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Dense Deposit Disease / Membranoproliferative Glomerulonephritis Type II

[*DDD/MPGNII*]

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Summary

Disease characteristics. Dense deposit disease (DDD)/membranoproliferative glomerulonephritis type II (MPGNII) is characterized by onset of hematuria and/or proteinuria, acute nephritic syndrome, or nephrotic syndrome. It most frequently affects children between ages five and 15 years. Spontaneous remissions are uncommon and about 50% of affected individuals develop end-stage renal disease (ESRD) within ten years of diagnosis. DDD/MPGNII can be associated with acquired partial lipodystrophy (APL). Drusen, whitish-yellow deposits within Bruch's membrane of the retina, often develop in the second decade of life; they initially have little impact on vision, but cause vision problems from subretinal neovascular membranes, macular detachment, and central serous retinopathy in about 10% of affected individuals.

Diagnosis/testing. The definitive diagnosis of DDD/MPGNII requires electron microscopy and immunofluorescence studies of a renal biopsy. The genes *CFH*, *CFHR5*, *C3*, and *LMNA* have been implicated in the pathogenesis of DDD/MPGNII, a complex genetic disease that is rarely inherited in a simple Mendelian fashion.

Management. *Treatment of manifestations:* Nonspecific therapies used in numerous chronic glomerular diseases are the mainstay; use of angiotensin-converting enzyme inhibitors, angiotensin II type-1 receptor blockers, and lipid-lowering agents (in particular hydroxymethylglutaryl coenzyme A reductase inhibitors) should be considered; renal allografts have a lower-than-average survival and an almost 100% risk of DDD/MPGNII recurrence. *Prevention of primary manifestations:* In individuals with pathologic mutations in *CFH*, plasma replacement therapy can control complement activation and prevent ESRD. *Surveillance:* periodic eye examinations including funduscopic examination. *Testing of relatives at risk:* If one homozygous or two heterozygous *CFH* disease-causing mutations have been identified in an affected individual, siblings can be offered molecular genetic testing to

identify those who have the same mutation(s) in order to facilitate early diagnosis and management of renal disease.

Genetic counseling. DDD/MPGNII is a complex genetic disease that is rarely inherited in a simple Mendelian fashion. Multiple affected persons within a single nuclear family are only reported occasionally; in these instances, parental consanguinity is common. In persons with DDD/MPGNII in whom two pathologic mutations can be identified in *CFH* or *CFHR5*, inheritance is autosomal recessive. In most persons with DDD/MPGNII, two pathologic mutations in *CFH* or *CFHR5* cannot be identified and risks to family members are not known.

Diagnosis

Clinical Diagnosis

Dense deposit disease (DDD) (also known as membranoproliferative glomerulonephritis type II [MPGNII]) is a complex genetic disease that is rarely inherited in a simple Mendelian fashion.

DDD/MPGNII is typically diagnosed in children age five to 15 years who present with one of the following:

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

Testing

Renal biopsy. The definitive diagnosis of DDD/MPGNII requires electron microscopy and immunofluorescence studies of a renal biopsy [Walker et al 2007].

- **Light microscopy** most commonly demonstrates mild mesangial cell hypercellularity (45% of cases), although membranoproliferative (25%), crescentric (18%), and acute proliferative and exudative (12%) patterns are also seen.
- **Electron microscopy** should demonstrate 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.

Serum C3 nephritic factor (C3NeF). Most persons with DDD/MPGNII have detectable levels of C3 nephritic factor (C3NeF) in the serum. C3NeF is an autoantibody that recognizes neoantigenic epitopes on C3bBb, the C3 convertase of the alternative pathway (AP) of the complement cascade [Schwertz et al 2001]. C3 convertases cleave C3 into C3b and C3a. In the presence of C3NeF the half-life of C3bBb is increased. As a result, in the presence of C3NeF in the serum, serum concentrations of C3 are usually low and serum concentrations of C3 breakdown products such as C3d are elevated.

Note: (1) Serum concentrations of C3NeF can vary over time and C3NeF may be detected in the serum of persons without renal disease [Appel et al 2005]. (2) C3NeF is also present in up to 50% of individuals with MPGNI and MPGNIII (see Differential Diagnosis).

Autoantibodies to factor H have been reported in the serum of one woman who developed a renal picture consistent with DDD/MPGNII and MPGN type I [Jokiranta et al 1999].

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.

Molecular Genetic Testing—Genes. *CFH*, *CFHR5*, *C3*, and *LMNA* have been implicated in the pathogenesis of DDD/MPGNII by mutation analysis and association studies.

