G

glomerular nephropathies with immune deposits may be characterised, on the basis of immunofluorescence analysis, by the composition of the deposits. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absence of immunoglobulins, two main types are recognised. Deposits containing immunoglobulins and classical pathway components are the hallmark of immune complex mediated diseases: primary membranoproliferative glomerulonephritis (MPGN I) and MPGN of immune complex mediated diseases. Depending on the presence or absent...
predispose to HUS.12–15 We screened for these mutations in 19 patients with glomerulonephritis C3, in the absence of HUS.

MATERIALS AND METHODS
Thirty two biopsies with glomerulonephritis C3 were referred to the Department of Pathology, Necker Hospital, Paris, France, between 1971 and 2004 and our analysis was restricted to cases for whom detailed clinical data, follow up and consent for genetic study were available. We included 19 patients with a definite diagnosis of glomerulonephritis C3 established at renal biopsy and without symptoms of HUS. Glomerulonephritis C3 is defined by isolated C3 deposits on immunofluorescence with no Ig deposits, and by the absence of dense intramembranous C3 deposits. Relevant clinical and biological data were collected through review of medical charts. Determination of C3 level was performed at the time of diagnosis in 18 patients before any immunosuppressive treatment. In the only remaining patient (patient No 12), measurement of C3 level was performed during follow up in the absence of any previous or concomitant immunosuppressive treatment. All laboratory tests were carried out as part of the routine follow up of these patients. Informed consent of patients (or parents of children) was obtained before DNA analysis.

Definitions
Creatinine clearance was estimated using the Cockroft–Gault formula. Stages of kidney disease were classed according to the K/DOQI clinical practice guidelines.16

Assays for complement components and genetic screening
All immunological and genetic analyses were performed at the reference laboratory for the investigation of the complement system (Hôpital Européen Georges Pompidou, France). EDTA plasma samples were obtained from all patients and stored at −80°C. Plasma protein concentrations of C3, factor H and factor I were measured as described previously.17 Membrane expression of MCP (CD46) was analysed on granulocytes using a FACScalibur flow cytometer (Becton-Dickinson, Heidelberg, Germany). Fluorescence staining was performed using anti CD46 PE conjugated monoclonal antibodies (IgG1; Serotec, Cergy, France). C3 nephritic factor (C3NeF) activity was determined as described previously18 by assessing the ability of purified IgG from plasma to stabilise the cell bound C3b, Bb convertase.

Direct sequencing of all CFH, IF or MCP exons was undertaken in all 19 patients. Information on the primers and reaction conditions of polymerase chain reaction has been reported previously (Dragon Durey and VFB) and can be provided on request (veronique.fremeaux-bacchi@aphp.fr). To determine whether a mutation was also present in a control collective and therefore more likely be a rare polymorphism than a deleterious mutation, we studied a control population consisting of a panel of 100 locally recruited healthy subjects. These controls were analysed for the presence of all mutations identified in this study using the same technique (200 chromosomes).

RESULTS
Pathological and clinical data
The 19 patients had a peculiar type of glomerulonephritis characterised by overt isolated mesangial C3 deposits (glomerulonephritis C3). They were divided in two groups based on renal pathology findings. In group I (n = 13), renal biopsy disclosed typical features of type I MPGN (glomerulonephritis C3 with MPGN) with mesangial proliferation, subendothelial, mesangial and, less frequently, epimembranous deposits, diffuse “double contours” aspect (fig 1) and accumulation of mesangial matrix with a nodular aspect in four cases (patient Nos 4, 6, 7 and 8). In group II (n = 6), renal biopsy showed a peculiar pattern of mesangial and epimembranous deposits (glomerulonephritis C3 without MPGN) without subendothelial C3 deposits or mesangial proliferation (fig 2).

In all cases, immunofluorescence showed isolated C3 deposits (figs 1, 2) while dense intramembranous deposits with ribbon-like aspects were not detected by light microscopy. C1q and IgG staining was negative. The absence of dense intramembranous deposits was confirmed in two cases (patient Nos 18 and 10) by electron microscopy (fig 2). In these two
cases, mesangial deposits as well as “humps” were present in the absence of dense deposits in the basement membrane.

Patient clinical and biological data for the two groups are shown in tables 1 and 2. There were 10 women and nine men, all caucasian. Median age at onset was 29.9 years (range 7–70), and median follow up was 12.3 years (range 0.4–34.0). Renal symptoms at diagnosis included the following: hypertension in nine cases, stage 1 kidney disease in seven cases, stage 2 kidney disease in seven cases, stage 3 in three cases, stage 4 in one case and stage 5 in one case. Median proteinuria was 3.3 g/day (0.2–9.0), with no proteinuria in one case, a nephrotic syndrome in three cases and microhaematuria in 12 cases. Seological test for hepatitis C was negative in all patients.

