




## EXCEPTIONAL CASE

# Low factor H-related 5 levels contribute to infection-triggered haemolytic uraemic syndrome and membranoproliferative glomerulonephritis

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## ABSTRACT

Dysregulation of the alternative complement pathway is a major pathogenic mechanism in two rare renal diseases: atypical haemolytic uraemic syndrome (aHUS) and membranoproliferative glomerulonephritis (MPGN). We report on a 66-year-old male with chronic hepatitis C virus (HCV) infection and a combined liver–kidney transplant that was diagnosed with MPGN at the age of 63 years and a 5-year-old boy who presented with aHUS at the age of 21 months following a *Streptococcus pneumoniae* infection. Both patients carried similar frameshift variants in the complement CFHR5 gene that segregate with reduced levels of factor H-related 5 (FHR-5). We conclude that low FHR-5 levels may predispose to viral and bacterial infections that then trigger different renal phenotypes.

**Keywords:** CFHR5, complement, HCV, HUS, MPGN, *Streptococcus pneumoniae*

## BACKGROUND

Pathogenic variants in complement genes that cause dysregulation of the alternative complement pathway are associated with several renal diseases. We describe two patients carrying similar frameshift variants in complement CFHR5 who developed haemolytic uraemic syndrome (HUS) or membranoproliferative glomerulonephritis (MPGN).