***CFH*, *CFHR5*.** *CFH* (the gene encoding complement factor H) and *CFHR5* (the gene encoding factor H-related 5) have been implicated in DDD/MPGNII by the following:

- A report of two sisters with DDD/MPGNII who were homozygous for the ΔLys224 mutation of *CFH* [Licht et al 2006, Zipfel et al 2006]. As a result of this amino acid deletion in factor H, the N-terminal activities of the mutant protein (C3b binding and complement regulation) were defective, indicating that dysfunctional factor H protein is associated with the development of DDD/MPGNII [Licht et al 2006].
- Studies of skin fibroblasts from a factor H-deficient child with chronic hypocomplementemic renal disease. Normal amounts of 4.3- and 1.8-kb messages were observed, but secretion of the 155-kd protein was blocked; the 45-kd protein was secreted with normal kinetics. Consistent with this finding, the affected individual's plasma lacked the 155-kd factor H protein but contained the smaller factor H-like 1 protein. The 155-kd factor H protein was retained in the endoplasmic reticulum and was not degraded even after 12 hours. Mutation screening of *CFH* revealed a 1679T>C substitution on one allele and a 2949G>A substitution on the other, predicting a p.Cys518Arg mutation in short consensus repeat (SCR) 9 and a c.Cys991Tyr mutation in SCR16, respectively. Both mutations affect conserved cysteine residues characteristic of the SCR modules of factor H and therefore predict profound changes in the higher-order structure of the 155-kd protein [Ault et al 1997].
- Mutation screening results in two brothers with MPGN who were homozygous for a p.Arg127Leu amino acid change in *CFH* [Dragon-Durey et al 2004]
- A significant association between the *CFH* single nucleotide polymorphism (SNP) His402 and DDD/MPGNII [Abrera-Abeleda et al 2006]. Abrera-Abeleda and colleagues (2006) also reported significant associations between several SNPs in the *CFHR5* gene and DDD/MPGNII. The His402 polymorphism of CFH lies in SCR7 and contributes to a glycosaminoglycan (GAG)-recognition site and a C-reactive protein (CRP) binding site [Skerka et al 2007]. Although CFH His402 is a normal variant of CFH, its functional properties differ from the CFH Tyr402 variant. These differences are believed to contribute to the development of DDD/MPGNII.

***CFHR5*.** *CFHR5* (the gene encoding factor H-related 5) has been implicated in DDD/MPGNII by mutation analysis. The function of *CFHR5* remains unknown.

***C3*.** The C3 protein, the third component of complement, exists in two common allotypic forms, C3S (slow) and C3F (fast), distinguished by differences in migration rates on protein electrophoresis.

- The allele for C3S, the more common protein variant, encodes an arginine at position 80 (Arg80).
- The allele for C3F, the rarer protein variant, encodes a glycine at position 80 (Gly80).

The protein variant C3F is present in 20% of whites, 5% of blacks, and 1% of Asians [Poznansky et al 1989] and is overrepresented in the DDD/MPGNII population [Finn & Mathieson 1993]. This finding is noteworthy because the majority of individuals with DDD/MPGNII have C3 nephritic factor (C3NeF) detected in their serum. C3 undergoes a marked conformation change when it is converted to C3b. These conformational differences may lead to functional differences between C3S and C3F, and also may expose different epitopes that can trigger C3NeF formation [Ajees et al 2006, Janssen et al 2006].

- With an arginine at amino acid position 80 (C3S), an electronegative interface is created on MG1 of C3b that can interact with a strong electropositive region on the exposed surface of the TED domain to stabilize C3b.
- A glycine at amino acid position 80 (C3F), in contrast, is not electronegative and in the absence of stabilizing electrostatic interactions, various conformations of C3b become possible.

Currently these data are not useful diagnostically but in aggregate support other data implicating dysregulation of the alternative complement pathway at the level of the C3 convertase, C3bBb, in the pathogenesis of DDD/MPGNII.

***LMNA*.** The sporadic form of partial lipodystrophy is characterized by fat loss from the face and upper body. It is associated with complement abnormalities and DDD/MPGNII, suggesting that the two conditions may share a common etiology. In support of this possibility, Owen et al (2004) reported an individual with a mutation in *LMNA* who had both familial partial lipodystrophy and DDD/MPGNII.

Clinical testing. Sequence analysis of *CFH* and *CFHR5* is clinically available.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in DDD/MPGNII

Gene Symbol	Proportion of Inherited DDD/MGNPII Attributed to Pathologic Mutations in This Gene	Test Method	Mutation Detection Frequency by Test Method	Test Availability
CFH	~1% [1]	Sequence analysis	Unknown but presumed near 100%	Clinical Testing
CFHR5	Unknown [2]			Clinical Testing

1. Only a few persons with DDD/MPGNII have obvious pathologic mutations [Licht et al 2006, Zipfel et al 2006], which are detected by sequence analysis of *CFH*; 85% of persons with DDD/MPGNII carry at least one copy of the His402 variant of *CFH*.
2. Pathologic mutations have not yet been reported in *CFHR5*. However, 7% of persons with DDD/MPGNII carry at least one copy of the Ser46 variant of *CFHR5* [Abrera-Abeleda et al 2006].