Renal disease tended to be more severe in patients with glomerulonephritis C3 with MPGN compared with those with glomerulonephritis C3 without MPGN, with a higher median proteinuria at diagnosis (1.7 vs 0.3 g/day) and a higher percentage of patients reaching ESRD (3/16 vs 0/6) (table 2).

Five patients received steroid treatment (patient Nos 4, 6, 9, 13 and 17) and eight (patient Nos 4, 6, 7, 11, 13, 14, 16 and 18).

Table 1: Clinical and biological data in 19 patients with glomerulonephritis C3

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age* (y)</th>
<th>Sex</th>
<th>HBP*</th>
<th>CrCl* (ml/min)</th>
<th>Puria* (g/day)</th>
<th>Huria*</th>
<th>Follow up (y)</th>
<th>CrCl at last follow up (ml/min)</th>
<th>Puria at last follow-up (g/day)</th>
<th>Histological type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>F</td>
<td>+</td>
<td>117.4</td>
<td>7.7</td>
<td>+</td>
<td>7.0</td>
<td>11.2</td>
<td>4.5†</td>
<td>Group I</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>M</td>
<td>+</td>
<td>97.2</td>
<td>1.7</td>
<td>–</td>
<td>16.5</td>
<td>–</td>
<td>HDI</td>
<td>Group I</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>M</td>
<td>–</td>
<td>115.3</td>
<td>1.5</td>
<td>–</td>
<td>30.0</td>
<td>86.8</td>
<td>4.7</td>
<td>Group I</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>F</td>
<td>–</td>
<td>65.3</td>
<td>6.5†</td>
<td>+</td>
<td>1.2</td>
<td>116.5</td>
<td>1.7</td>
<td>Group I</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>+</td>
<td>51.3</td>
<td>5.7†</td>
<td>+</td>
<td>0.5</td>
<td>46.3</td>
<td>0.9</td>
<td>Group I</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>F</td>
<td>+</td>
<td>68.2</td>
<td>1.3</td>
<td>+</td>
<td>9.0</td>
<td>39.2</td>
<td>1.5</td>
<td>Group I</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>M</td>
<td>+</td>
<td>122.6</td>
<td>0.3</td>
<td>+</td>
<td>14.0</td>
<td>64.8</td>
<td>0.4</td>
<td>Group I</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>M</td>
<td>–</td>
<td>91.6</td>
<td>6.6</td>
<td>–</td>
<td>10.0</td>
<td>28.6</td>
<td>2.8</td>
<td>Group I</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>M</td>
<td>–</td>
<td>102.8</td>
<td>8.2</td>
<td>–</td>
<td>5.5</td>
<td>HDI</td>
<td>1.4</td>
<td>Group I</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>M</td>
<td>–</td>
<td>78.3</td>
<td>0.3</td>
<td>–</td>
<td>0.4</td>
<td>78.0</td>
<td>2.4</td>
<td>Group I</td>
</tr>
<tr>
<td>11</td>
<td>21</td>
<td>F</td>
<td>–</td>
<td>120.6</td>
<td>2.6</td>
<td>–</td>
<td>24.0</td>
<td>66.4</td>
<td>0.1</td>
<td>Group I</td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>F</td>
<td>–</td>
<td>78.6</td>
<td>0.2</td>
<td>+</td>
<td>23.0</td>
<td>HD</td>
<td></td>
<td>Group I</td>
</tr>
<tr>
<td>13</td>
<td>7</td>
<td>F</td>
<td>+</td>
<td>66.6</td>
<td>9.0</td>
<td>+</td>
<td>1.5</td>
<td>54.0</td>
<td>0.3</td>
<td>Group I</td>
</tr>
<tr>
<td>14</td>
<td>9</td>
<td>F</td>
<td>–</td>
<td>44.8</td>
<td>0.7</td>
<td>+</td>
<td>2.5</td>
<td>71.7</td>
<td>0.8</td>
<td>Group II</td>
</tr>
<tr>
<td>15</td>
<td>26</td>
<td>M</td>
<td>+</td>
<td>81.8</td>
<td>0.3</td>
<td>–</td>
<td>23.0</td>
<td>79.5</td>
<td>0.0</td>
<td>Group II</td>
</tr>
<tr>
<td>16</td>
<td>56</td>
<td>F</td>
<td>+</td>
<td>49.8</td>
<td>0.0</td>
<td>+</td>
<td>5.0</td>
<td>40.3</td>
<td>0.0</td>
<td>Group II</td>
</tr>
<tr>
<td>17</td>
<td>70</td>
<td>F</td>
<td>–</td>
<td>28.7</td>
<td>0.3</td>
<td>+</td>
<td>1.5</td>
<td>14.6</td>
<td>5.2†</td>
<td>Group II</td>
</tr>
<tr>
<td>18</td>
<td>37</td>
<td>M</td>
<td>+</td>
<td>97.2</td>
<td>6.2†</td>
<td>+</td>
<td>34.0</td>
<td>66.3</td>
<td>0.0</td>
<td>Group II</td>
</tr>
<tr>
<td>19</td>
<td>21</td>
<td>F</td>
<td>–</td>
<td>83.3</td>
<td>1.6</td>
<td>+</td>
<td>25.0</td>
<td>110.8</td>
<td>0.5</td>
<td>Group II</td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; F, female; FH, factor H; FI, factor I; Group I: GN C3 (glomerulonephritis with isolated C3 deposits) with MPGN; Group II: GN C3 without MPGN; HBP, high blood pressure; HD, haemodialysis; Huria, haematuria; M, male; Puria, proteinuria.

