CFHR5 Nephropathy in a Greek-Cypriot Australian Family: Ancestry-Informed Precision Medicine

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INTRODUCTION

C3 glomerulopathy is caused by alternative complement pathway dysfunction, leading to abnormal complement activation, deposition, and degradation in the glomerulus. This disorder manifests as predominant glomerular C3 fragment deposition on immunofluorescence, with absent or scant Ig deposition, and electron-dense deposits on electron microscopy.1 C3 glomerulopathy is subsequently classified into dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), based on ultrastructure. Light microscopy of C3GN is more varied compared to DDD, with mesangial matrix expansion, mesangial proliferation, glomerular basement membrane thickening, endocapillary proliferation, leukocyte infiltration, and crescent formation. Electron microscopy demonstrates subendothelial, subepithelial, and mesangial deposits that are less electron dense and less confluent compared with those in DDD. Patients with C3 glomerulopathy can present with persistent microscopic hematuria, synpharyngitic macroscopic hematuria, heavy proteinuria, and progressive renal impairment.2

The alternative complement pathway is a component of the innate immune system, the activation of which leads to pathogen opsonization and killing (Figure 1).1 This process is initiated by the spontaneous hydrolysis of C3 to form C3(H2O), which binds factor B to form C3 convertase. C3 convertase cleaves additional complement factors, which leads to phagocytosis (iC3b), chemotaxis (C5a), and cellular lysis (C5b9). Complement factor H (CFH) and CFH-related proteins regulate C3 convertase activity to prevent uncontrolled complement activation. The 5 CFH-related proteins (CFHR1–CFHR5) are located in the regulator of complement activation gene cluster on chromosome 1. Complement factor H–related protein 5 (CFHR5) is a 65-kDa protein with 9 short consensus repeats.1 CFHR5 downregulates the alternative complement pathway by (i) competitively binding C3b to prevent C3 convertase activity and (ii) acting as a cofactor for the proteolytic inactivation of C3b by complement factor 1.4 CFHR5 mutations involving intragenic duplications (exon 2–3), amino acid substitutions (p.Cys269Arg), and the creation of fusion proteins (CFHR1–CFHR5, CFHR2–CFHR5, CFHR5–CFHR2) have been identified as rare causes of heritable C3GN and DDD (Table 1).5–10

This case presents the first reported Australian family with genetically confirmed CFHR5 nephropathy and discusses the importance of making such a diagnosis, the challenges in its confirmation, and the implications for affected and at-risk family members.

Case Presentation

A 41-year-old sugarcane farmer was referred for further assessment of decreased renal function found incidentally during an admission for an unrelated acute medical condition. He denied any known history of gross hematuria, renal stones, recurrent urinary tract infections, or pyelonephritis. Past medical history was significant for hypertension, dyslipidemia, thalassemia minor, gastroesophageal reflux disease with esophagitis, and diverticular disease. His medications included
escitalopram 20 mg once daily and esomeprazole 20 mg once daily.

A detailed family history confirmed that the patient’s grandfather emigrated from Cyprus to Australia in the late 1920s; the family identified as Greek-Cypriot. The patient’s father, his father’s identical twin (the patient’s paternal uncle), and his paternal aunt were affected by renal disease (Figure 2). Historic renal biopsy samples from affected family members were reported to show membranoproliferative glomerulonephritis with C3 (++++) deposition, but no Ig, C1q, or fibrin deposition. Electron microscopy demonstrated mesangial, subendothelial, and rare subepithelial electron-dense deposits. The patient’s father and paternal uncle progressed to end-stage kidney disease and received kidney transplants in their 50s. The patient’s father survived to 73 years of age, with the cause of death being colon cancer. In contrast, his paternal uncle was diagnosed with biopsy-proven disease recurrence at 76 years of age and is currently alive. The paternal aunt did not proceed to transplantation and died of breast cancer at 51 years of age. A summary of the clinical, histopathological, and genetic features of the family are provided in Table 2.

On examination, the patient’s blood pressure was elevated at 150/100 mm Hg, and his heart rate was 70 bpm. His chest was clear to auscultation, and heart sounds were dual. His abdomen was soft and nontender, with no organomegaly. His jugular venous pressure was not elevated, and there was no pedal edema.