Testing Strategy

To confirm the diagnosis in a proband

- The diagnosis of DDD/MPGNII must be made by renal biopsy, using electron microscopy to demonstrate dense deposits in the GBM.
  - As a histologically defined disease, DDD/MPGNII lacks unequivocal diagnostic serologic markers of disease activity, although nearly 90% of

individuals have C3NeF detectable in serum. (A subgroup of individuals with MPGNI also has C3NeF detectable in serum.)

- In addition, nearly 80% of individuals with DDD/MPGNII have evidence of activation of the AP of complement as reflected in the serum by low concentrations of C3 and high concentrations of C3 degradation products, including C3d [Appel et al 2005].

- In persons with a histologic diagnosis of DDD/MPGNII, molecular genetic testing of *CFH* to detect pathologic mutations is appropriate, because identification of such a mutation helps to direct treatment. Most treatment for DDD/MPGNII is ineffective, but in individuals with pathologic mutations in *CFH*, plasma replacement therapy to replace factor H can control complement activation and prevent ESRD [Licht et al 2006].
- At this time, the presence of the His402 variant in factor H cannot be used to direct therapy in individuals with DDD/MPGNII.
- At this time, the presence of the Ser46 variant in *CFHR5* cannot be used to direct therapy in individuals with DDD/MPGNII.

Genetically Related (Allelic) Disorders

***CFH*.** Mutations in *CFH* also cause atypical hemolytic uremic syndrome (aHUS), characterized by hemolytic anemia, thrombocytopenia, and renal failure. The thrombotic microangiopathy of aHUS damages endothelial cells and causes detachment of the basement membrane.

Although most typical HUS is caused by Gram-negative bacteria that produce shiga toxin (*Shigella dysenteriae* serotype 1; *Escherichia coli* serotypes O-157, O-111, O-26), atypical HUS is caused by mutations in several genes encoding proteins that control the AP of complement, including *CFH*, *CFHR1*, *CFHR3*, *CFB*, *CFI*, and *MCP* [Goodship et al 2006, Zipfel et al 2006]. The result is impaired protection of host surfaces against complement activation [Saunders et al 2007].

Mutations in *CFH* are reported in 20%-30% of individuals with aHUS. Over 40% of the identified mutations are located in a portion of *CFH* that encodes SCRs 19 and 20 of the factor H protein [Saunders et al 2007]. These mutations, which affect only one allele and lead to haploinsufficiency, include:

- Mutations that lead to premature stop codons;
- Mutations that affect framework cysteine residues and prevent disulfide bond formation and the adoption of the appropriate conformational structure;
- Non-framework mutations that affect protein expression, result in a defective secreted protein, or severely impair capability to bind to endothelial cell surfaces.

***LMNA*.** More than ten other diseases and conditions with mutations or variations in the *LMNA* gene have been identified. See OMIM 150330. The most widely recognized:

- Hutchinson-Gilford progeria syndrome
- Autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD)
- Autosomal recessive Emery-Dreifuss muscular dystrophy (AR-EDMD)
- Autosomal dominant familial dilated cardiomyopathy and conduction system defects (CMD1A) (see Dilated Cardiomyopathy Overview)

- Autosomal dominant Dunnigan-type familial partial lipodystrophy (FPLD)
- Autosomal dominant limb-girdle muscular dystrophy 1B (LGMD1B)
- Autosomal recessive axonal neuropathy Charcot-Marie-Tooth disease 2B1 (CMT2B1)
- Autosomal recessive mandibuloacral dysplasia (MAD) [Cao & Hegele 2003]

Clinical Description

Natural History

Renal disease. Individuals with dense deposit disease/membranoproliferative glomerulonephritis type II (DDD/MPGNII) typically present with one of the five following findings:

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

DDD/MPGNII affects females slightly more frequently than males. The DDD Database, a registry that currently contains information on 56 individuals with DDD/MPGNII, reports a 3:2 female:male bias [Lu et al 2007].

Spontaneous remissions of DDD/MPGNII are uncommon [Habib et al 1975, Cameron et al 1983, Marks & Rees 2000]. Although 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.