To convert CrCl in ml/min to ml/s, multiply by 0.01667.
*At diagnosis.
†Nephrotic syndrome.
‡Underwent renal transplantation.
were treated with an angiotensin converting enzyme inhibitor. Outcome was very heterogeneous without any significant influence of treatment on renal function. At the last follow up, renal function remained normal in nine cases, was decreased in seven cases and three patients, all in the glomerulonephritis C3 with MPGN group, had end stage renal disease (patient Nos 2, 9, and 12). Patient Nos 2 and 9 underwent transplantation. Recurrence of glomerulonephritis C3 was observed on renal biopsy in patient No 9, one month after transplantation, with proteinuria (1.4 g/day) and normal renal function (CrCl 94.7 ml/min), while no recurrence was noted two months after transplantation in patient No 2 on renal transplant biopsy.

**Complement component assessment**

Plasma complement levels at the time of genetic analysis are shown in table 3.

Seven of the 19 patients presented with a decrease in C3 at the time of the investigation. Five of 16 patients in the glomerulonephritis C3 with MPGN group had low C3 levels compared with 2/6 patients in the glomerulonephritis C3 without MPGN group. In three patients, low C3 level was associated with decreased factor B plasma levels (patient Nos 9, 14 and 16), a finding suggestive of mild CAP activation. Absence of detectable CAP activation, with normal antigenic levels of C3 and factor B, was observed in 12 patients. C3 level was stable during follow up in 13 of 14 patients for whom sequential measurements of C3 were available. In one case (patient No 11), very low levels of C3 were noted at the time of diagnosis while C3 was normal 10 years later at inclusion in the study. All C4 values were normal, which confirm the absence of activation of the complement classical pathway.

All patients except one (patient No 16) had normal factor H antigenic levels. Patient No 16 presented with CAP activation with mildly decreased C3 and factor B and half normal levels of plasma factor H. All others patients had normal factor H antigenic levels. Antigenic levels of factor I were normal in all patients. MCP expression was normal in all tested patients.

At the time of the investigation, C3NeF was detected in the IgG fraction isolated from plasma in 5/13 patients with glomerulonephritis C3 with MPGN and 2/6 patients with glomerulonephritis C3 without MPGN, one of whom had a factor H mutation. The absence of nephritic factor activity was defined by the lack of C3bBb stabilising activity of the patient’s IgG, tested at increasing inputs up to 400 g/assay. In patient No 11, a first blood sample, obtained at the time of diagnosis, showed very low plasma levels of C3 (90 mg/l) with C3NeF activity. A second blood sample was collected 10 years later and showed normal levels of C3 and factor B. At this time, C3NeF activity was no longer detected in plasma. This patient did not receive any immunsuppressive treatment that could alter the assay results.

**Molecular characterisation of mutations**

The complete CFH, IF and MCP sequence was analysed in 19 patients with glomerulonephritis C3 by direct sequencing. Two previously reported mutations (R1210C in the CFH gene and A304V in the MCP gene) and five new mutational events were found in six patients, as summarised in table 4. A unique C3NeF, C3 nephritic factor; CrCl, creatinine clearance; ESRD, end stage renal disease; F, female; FH, factor H; Fl, factor I; GN C3, glomerulonephritis with isolated C3 deposits; M, male; MPGN, membranoproliferative glomerulonephritis; Puria, proteinuria.