Full blood count demonstrated microcytic anemia (hemoglobin 12.2 g/dl, mean corpuscular volume 61 μm³, red cell count 6.53 × 10¹²/l, normal iron study results) consistent with thalassemia minor. White blood cell and platelet counts were normal at 10.9 × 10⁹/l and 284 × 10⁹/l, respectively. Serum biochemistry showed normal sodium (142 μmol/l), potassium (4.0 μmol/l), and albumin (45 g/l). Serum creatinine and urea were elevated to 180 μmol/l and 11.6 μmol/l, respectively. Estimated glomerular filtration rate (based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) was 39 ml/min per 1.73 m². Complement C3 and C4, antinuclear antibody, and anti-double-stranded DNA antibody were within normal limits. There was an active urinary sediment with >500 red blood cells per high-power field. Urine albumin:creatinine ratio was 24 mg/mmol creatinine, demonstrating subnephrotic proteinuria.

A renal biopsy was performed, and the sample included 13 glomeruli, of which 4 were globally sclerosed. There was diffuse mild mesangial hypercellularity (Figure 3a). No duplication of the basement membrane and no crescents were evident. There was moderate interstitial fibrosis and tubular atrophy, replacing 30% of the cortex. Immunofluorescence was 2 to 3+ positive for C3 deposition in the mesangium and peripheral capillary wall (Figure 3b). There was no Ig or C1q deposition. Electron microscopy showed electron-dense deposits that were subendothelial, mesangial, and subepithelial in location (Figure 3c).

The patient was subsequently referred to the statewide renal genetics clinic based on his prominent family history of C3 glomerulopathy. The clinical and histological phenotypes were evidential of an inherited
Table 1. Reported cases of CFHR5 nephropathy

<table>
<thead>
<tr>
<th>Paper</th>
<th>CFHRS mutation</th>
<th>Age (yr)/gender</th>
<th>Ethnicity</th>
<th>Proteinuria</th>
<th>Hematuria</th>
<th>Serum C3/C4</th>
<th>Renal biopsy</th>
<th>ESKD</th>
<th>Inheritance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gale et al. 2010,6</td>
<td>Exon 2 + 3 duplication; heterozygous</td>
<td>30–80 Male and female</td>
<td>Greek-Cypriot</td>
<td>Mostly absent, &lt;1.7 g/d if present</td>
<td>Recurrent symphatogenic hematuria, microscopic hematuria</td>
<td>C3: normal</td>
<td>C4: normal</td>
<td>C3GN</td>
<td>Yes</td>
<td>AD</td>
</tr>
<tr>
<td>Athanasiou et al. 201110</td>
<td>Exon 2 + 3 duplication; heterozygous</td>
<td>46 Male</td>
<td>Caucasian</td>
<td>Absent</td>
<td>Recurrent symphatogenic hematuria</td>
<td>C3: normal</td>
<td>C4: normal</td>
<td>C3GN</td>
<td>Yes</td>
<td>AD</td>
</tr>
<tr>
<td>Medenaki-Thomas et al. 20133</td>
<td>Exon 2 + 3 duplication; heterozygous</td>
<td>16 Female</td>
<td>Turkish</td>
<td>2.086 g/d</td>
<td>NR</td>
<td>C3: low</td>
<td>C4: normal</td>
<td>C3GN</td>
<td>No</td>
<td>No family affected</td>
</tr>
<tr>
<td>Bestas et al. 201414</td>
<td>p.Cys269Arg substitution; heterozygous</td>
<td>26 Female</td>
<td>European American</td>
<td>High-grade</td>
<td>Present</td>
<td>C3: normal</td>
<td>C4: normal</td>
<td>C3GN, DDD</td>
<td>Yes</td>
<td>AD</td>
</tr>
<tr>
<td>Xiao et al. 201610</td>
<td>CFHR5–CFHR2 fusion protein; heterozygous</td>
<td>8 Female</td>
<td>Indian</td>
<td>1.1 g/d</td>
<td>Microscopic hematuria</td>
<td>C3: low</td>
<td>C4: normal</td>
<td>C3GN</td>
<td>NR</td>
<td>AD</td>
</tr>
<tr>
<td>Togarsimalemath et al. 20168</td>
<td>CFHR1–CFHR5 fusion protein; heterozygous</td>
<td>2 Female</td>
<td>German</td>
<td>Present</td>
<td>Present</td>
<td>C3: low</td>
<td>C4: normal</td>
<td>DDD</td>
<td>Yes</td>
<td>AD</td>
</tr>
<tr>
<td>Chen et al. 20149</td>
<td>CFHR2–CFHR5 fusion protein; heterozygous</td>
<td>2 Female</td>
<td>German</td>
<td>Present</td>
<td>Present</td>
<td>C3: low</td>
<td>C4: normal</td>
<td>DDD</td>
<td>Yes</td>
<td>AD</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; ESKD, end-stage kidney disease; NR, not reported.