About half of affected individuals develop ESRD within ten years of diagnosis [di Belgiojoso et al 1977, Droz et al 1982, Swainson et al 1983, McEnery 1990, Lu et al 2007], occasionally with the late comorbidity of impaired visual acuity [Colville et al 2003]. Consistent with these studies, the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) database reports that of the 119 registered children with DDD/MPGNII, 81 have progressed to ESRD [William Harmon, personal communication]. Progression to ESRD develops rapidly, usually within four years of diagnosis, and is the more likely outcome in individuals age ten years or younger than in older persons (p=0.006) [Smith et al 2007]. Girls may have a more aggressive disease course than boys (p=0.16).

Acquired partial lipodystrophy (APL). DDD/MPGNII can be associated with APL [Eisinger et al 1972]. In persons with APL the loss of subcutaneous fat in the upper half of the body usually precedes the onset of kidney disease by several years.

Misra et al (2004) reported that approximately 83% of individuals with APL have low serum concentrations of C3 and polyclonal C3NeF, and that about 20% develop DDD/MPGNII approximately eight years after the onset of lipodystrophy. Individuals who develop DDD/MPGNII have an earlier age of onset of lipodystrophy (12.6 ± 10.3 yr vs. 7.7 ± 4.4 yr, respectively; p<0.001) and a higher prevalence of C3 hypocomplementemia (78% vs. 95%, respectively; p=0.02), suggesting that the disease is more virulent in these individuals [Misra et al 2004].

Owen et al (2004) described DDD/MPGNII in a person with Dunnigan-Kobberling syndrome, a form of partial lipodystrophy characterized by sparing of the face.

The association between partial lipodystrophy and DDD/MPGNII appears to be related to the effects of dysregulation of the AP of complement on both kidneys and adipose tissue [Mathieson & Peters 1997]. The deposition of activated components of complement in adipose tissue results in the destruction of adipocytes in areas where factor D (fD, adipsin) is high.

Eye findings. Individuals with DDD/MPGNII develop drusen, often in the second decade of life. These whitish-yellow deposits lie within Bruch's membrane beneath the retinal pigment epithelium (RPE) of the retina. The distribution of drusen in individuals with DDD/MPGNII is variable [Duvall-Young et al 1989, Colville et al 2003, Holz et al 2004] and initially has little impact on visual acuity or visual fields.

Over time, however, tests of retinal function such as dark adaptation, electroretinography, and electro-oculography can become abnormal, and vision can deteriorate as subretinal neovascular membranes, macular detachment, and central serous retinopathy develop [Colville et al 2003]. The long-term risk of visual problems in individuals with DDD/MPGNII is approximately 10%.

No correlation exists between disease severity in the kidney and the eye.

Autoimmune diseases. Other autoimmune diseases including diabetes mellitus type 1 and celiac disease have been observed in families with DDD/MPGNII [Sacks et al 1987, Ludvigsson et al 2006].

Pathophysiology. Fluid-phase dysregulation of the AP of the complement cascade is the triggering pathophysiologic event in DDD/MPGNII. During disease progression, activation of downstream complement proteins in the solid phase, in particular cleavage of C5 to C5a and C5b, contributes to tissue injury [Appel et al 2005, Smith et al 2007].

C3NeF persists in serum throughout the disease course [Schwertz et al 2001]. Its presence is nearly always associated with evidence of complement activation such as reduction in serum concentration of CH50, decrease in serum concentration of C3, and increase in serum concentration of C3 degradation products such as C3d. However, the relationship between C3NeF, C3, and prognosis is not clear. Some investigators have reported no correlation between C3 serum concentrations and clinical course [Eisinger et al 1972, di Belgiojoso et al 1977, Davis et al 1978, Bennett et al 1989], while others found that persistent hypocomplementemia indicates a poor prognosis [Klein et al 1983, Kashtan et al 1990].

The observed differences may be reconciled by noting that not all C3NeFs are the same: the triggering epitopes can differ and even change over time.

- Ohi and colleagues (1992) provided evidence that triggering epitopes can differ; their report of six individuals with detectable serum concentration of C3NeF in the absence of hypocomplementemia showed that in these individuals serum C3NeF did not interfere with factor H (fH)-induced inactivation of C3bBb.
- Spitzer and Stitzel (1996) documented that triggering epitopes can change over time; serum concentration of C3 in three affected persons eventually normalized despite continued C3NeF production. C3NeF isolated from these individuals and added to normal sera mediated consumption of C3, as did the addition of normal factor B (fB) to their sera, consistent with a change in the fB autoantigen in these individuals.

Drusen are deposits similar in composition and structure to the deposits observed in the kidney, reflecting similarities between the choriocapillaris-Bruch's membrane-retinal pigment epithelial interface and the capillary tuft-GBM-glomerular epithelial interface.