Excluding patient No 15 with C3 NeF and FH mutation.
DISCUSSION

In the present study, we have reported a series of 19 patients with glomerulonephritis C3, associated with genetic abnormalities of the regulation of the alternative pathway (AP) in 70% of cases, and which may have a severe outcome.

Regulation of CAP activation depends on a complex system of circulating and/or membrane bound factors, including factor H, factor I and MCP. This regulatory process takes place both in the fluid phase and at the cell surface level, preventing systemic activation of the CAP and complement induced cell lesions, including renal endothelial cells. Several studies have established that uncontrolled activation of the CAP, as a result of factor H, factor I or MCP gene defects or anti-factor H antibodies, is a risk factor for HUS, 12–15 a disease characterised by damage to endothelial cells, erythrocytes and kidney glomeruli, probably through reduced complement regulatory activity at the endothelial cell surface.16 In some rare forms of HUS, mesangial C3 deposits were reported.17 Additional mutations with homozygous factor H deficiency have been associated with MPGN II.

We have observed several cases of an unusual primary glomerulonephritis characterised by isolated mesangial C3 deposits manifest on immunofluorescence. Some patients had typical features of type I membranoproliferative glomerulonephritis (GN C3 with MPGN) and others had mesangial and epimembranous C3 deposits in the absence of mesangial proliferation (GN C3 without MPGN). The recurrence in renal allografts of identical lesions to those in the native kidney proves the existence of a specific entity. Our data indicate that patients with C3 deposits can be divided in two distinct groups based on:

(a) renal pathology features which distinguish patients with typical type I MPGN (glomerulonephritis C3 with MPGN) from those with glomerulonephritis C3 without MPGN (that is, mesangial and epimembranous C3 deposits in the absence of mesangial proliferation). Renal disease tended to be more severe in patients in the first group.

(b) the type of CAP dysregulation that is associated with these glomerular nephropathies. Factor H, factor I or MCP mutations were more frequent in glomerulonephritis C3 without MPGN compared with glomerulonephritis C3 with MPGN patients in which C3NeF was more frequently detected.

C3NeF is a circulating autoantibody that prolongs the half life of the CAP C3 convertase with increased resistance to factor H. The high incidence of C3NeF (and hence the high frequency of decreased C3 levels) in patients with glomerulonephritis C3 with MPGN is consistent with previous reports of a high incidence of C3NeF in type II MPGN as well as in type I (42%) and type III MPGN (50%). The high incidence of C3NeF in our series is of interest. However, the direct pathogenic effect of C3NeF is a matter of debate and it could be an epiphenomenon. Interestingly, in patient No 7, C3NeF was associated with a mutation in factor H, which suggests that these abnormalities may coexist and that unusual types of factor H mutations may increase the risk of the occurrence and/or persistence of C3NeF.

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**Table 4** Molecular characterisation of the genetics defects

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Codon change</th>
<th>Protein domain</th>
<th>Mutation characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH gene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>R1210C</td>
<td>SCR20</td>
<td>Located in SCR20. Previously reported in several unrelated patients with HUS. Is associated with a reduced binding of FH to the central complement component C3b/C3d, as well as to endothelial cells.18 19</td>
</tr>
<tr>
<td>16</td>
<td>P76-X</td>
<td>SCR2</td>
<td>One nucleotide deletion in exon 2 leading to half antigenic levels of FH. Previously reported in more than 10 cases of HUS.</td>
</tr>
<tr>
<td>6</td>
<td>G650V</td>
<td>SCR11</td>
<td>Located in SCR11 close to the C3b binding domain. Other mutations in the same domain have been reported in two patients with atypical HUS.20 21</td>
</tr>
<tr>
<td>CFI gene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>A222G</td>
<td>LDLRA-1</td>
<td>Both mutations are located in two LDLr domains in the heavy chain of FI. The LDLr domains are highly conserved cysteine-rich regions possibly involved in FI ligand binding. These mutations have been reported in 10 patients with HUS.22 23</td>
</tr>
<tr>
<td>18</td>
<td>G243D</td>
<td>LDLRA-2</td>
<td></td>
</tr>
<tr>
<td>MCP gene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>V181M + A304V</td>
<td>SCR3</td>
<td>Two heterozygous mutations associated with normal expression of the protein at the surface of granulocytes. c.747G→A is located in the CFP-3 domain which is highly implicated in the active site of the protein (binding to C4b and C3b), as previously demonstrated using mutagenesis.24 A304V has been reported in patients with HUS.25</td>
</tr>
</tbody>
</table>

HUS, haemolytic uraemic syndrome; LDLr, low density lipoprotein receptor; MCP, membrane cofactor protein. 