*ESKD in any affected family members.
primarily to detect point mutations, such as Sanger sequencing and massively parallel sequencing, are typically unable to detect copy number changes, as was observed in this case. It follows that genetic testing should be tailored toward the suspected condition and its known specific genetic mechanisms. In addition, the use of a renal—histopathologic—genetic multidisciplinary approach was key for the diagnosis of this rare inherited kidney disease.

The CFHR5 nephropathy prevalent in Greek-Cypriot populations is caused by an intragenic duplication of exons 2 and 3 of the CFHR5 gene. The resultant mutant protein binds less effectively to surface-bound complement factors on glomerular membranes compared to wild-type CFHR5. This leads to dysregulated complement activation, resulting in mesangio-proliferative glomerulonephritis and glomerular C3 deposition. CFHR5 nephropathy is inherited in an autosomal-dominant manner with 90% penetrance. In 91 patients across 16 families, CHFR5 nephropathy manifested with microscopic hematuria, synpharyngitic macroscopic hematuria, and proteinuria. Microhematuria was observed in individuals of both genders under the age of 30 years. Of the men, 80% progressed to chronic kidney disease and end-stage kidney disease at age 51 to 85 years. In contrast, only

![Figure 2. Pedigree of family.](image)

Table 2. Clinical, histopathological, and genetic features of affected members of family

<table>
<thead>
<tr>
<th>Feature</th>
<th>II:2</th>
<th>II:3</th>
<th>II:4</th>
<th>III:11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relationship</td>
<td>Aunt</td>
<td>Uncle (twin)</td>
<td>Father (twin)</td>
<td>Proband</td>
</tr>
<tr>
<td>Age at presentation (yr)</td>
<td>38</td>
<td>49</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Proteinauria at diagnosis</td>
<td>4 g/d</td>
<td>Present</td>
<td>3 g/d</td>
<td>Subnephrotic</td>
</tr>
<tr>
<td>Hematuria at diagnosis</td>
<td>Microscopic</td>
<td>Microscopic</td>
<td>Macroscopic</td>
<td>Microscopic</td>
</tr>
<tr>
<td>CKD stage</td>
<td>Pre-ESKD</td>
<td>5</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>Age of native kidney biopsy (yr)</td>
<td>First: 38</td>
<td>First: 49</td>
<td>First: 38</td>
<td>First: 41</td>
</tr>
<tr>
<td></td>
<td>Second: 47</td>
<td></td>
<td>Second: 48</td>
<td></td>
</tr>
<tr>
<td>Histopathology</td>
<td>MPGN type 1</td>
<td>MPGN type 1</td>
<td>MPGN type 1</td>
<td>Mesangial expansion and hypercellularity</td>
</tr>
<tr>
<td></td>
<td>FSFGS</td>
<td>Lymphocytic interstitial infiltrate (patchy)</td>
<td>Lymphocytic interstitial infiltrate (patchy)</td>
<td>Lymphocytic interstitial infiltrate (patchy)</td>
</tr>
<tr>
<td>Immunofluorescence</td>
<td>Unknown</td>
<td>Complement C3 positive (+) in capillary walls</td>
<td>Complement C3 positive</td>
<td>Complement C3 positive (+/++/+ ++++) in mesangium + capillary loops</td>
</tr>
<tr>
<td>Ultrastructure</td>
<td>Dense deposits: subendothelial mesangial epimembranous (rare)</td>
<td>Dense deposits: subendothelial mesangial epimembranous (rare)</td>
<td>Dense deposits: subendothelial mesangial epimembranous (rare)</td>
<td>Dense deposits: subendothelial mesangial subepithelial</td>
</tr>
<tr>
<td>Genotype</td>
<td>Untested CFHR5 Exon 2 + 3 duplication, heterozygous</td>
<td>Untested CFHR5</td>
<td>Exon 2 + 3 duplication, heterozygous</td>
<td></td>
</tr>
<tr>
<td>Age at transplantation</td>
<td>—</td>
<td>55</td>
<td>51</td>
<td>—</td>
</tr>
<tr>
<td>Graft recurrence</td>
<td>N/A</td>
<td>Positive</td>
<td>Negative</td>
<td>N/A</td>
</tr>
<tr>
<td>Years posttransplantation at recurrence</td>
<td>N/A</td>
<td>21</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Age of death</td>
<td>51</td>
<td>—</td>
<td>73</td>
<td>—</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Breast cancer</td>
<td>N/A</td>
<td>Colon cancer</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; ESKD, end-stage kidney disease; FSFGS, focal segmental glomerulosclerosis; MPGN, mesangioproliferative glomerulonephritis; N/A, not applicable.
20% of women progressed to chronic kidney disease at 88 years of age, with the majority exhibiting only microhematuria throughout life. Vernon et al. reported the first case of CFHR5 nephropathy recurrence in a transplant kidney, demonstrating that donor renal-derived CFHR5 protein was insufficient to prevent disease pathogenesis. A single nucleotide polymorphism, miRSNP 1936T in the heparin binding epidermal growth factor (HBEGF) gene was associated with increased progression to chronic renal failure in 78 patients with CFHR5 nephropathy. However, there is currently no clear method of predicting which individuals are at greater risk for progressing to end-stage renal disease.