Genotype-Phenotype Correlations

To date, no correlations have been reported for the DDD/MPGNII phenotype as a function of genotype. Too few cases have had pathogenic mutations of *CFH* to explore phenotype-genotype relationships. It is also possible that pathogenic heterogeneity exists with a final common pathway.

The likelihood of finding a mutation in *LMNA* in a person with lipodystrophy and DDD/MPGNII is not known.

Penetrance

DDD/MPGNII is a complex genetic disease caused by defective regulation of the alternative complement pathway.

Anticipation

Anticipation is not observed.

Nomenclature

The designation 'dense deposit disease' (DDD)/MPGNII refers to the electron-dense transformation of the glomerular basement membrane.

Prevalence

The prevalence of DDD/MPGNII is estimated to be 2-3:1,000,000 population.

Epidemiologic data from the past 30 years indicate that the incidence of the membranoproliferative glomerulonephritides, in general, is declining in developed countries [Jungers et al 1982, Simon et al 1984, Barbiano di Belgiojoso 1985, Jungers et al 1985, Gonzalo et al 1986, Simon et al 1987, Study Group of the Spanish Society of Nephrology 1989, Study Group of the Spanish Society of Nephrology 1990, Simon et al 1994]; most, if not all, of this change can be attributed to a decrease in the incidence of MPGNI. The prevalence of DDD/MPGNII appears to be stable.

Differential Diagnosis

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

The membranoproliferative glomerulonephritides are diseases of diverse and often obscure etiology and pathogenetic mechanisms; they account for approximately 4% and 7% of primary renal causes of nephrotic syndrome in children and adults, respectively [Orth & Ritz 1998].

Based on immunopathology and ultrastructure analysis of the kidney, and of the glomerulus in particular, three subtypes of membranoproliferative glomerulonephritides are recognized.

- **Membranoproliferative glomerulonephritis types I and III (MPGNI, MPGNIII)** are variants of immune complex-mediated disease. MPGNI is characterized by the presence of subendothelial deposits and MPGNIII by the concomitant presence of subendothelial and subepithelial deposits, suggesting that MPGNIII is possibly a morphologic variant of MPGNI, given their clinical, immunologic, and immunohistologic similarities [Ferrario & Rastaldi 2004]. Of note,

however, treatment outcomes following alternate-day prednisone therapy are better for those with MPGNI than for those with MPGNIII [Braun et al 1999].

- **DDD/MPGNII** has no known association with immune complexes. In DDD/MPGNII, pathognomonic dense intramembranous deposits cause capillary wall thickening. Although the list of diseases associated with an MPGN-like pattern and capillary wall thickening is constantly growing, the differences in histology and immunology are sufficient to consider DDD/MPGNII an entity separate and discrete from either MPGNI or III. DDD/MPGNII accounts for fewer than 20% of children with MPGN and fewer than 1% of adults with MPGN [Habib et al 1975].

Other diseases to consider in the differential diagnosis of the renal manifestations of DDD/MPGNII:

- **Juvenile acute non-proliferative glomerulonephritis (JANG),** a disease exclusively of the young (no affected individual exceeded age 12 years in the report by West et al 2000). JANG is characterized by rapid crescent formation but no mesangial cell proliferation. Large subepithelial deposits that contain C3 and C5 but no IgG develop on the paramesangial portion of the GBM. JANG can be distinguished from DDD/MPGNII on clinical grounds as the latter is typically associated with C3NeF-induced hypocomplementemia, often with nephrotic syndrome and hypertension, while in JANG, serum concentrations of C3 remain at the lower limits of normal [West et al 2000].
- **Familial lecithin-cholesterol acyltransferase (LCAT) deficiency,** an autosomal recessive disorder characterized by corneal opacities, normochromic normocytic anemia, and renal dysfunction that can progress to ESRD. High serum concentrations of an abnormal lipoprotein (lipoprotein X) cause glomerular capillary endothelial damage and glomerular deposition of membrane-like, cross-striated structures and vacuole structures. One individual with LCAT deficiency showed glomerular histologic lesions and an immunofluorescent glomerular pattern typical of DDD/MPGNII [Sessa et al 2001].
- **Partial lipodystrophy (PLD)** can be associated with DDD/MPGNII [Eisinger et al 1972]. In persons with PLD, the loss of subcutaneous fat in the upper half of the body usually precedes the onset of kidney disease by several years. The relationship between the two diseases reflects the effects of dysregulation of the AP of the complement cascade on kidney and adipose tissue [Mathieson & Peters 1997]. The deposition of activated components of complement in adipose tissue results in the destruction of adipocytes in areas high in content of factor D (fD, adipsin).