FH gene, exon 11 encodes for the transmembrane domain 1. The amino acid numbering refers to the start codon of the sequence after the peptide signal (Met +34).

FI gene, the nucleotide number one is nucleotide located 29 before the start of the peptide signal sequence. The start codon of the sequence after the peptide signal was used as the first amino acid of the protein.

CFI gene, the nucleotide number one is nucleotide located 73 before the ATG used as the first amino acid of the protein.

MCP gene, exon 11 which codes for the MCP transmembrane domain at position 304 (A304V).

Factor H, factor I or MCP mutations were detected in 4/6 patients in the glomerulonephritis C3 without MPGN group compared with 2/13 patients in the glomerulonephritis C3 with MPGN group (table 3). None of the mutations was detected in 100 normal individuals from the same ethnic background.

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Primary glomerulonephritis with isolated C3 deposits

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HUS, haemolytic uraemic syndrome; LDLr, low density lipoprotein receptor; MCP, membrane cofactor protein.
Experimental data support a role for factor H mutations in the occurrence of C3 deposits. Cfh deficient mice, created by gene targeting in which factor H gene has been inactivated (factor H−/−), develop a type of glomerulonephritis C3 with MPGN. The introduction of a second mutation into the gene encoding complement factor B prevents C3 turnover in vivo and obviates the development of glomerulonephritis C3. Conversely, none of the heterozygous deficient (factor H+/−) mice had histological evidence of glomerulonephritis C3 even though plasma C3 levels were depressed, which suggests that in this particular model factor H haploinsufficiency impairs normal C3 convertase control mechanisms but not complement regulatory activity at the cell level. Interestingly, Pickering et al have shown that prevention of C5 activation ameliorates glomerulonephritis C3 in these mice.23

In humans, homozygous factor H deficiencies have been reported previously in rare cases of type II MPGN. Heterozygous factor I deficiency was reported in more than 10 cases with sporadic HUS12,22 and, interestingly, in one case report of immune complex glomerulonephritis with glomerular deposits of immunoglobulin and C3. C3NeF, C3 nephritic factor.

To date, MCP mutations have been published in more than 40 patients with familial HUS pedigrees27–29 and no mutation in MCP has been associated with atypical HUS, is associated with a reduced binding of factor H to surface attached C3b molecules and reduced complement regulatory activity at the cell surface. Several short deletions of one nucleotide in the factor H gene have been associated with heterozygous factor H deficiency in a patient with atypical HUS. Recently, Caprioli et al reported mutation A304V in one patient with a sporadic form of atypical HUS and perhaps an inefficient insert into the lipid bilayer in normal cells. Functional studies were not available for the three new heterozygous mutations. These mutations were not found in over 100 healthy controls, which excludes the fact that the mutations may represent polymorphisms. Most likely these change may also impair the capacity of the regulation of the AP.

Our data show that HUS and glomerulonephritis C3 share common genetic susceptibility factors and that acquired or constitutional uncontrolled activation of the CAP leads to various diseases, ranging from HUS to glomerulonephritis C3 (fig 3). Our results suggest that C3NeF leads to systemic uncontrolled CAP activation, as represented by the C3 consumption noted in patients with glomerulonephritis C3 with MPGN. Conversely, patients in the glomerulonephritis C3 without MPGN group with factor H or factor I mutations had normal C3 (except for patient No 7 with a factor H heterozygous deficiency) which suggests that mutations observed in CAP regulatory genes lead to tissue restricted uncontrolled CAP activation causing C3 deposition, usually in the absence of systemic activation. The difference in CAP activation patterns may explain the wide spectrum of renal diseases associated with CAP dysregulation. Interestingly, in three patients, C3 levels were decreased in the absence of detectable C3Nef or factor H, factor I and MCP mutations. Thus other unidentified genetic or acquired factors may lead to abnormal CAP regulation and renal disease. For example, complement component deficiencies were found with significantly higher frequency among patients with MPGN type I and III in the study of Coleman et al.24

In summary, glomerulonephritis C3 should be added to the expanding spectrum of diseases associated with factor H, factor I and MCP genes mutations. Thus genetic screening is required in patients with glomerulonephritis C3, regardless of the level of circulating C3. The evolution of glomerulonephritis C3 is highly unpredictable, with 15% of our patients reaching end stage renal disease. To date, there is no treatment that has proven efficacy in these patients. The detection of C3NeF and factor H, factor I or MCP mutations in some of our patients suggests that new therapies specifically aimed at controlling CAP activation may represent a possible treatment option for glomerulonephritis C3.

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