Anticomplement therapies such as eculizumab have been proposed as a specific treatment for C3 glomerulopathy. In several case studies and small trials, eculizumab improved proteinuria, serum creatinine, and renal biopsy findings. OMS721, a novel antibody against mannan binding lectin serine peptidase 2 (MASP-2), a lectin complement pathway effector, is currently undergoing phase II clinical trials for the treatment of IgA nephropathy, lupus nephritis, membranous nephropathy, and C3 glomerulopathy (NCT02682407). Early results from phase 2 clinical trials showed that OMS721 improved serum creatinine in complement-mediated thrombotic microangiopathy. In a retrospective cohort analysis of 60 patients with C3GN, steroid and mycophenolate mofetil combinations improved renal survival compared with other immunosuppressive regimens and untreated patients. None of these treatments have been specifically applied to patients with CFHR5 nephropathy. However, the rapid development and

Moreover, a genetic diagnosis of CFHR5 nephropathy provides limited information about the development and severity of subsequent renal disease. Among individuals with a causative CFHR5 mutation, 10% do not express clinical features of CFHR5 nephropathy. A single nucleotide polymorphism, miRSNP 1936T in the heparin binding epidermal growth factor (HBEGF) gene was associated with increased progression to chronic renal failure in 78 patients with CFHR5 nephropathy. However, there is currently no clear method of predicting which individuals are at greater risk for progressing to end-stage renal disease.

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Figure 3. Renal biopsy findings. (a) Light microscopy showed diffuse mesangial hypercellularity. (b) C3-dominant immunofluorescence was observed. (c) Subepithelial and subendothelial deposits were observed on electron microscopy.
characterization of treatment modalities for C3 glomerulopathy makes this a candidate therapeutic space for significant change in the next few years.

Notably, CFHR5 nephropathy has been identified in single families of Caucasian (exon 2 and 3 duplication), European American (CFHR5–CFHR2 fusion), Indian (CFHR1–CFHR5 fusion), German (CFHR2–CFHR5 fusion), and Turkish (p.Cys269Arg) descent. Interestingly, CFHR5 nephropathy secondary to fusion proteins tended to present with high-grade proteinuria and facial edema in contrast to CFHR5 nephropathy secondary to intragenic duplications, which predominantly presented with hematuria and/or proteinuria. Together, these findings highlight the value of maintaining suspicion of CFHR5 nephropathy in non-Cypriot patients presenting with nephrotic syndrome.

This case study reports the first diagnosed and confirmed case of CHFR5 nephropathy in an Australian Greek-Cypriot family (Table 3). It highlights the value of obtaining detailed family medical and ethnic history for the diagnosis of rare genetic diseases in everyday nephrology clinical practice. This case also highlights the benefits of a multidisciplinary team approach, along with genetic testing, for identifying and confirming a genetic renal diagnosis.

DISCLOSURE

All the authors declared no competing interests.

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