The retinal abnormalities of DDD/MPGNII are similar to those seen in the following:

- **Age-related macular degeneration (AMD),** the most common cause of visual loss in the United States in persons over age 50 years. AMD is characterized by the development of whitish-yellow deposits within Bruch's membrane beneath the RPE. In DDD/MPGNII, drusen develop at an early age and are often detectable in the second decade of life. Both AMD and DDD/MPGNII are associated with common 'at-risk' alleles of *CFH* [Hageman et al 2005].
- **Malattia leventinese** and **Doyne honeycomb retinal dystrophy,** two autosomal dominant disorders in which drusen accumulate beneath the RPE. The two disorders are phenotypically similar to AMD [Stone et al 1999].

Management

Evaluations Following Initial Diagnosis

After the diagnosis of dense deposit disease/membranoproliferative glomerulonephritis type II (DDD/MPGNII) has been made, the following evaluations are recommended:

- Assess the status of the complement system by measuring serum concentration of CH50, APH50, C3, C3d, C4, and factor H. (For a list of laboratories providing these tests, contact either Richard Smith or Peter Zipfel. See Author Information.)
  - Complement protein measures in DDD/MPGNII are distinctive, with most patients having only low serum concentrations of C3, while serum concentrations of properdin, C5, and other terminal proteins are within the normal range.
  - Factor H serum concentrations can be low, as has been reported with missense mutations in the *CFH* coding sequence that block protein secretion from the endoplasmic reticulum [Ault et al 1997, Dragon-Durey et al 2004].
- Measure serum concentration of C3NeF.
- Screen *CFH* for mutations using bidirectional sequencing.
- Establish the extent of renal disease by measuring serum creatinine concentration, and monitoring creatinine clearance and amount of proteinuria and hematuria.
- Perform ophthalmologic examination [McAvoy et al 2004].

Treatment of Manifestations

Nonspecific therapies have been shown to be effective in numerous chronic glomerular diseases and should be initiated. The judicious use of these agents, along with optimal blood pressure control, may be of benefit in individuals with DDD/MPGNII.

- **Angiotensin-converting enzyme inhibitors and angiotensin II type-1 receptor blockers** decrease proteinuria in many glomerular diseases and slow progression to renal failure [Ruggenenti et al 1999, Brenner et al 2001].
- **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 [Nickolas et al 2003, Maisch & Pezzillo 2004]. These agents are not widely used in children.

Renal allografts. Fewer than 200 individuals with DDD/MPGNII have undergone transplantation [Braun et al 2005]. Five-year allograft survival approximates 50%, which is significantly worse than for the NAPRTCS database as a whole (p=0.001). Living related donor grafts fair better than deceased donor grafts (p<0.005).

DDD/MPGNII recurs in nearly all grafts and is the predominant cause of failure in 15%-50% of transplant recipients [Appel et al 2005]. There are little data to suggest that any therapeutic interventions have an impact in reversing this course, although isolated reports have described the use of plasmapheresis, which appears to be of equivocal benefit [Fremeaux-Bacchi et al 1994, Kurtz & Schlueter 2002].

Prevention of Primary Manifestations

Although most treatment for DDD/MPGNII is ineffective, plasma replacement therapy in patients with pathologic mutations in *CFH* can control complement activation and prevent ESRD [Licht et al 2006].

Surveillance

Periodic funduscopic assessment is appropriate [McAvoy et al 2004].

Testing of Relatives at Risk

If one homozygous or two heterozygous *CFH* disease-causing mutations have been identified in an affected individual, siblings can be offered molecular genetic testing to identify those who have the same mutation(s) in order to facilitate early diagnosis and management of renal disease. Penetrance rates, however, are not known.

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

Therapies Under Investigation

A clinical study using sulodexide in persons with DDD/MPGNII who are under 21 years of age is ongoing [ClinicalTrials.gov].

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

Other

The impact of genotype on graft survival has not yet been explored.

Experience with intravenous immunoglobulin (IVIg) and B cell suppression is limited.

The following treatment modalities are of unproven value:

Plasmapheresis to remove or suppress serum C3NeF activity:

- In one study, one of three adults with DDD/MPGNII experienced improvement in serum creatinine during plasmapheresis [McGinley et al 1985].
- Another study reported success using plasmapheresis to treat a five-year-old boy with recurrent DDD/MPGNII after transplantation. Twelve phereses were performed over 24 days, and the child continued to have improved renal function one year later [Oberkircher et al 1988].
- In another report, a 15-year-old girl with rapidly progressive recurrent DDD/MPGNII in her allograft underwent 73 phereses over 63 weeks, stabilizing her creatinine and improving her creatinine clearance. Serial biopsies during this time demonstrated persistent DDD/MPGNII without development of tubular atrophy. During the course of therapy, serum C3NeF activity decreased and C3NeF activity was detected in the removed plasma. Because of the morbidity associated with repeated phereses, treatment was discontinued and graft failure ensued [Kurtz & Schlueter 2002].
- In another report, two patients with a pathologic mutation in *CFH* were successfully treated with fresh frozen plasma [Licht et al 2006].