## CASE REPORTS

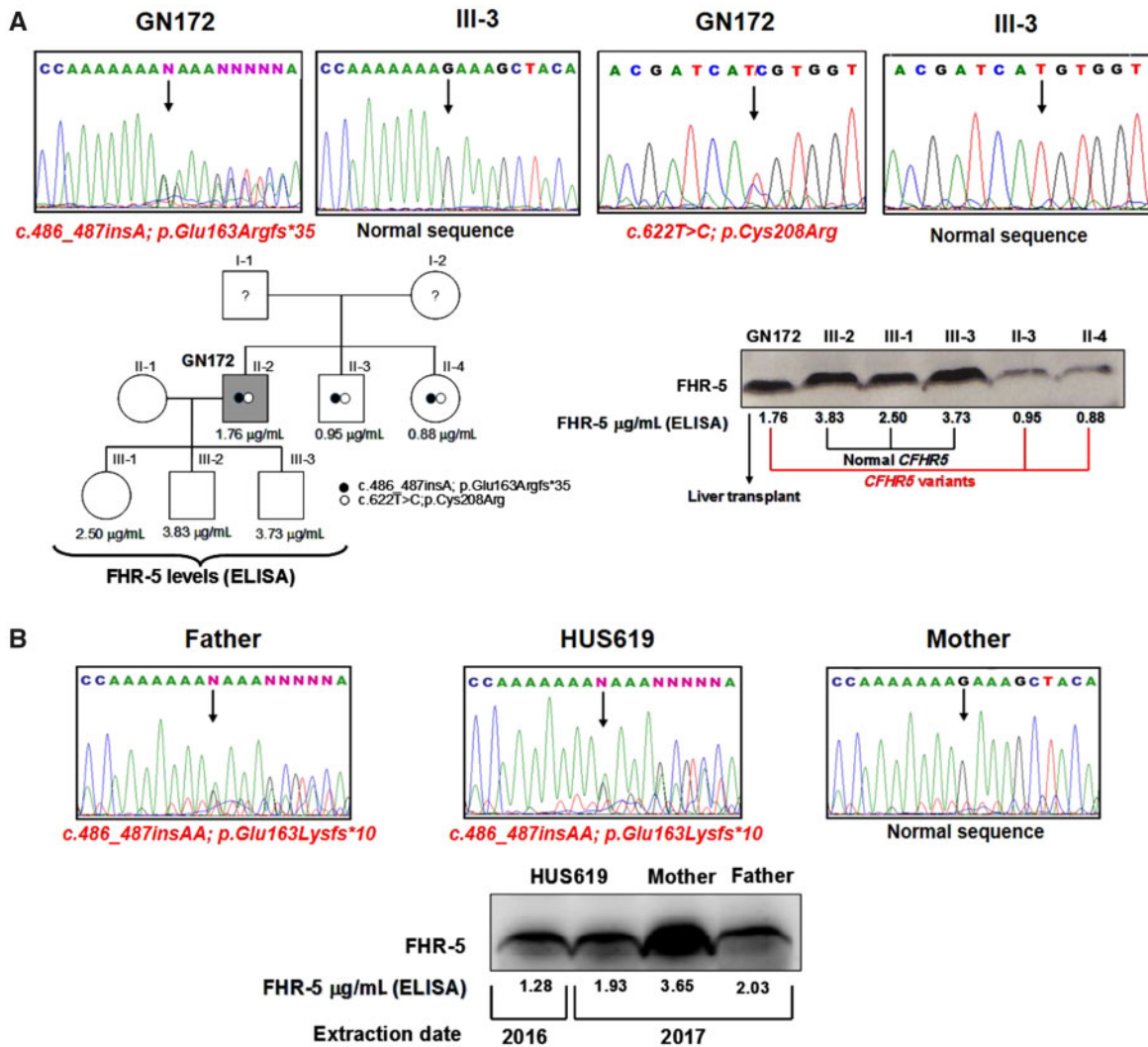
### Patient GN172

In 1997, a 45-year-old male with cirrhosis secondary to chronic hepatitis C virus (HCV) infection received his first orthotopic liver transplantation (OLT). In 2002 he presented with acute renal failure, mild proteinuria and microhaematuria. A renal biopsy was contraindicated because of thrombocytopenia and coagulopathy and the

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**FIGURE 1:** Genetic variants and protein levels in patients GN172 and HUS619. (A) Two genetic variants in *CFHR5* exon 4 (c.486\_487insA; p.Glu163Argfs\*35) and *CFHR5* exon 5 (c.622T>C; p.Cys208Arg) that segregated in the same allele were observed in patient GN172 and his two brothers, but in none of his children. Carriers of the double-mutated *CFHR5* allele have lower FHR-5 levels, as determined by Western blot and enzyme-linked immunosorbent assay. FHR-5 levels in the patient GN172 are higher than in his two brothers because he has a liver transplant. (B) Patient HUS619, who developed HUS in the context of an *Streptococcus pneumoniae* infection, has a similar variant in the *CFHR5* exon 4 (c.486\_487insAA; p.Glu163Lysfs\*10) that was inherited from his father, and that determines lower FHR-5 levels. Patients GN172 and HUS619 did not present mutations in the *CFH*, *CFI*, *MCP*, *C3*, *CFB*, *CFHR1-4*, *THBD* or *DGKE* genes.

patient was started on haemodialysis. In 2003 he required a second OLT but the transplant failed acutely because of an arterial thrombosis. Subsequently the patient received his third OLT and his first kidney transplant. The patient progressed satisfactorily while receiving tacrolimus and prednisone. A further HCV recurrence on the liver graft was treated successfully with ribavirin and interferon. In 2015 the patient presented with oedema and hypertension. Laboratory tests revealed acute renal failure, hypoalbuminaemia, nephrotic proteinuria and microhaematuria. Anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies, anti-DNA, anti-glomerular basement membrane, anti-human leucocyte antigen antibodies, cryoglobulins and HCV viraemia were all negative. A renal biopsy showed thickening of the capillary walls and mesangial matrix proliferation, with immunoglobulins, light chains and complement deposits suggesting immune complex-mediated MPGN (Supplementary data, Figure S1). Despite 6-methylprednisone and rituximab treatment, the patient finally required dialysis. C3 nephritic factor and anti-factor H antibodies were negative, but low C3 with normal C4 levels suggested

activation of the alternative complement pathway. Two heterozygous changes in the *CFHR5* gene determining low plasma factor H-related 5 (FHR-5) levels were detected (Figure 1A). After a second kidney transplant in 2017 with pre-emptive eculizumab for 6 months, the patient has remained stable while receiving the standard immunosuppression and there have been no signs of disease recurrence.

