Benign variants. Several *DGKE* variants (some of which are common in the population) are associated with C3G and define an at-risk haplotype [Osborne et al 2018].

Pathogenic variants. Several loss-of-function variants have been associated with C3G including the following:

- p.Gln43Ter [Ozaltin et al 2013]
- p.Lys101Ter [Westland et al 2014]
- c.610delA [Ozaltin et al 2013]
- p.Trp322Ter [Azukaitis et al 2017]
- p.Trp350Ter [Ozaltin et al 2013]

Table 9. *DGKE* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.127C>T	p.Gln43Ter	NM_003647.2 NP_003638.1
c.301A>T	p.Lys101Ter	
c.610delA	p.Thr204GlnfsTer6	
c.966G>A	p.Trp322Ter	
c.1050G>A	p.Trp350Ter	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *DGKE* is unrelated to the complement pathway. *DGKE* encodes diacylglycerol kinase epsilon (DGKE), a lipid kinase of 567 amino acids expressed in podocytes, glomerular capillary endothelial cells, and platelets. DGKE plays a key role in signal transduction by affecting the balance between diacylglycerol kinase and phosphatidic acid, thus controlling DAG levels within the cell [Lemaire et al 2013]. The role of DGKE in complement activation is minimal; however, it is believed to play an essential role in normal podocyte function [Ozaltin et al 2013].

In the kidney, DGKE is ubiquitously expressed in podocytes and endothelial cells. Although *Dgke* null mice do not have spontaneous clinical signs of kidney disease and have normal serum creatinine and urinary albumin, they develop subclinical microscopic anomalies of the glomerular endothelium that worsen with age, as well as glomerular capillary occlusion when exposed to nephrotoxic serum [Zhu et al 2016].

Abnormal gene product. Abnormal DGKE may lead to prothrombosis through sustained signaling by arachidonic acid-containing diacylglycerol (AA-DAG) [Lemaire et al 2013].

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