Prednisone. Long-term controlled studies of prednisone therapy have suggested a possible benefit as measured by a decrease in proteinuria and prolonged renal survival in children with MPGN type I-III [West 1986, McEnery 1990].

However, a randomized placebo-controlled study found that while evidence showed an overall benefit in individuals with MPGNI, II, and III combined, children with DDD/MPGNII had no better response to prednisone than to lactose, with treatment failure defined as a creatinine greater than 350 mmol/L (4 mg/dL) in 55.6% (5/9) and 60% (3/5) of individuals, respectively [Tarshish et al 1992].

Available data on steroid therapy in adults with DDD/MPGNII suggest a similar lack of efficacy [Donadio & Offord 1989].

Note: The use of steroid therapy is extremely effective in JANG, which can be confused with DDD/MPGNII. The two diseases can be distinguished clinically, as DDD/MPGNII is typically associated with C3NeF-induced hypocomplementemia, often with nephrotic syndrome and hypertension, while in JANG, C3 levels remain at the lower limit of normal [West et al 2000].

Calcineurin inhibitors. When evaluated in small numbers of individuals, the calcineurin inhibitors do not improve renal survival in DDD/MPGNII. Furthermore, in vitro studies with two calcineurin inhibitors, cyclosporin and tacrolimus, have shown that at therapeutic concentrations neither drug suppresses C3 transcription [Sacks & Zhou 2003]. Given the evidence that uncontrolled activation of the AP of the complement cascade is the basis of MPGNII/DDD, it is not surprising that these drugs are clinically ineffective immunomodulatory treatment modalities.

Genetics clinics are a source of 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.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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

Dense deposit disease/membranoproliferative glomerulonephritis type II (DDD/MPGNII) is a complex genetic disease that is rarely inherited in a simple Mendelian fashion. Multiple affected persons within a single nuclear family are only reported occasionally; in these instances, parental consanguinity is common [Licht et al 2006]. In persons with DDD/MPGNII in whom two pathologic mutations can be identified in *CFH* or in *CFHR5*, inheritance is autosomal recessive. In most persons with DDD/MPGNII, two pathologic mutations in *CFH* or in *CFHR5* cannot be identified and risks to family members are not known.

Risk to Family Members — Autosomal Recessive DDD/MPGNII

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with DDD/MPGNII are obligate heterozygotes (carriers) for a disease-causing mutation in *CFH* or *CFHR5*.

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

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis if two *CFH* or *CFHR5* mutations have been identified in the proband.

Risk to Family Members — Other Etiologies

Parents, sibs, and offspring of a proband. The risk to the family members of a proband who does not have *CFH* mutations, *CFHR5* mutations, or a family history consistent with autosomal recessive inheritance is low.

Related Genetic Counseling Issues

DDD/MPGNII can be seen in families in which other members have other complex autoimmune diseases, such as diabetes mellitus type 1 and celiac disease [Smith et al 2007].

Family planning. The optimal time for determination of genetic risk and clarification of carrier status is before pregnancy.

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.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of MPGNII/DDD caused by *CFH* or *CFHR5* mutations are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Dense Deposit Disease / Membranoproliferative Glomerulonephritis Type II

Gene Symbol	Chromosomal Locus	Protein Name
CFH	1q32	Complement factor H
CFHR5	1q32	Complement factor H-related protein 5

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Dense Deposit Disease / Membranoproliferative Glomerulonephritis Type II

134370	COMPLEMENT FACTOR H; CFH
608593	COMPLEMENT FACTOR H-RELATED 5; CFHR5
609814	COMPLEMENT FACTOR H DEFICIENCY

Table C. Genomic Databases for Dense Deposit Disease / Membranoproliferative Glomerulonephritis Type II

Gene Symbol	Locus Specific	Entrez Gene	HGMD
CFH	CFH	3075 (MIM No. 134370)	CFH
CFHR5		81494 (MIM No. 608593)	CFHR5