#### Patient HUS619

A 21-month-old boy not vaccinated against pneumococcus presented with pneumonia complicated by pleural empyema, and antibiotic treatment was started (Supplementary data, Figure S2). Polymerase chain reaction was positive for influenza B virus. Two days later he needed to be intubated and required mechanical ventilation; infusions of red blood cells, platelets and plasma, as well as vasoactive amines and continuous venovenous haemofiltration (CVVH) were also necessary. Analytical data were haemoglobin 6.4 g/dL, platelets 30 000/µL, ADAMTS13 54%, schistocytes 9%, haptoglobin <0.06 g/L, creatinine

119  $\mu\text{mol/L}$ , estimated glomerular filtration rate 30 mL/min/1.73  $\text{m}^2$ , cystatin C 1.62 mg/L, lactic dehydrogenase 4290 UI/L, direct Coombs test negative, erythrocyte poly-agglutination T test positive, CH50 <16.47 UI/mL, C3 46.4 mg/dL and C4 10.80 mg/dL. Serum analyses for cytomegalovirus, Epstein-Barr virus, human herpes virus type 6, hepatitis B virus, HCV, human immunodeficiency virus types 1 and 2, blood culture and enterohaemorrhagic *Escherichia coli* were negative, but pneumococcal antigen was detected in urine and pleural fluid and the patient was diagnosed with *S. pneumoniae* HUS (SP-HUS). Urinalysis showed microhaematuria and proteinuria (29.20 g/L, protein/creatinine 33450 mg/mmol) and renal ultrasound revealed increased bilateral echogenicity. The patient became hypertensive and needed CVVH for 13 days. On Day 30, a blood sample was drawn for genetic studies. A variant in the *CFHR5* gene was found to be heterozygous and shown to determine low FHR-5 levels (Figure 1B). The patient progressed well and was discharged on Day 52, remaining stable 3 years later.

## DISCUSSION

Genetic and/or acquired factors that result in dysregulation of the alternative complement pathway are present in many atypical haemolytic uraemic syndrome (aHUS) and immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) patients. A role for complement in the pathogenesis of HUS occurring after SP-HUS has been previously suggested [1], but only a few paediatric *Streptococcus pneumoniae*-associated HUS (SP-HUS) cases having complement genetic variants have been reported [2]. We describe a paediatric SP-HUS patient who had not been vaccinated against pneumococcus and an adult patient with chronic HCV infection status who developed IC-MPGN after liver-kidney transplant. The two patients presented with similar variants in the complement *CFHR5* gene that generate premature stop codons and result in reduced plasma levels of FHR-5. The *CFHR5* variant present in patient GN172 had been previously observed in a post-streptococcal MPGN case and suggested a predisposition to chronic kidney disease [3].

FHR-5 is a 65-kDa plasma protein that may locally enhance complement activation by different mechanisms, including binding to the extracellular matrix and to the acute phase protein pentraxin 3 [4]. Abnormal FHR-5 proteins that increase complement activation have been described in familial cases of C3 glomerulopathies, as initially reported in a large Cypriot pedigree [5]. Conversely, reduced FHR-5 levels should decrease complement activation and increase susceptibility to infections. Why an FHR-5 haploinsufficiency resulted in IC-MPGN (patient GN172) or SP-HUS (patient HUS619) is currently unknown; the viral or pneumococcal infections might have triggered different pathogenic mechanisms in these patients, but other genetic predisposing factors may also contribute.

In summary, we have shown that genetic variants leading to reduced FHR-5 levels may contribute to IC-MPGN or SP-HUS and recommend reconsidering complement genetic screening in these patients.

## PATIENT CONSENT

The patients gave informed consent to publish this case.

## SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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## AUTHORS' CONTRIBUTIONS

I.G.D. performed genetic studies and Western blot analyses and prepared figures. J.G.-T. carried out Western blot and enzyme-linked immunosorbent assay studies. G.M.F.R. and T.C. gathered and described clinical data and prepared figures. E.A. collected biological samples and searched the Spanish aHUS/C3G database ([www.ahusc3g.es](http://www.ahusc3g.es)). P.S.-C. designed the study, prepared figures and wrote the first draft of the manuscript. All the authors revised the data and contributed to the final version of the manuscript.

## CONFLICT OF INTEREST STATEMENT

None declared. P.S.-C. and G.M.F.R. have received speaking fees from Alexion Pharmaceuticals.

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