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

CFH

Normal allelic variants: *CFH* comprises 23 exons that encode complement factor H, a protein of 1234 amino acids. Of the several alleles of *CFH*, the one that encodes His402 is of particular interest because of the association of this amino acid substitution with DDD/MPGNII and AMD [Hageman et al 2005, Abrera-Abeleda et al 2006]. The p.Tyr402His polymorphism lies in SCR (short consensus repeat) 7, one of at least three glycosaminoglycan (GAG)-recognition sites in factor H. SCR7 participates in binding to C-reactive protein (CRP) and to a number of pathogens that sequester factor H as protection from complement-mediated destruction. Structural studies have shown that His402 lies toward the center of SCR7, away from its boundaries with SCR8 and 9. The 3D structures of both His402 and Tyr402 are otherwise identical [Herbert et al 2007]. In spite of this similarity, binding studies indicate that the p.Tyr402His change alters the specific types of GAGs that are recognized by SCR7. For example, binding to both human umbilical vein endothelial cells and to C-reactive protein is reduced for the His402 variant as compared to the Tyr402 variant [Laine et al 2007, Skerka et al 2007].

Pathologic allelic variants: See Table 2.

Table 2. Pathologic CFH Alleles

Mutation	Short Consensus Repeat (SCR) (Domain) of the Factor H protein	Type of Mutation	Reference
p.Arg127Leu [1]	SCR2	Missense, homozygous	Dragon-Durey et al 2004 [2]
ΔLys224 [1]	SCR4	Deletion, homozygous	Licht et al 2006
p.Cys518Arg p.Cys991Tyr [3]	SCR9 SCR16	Missense	Ault et al 1997

1. Signal peptide included
2. This paper includes additional *CFH* mutations associated with other types of MPGN.
3. Signal peptide not included

Normal gene product: The normal gene product encoded by *CFH* is complement factor H, a plasma glycoprotein (155 kd) present in blood at concentrations ranging from approximately 500 to 800 µg/mL. It is organized in repetitive elements termed short consensus repeats (SCRs) and controls the alternative pathway (AP) of complement activation, both in fluid phase and on cellular surfaces by binding to three sites on C3b destabilizing C3bBb. In the fluid phase, this interaction results in dissociation of C3bBb into inactive fBb (ifBb) and C3bfH, which is irreversibly inactivated into iC3b by factor I [Pangburn & Muller-Eberhard 1986]. On cellular surfaces, the inactivation of bound C3b is dependent on the chemical composition of the surface to which C3b is bound [Rodriguez de Cordoba et al 2004].

Abnormal gene product: Homozygosity for the p.Arg127Leu missense mutation is associated with absence of factor H in the serum, suggesting that this mutation results in sequestration of the protein in the endoplasmic reticulum. In contrast, theΔLys224 mutation is associated with normal serum and plasma concentrations of non-functional factor H [Zipfel et al 2006].

CFHR5

Normal allelic variants: *CFHR5* comprises ten exons that encode complement factor H related 5 (CFHR5), a protein of 551 amino acids organized into nine SCRs. Several allelic variants have been reported in the normal population; some of these variants are over-represented in persons with DDD/MPGNII and atypical hemolytic uremic syndrome [Abrera-Abeleda et al 2006, Monteferrante et al 2007].

Pathologic allelic variants: No unequivocally disease-causing pathologic allelic variants have been reported in *CFHR5* in association with DDD/MPGNII.

Normal gene product: The normal gene product encoded by *CFHR5* is complement factor H-related protein 5 (CFHR5), a plasma protein organized like CFH in repetitive SCRs. CFHR5 has nine SCRs and is the only CFHR protein that is like CFH in inhibiting C3 convertase in the fluid phase and possessing complement factor I-dependent cofactor activity that leads to inactivation of C3b [McRae et al 2001, McRae et al 2005, Rodriguez de Cordoba et al 2004]. In 92 renal biopsies from patients with different glomerular diseases, CFHR5 was present in all complement-containing glomerular immune deposits [Murphy et al 2002], suggesting that CFHR5 plays an important role in protecting the glomerulus from complement activation. However, the role of CFHR5 in the physiopathology of DDD/MPGNII remains to be elucidated.

Abnormal gene product: No abnormal gene product of *CFHR5* has been reported in association with DDD/MPGNII.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other

organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Kidneeds
Dedicated to the study of Membranoproliferative Glomerulonephritis Type II.
Email: kidneedsMPGN@yahoo.com
www.medicine.uiowa.edu/kidneeds

The Kidney Foundation of Canada
700-15 Gervais Drive
Toronto M3C 1Y8
Canada
Phone: 800-387-4474;416-445-0373
Fax: 416-445-7440
Email: centralontario@kidneycob.on.ca
www.kidney.on.ca

Medline Plus
Glomerulonephritis

National Kidney Foundation
30 East 33rd Street Suite 1100
New York NY 10016
Phone: 800-622-9010; 212-889-2210
Fax: 212-689-9261
Email: info@kidney.org
www.kidney.org

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

Published Statements and Policies Regarding Genetic Testing

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

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