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CFH/CFHR1 Gene-Linked Mutations Causing Atypical Hemolytic Uremic Syndrome: A Case Report and Literature Review

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ABSTRACT An unusual case of atypical hemolytic uremic syndrome (aHUS) featuring both diffuse alveolar haemorrhage (DAH) and renal-significant monoclonal gammopathy (MGRS) is reported. The researchers describe the clinical course, laboratory findings, genetic analysis, and treatment response of a 38-year-old male patient, supplemented by a review of reported cases with similar genetic variants. The patient exhibited haemolytic anaemia, thrombocytopenia, acute kidney injury, and haemoptysis. Whole exome sequencing identified heterozygous mutations in both CFH (c.3547T>A; p.Trp1183Arg) and CFHR1 (c.700G>C; p.Glu234Gln). The condition improved following plasma exchange and high-dose methylprednisolone, with no recurrence over six months. The researchers present an uncommon manifestation of atypical haemolytic uremic syndrome associated with concomitant CFH and CFHR1 mutations. In regions where eculizumab is unavailable, plasma exchange and steroid therapy remain effective.

INTRODUCTION

The diagnosis of thrombotic microangiopathy (TMA) is primarily reliant on tissue biopsy, most commonly kidney biopsy (Leisring et al. 2024). In normal haemostasis, microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia often co-occur with evidence of organ injury (Leisring et al. 2024). The diagnosis is generally inferred from the coexistence of MAHA, thrombocytopenia, and relevant clinical features. Genetic anomalies in complement system proteins are identified in 50 to 60 percent of individuals with atypical haemolytic uremic syndrome (aHUS), a thrombotic microangiopathy (TMA) subtype (Noris and Remuzzi 2009; Brocklebank et al. 2023; Gupta et al. 2026). The CFH gene and downstream complement factor H-related genes (CFHR3, CFHR1, CFHR4, CFHR2, CFHR5) are located in the CFH/CFHR cluster at chromosome 1q32 (Díaz-Guillén et al. 1999; Zipfel et al. 2020). These genes are critical regulators of the alternative complement pathway (Kopp et al. 2012). Due to high sequence homology, this region is prone to NAHR, leading to deletions, duplications, or rearrangements (Piras et al. 2022; Tasaki et al. 2024). Various CFH/CFHR hybrid genes have been described in aHUS. Here, the researchers report a patient carrying *linked CFH/CFHR1 mutations* presenting with diffuse alveolar haemorrhage (DAH) and monoclonal gammopathy of renal significance (MGRS), representing the first such report in an East Asian population.

Objective

To report an unusual case of aHUS presenting with DAH and MGRS, associated with combined CFH/CFHR1 gene mutations, and to review the relevant literature on CFH/CFHR gene cluster abnormalities in aHUS.

METHODOLOGY

Study Design and Ethics

In accordance with the Declaration of Helsinki, the Institutional Review Board of the First Medical

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Centre, Chinese PLA General Hospital, reviewed and approved the study protocol. Written informed consent was obtained from every participant or guardian.

Clinical and Laboratory Evaluation

Clinical data were extracted from electronic medical records, including demographics, presenting symptoms, laboratory parameters, and imaging studies.

Genetic Analysis and Bioinformatic Prediction

Whole-exome sequencing (WES) was performed in the proband, and candidate variants were validated by Sanger sequencing in relatives. Pathogenicity was predicted with REVEL (>0.75: pathogenic) and ClinPred (>0.5: pathogenic). Functional impact of amino acid substitutions was evaluated using SIFT (d”0.05: damaging) and PolyPhen-2 (0.447-0.909: possibly damaging). Pedigree analysis was performed using the R package *kinship2*, and physical gene maps with *ggplot2*.

RESULTS

Case Presentation

A 38-year-old male farmer was admitted with elevated serum creatinine for one month. One month earlier, he experienced abdominal pain and diarrhoea after ingesting contaminated food, which improved with oral anti-inflammatory medications. Subsequently, he developed fatigue, chest tightness, palpitations, and dizziness. Upon admission, key laboratory results included haemoglobin 74 g/L, platelets 37 × 10y/L, urea 28.6 mmol/L, creatinine 690.3 ìmol/L, uric acid 777 ìmol/L, and lactate dehydrogenase (LDH) 2195 U/L. Urinalysis revealed haematuria (+++), proteinuria (++), 34 red blood cells/HPF, with 5.8 percent schistocytes. Complement C3 was reduced (51.0 mg/dL), with an undetectable haptoglobin level (<6.63 mg/dL) and elevated free light chains (ê: 5.37 mg/dL; ë: 15.5 mg/dL). Serum immunofixation electrophoresis detected IgA-ë monoclonal protein. Figure 1 shows the lung imaging characteristics of this patient.

Bone marrow aspiration showed 2.2 percent abnormal plasma cells. ANCA, anti-GBM antibodies, and Coombs test were negative. Bilirubin was normal. ADAMTS13 activity was 101.01 percent, with no inhibitory antibodies detected. Stool culture was negative. Renal ultrasound revealed cortical thinning, blurred corticomedullary junction, and multiple bilateral renal cysts.

WES revealed two heterozygous missense mutations, that is, CFH c.3547T>A (p.Trp1183Arg) and CFHR1 c.700G>C (p.Glu234Gln). Family analysis indicated maternal samples were negative, and the father (deceased, with history of uremia and pulmonary hemorrhage) could not be tested, suggesting paternal origin (Fig.2). Among six offspring of the proband and his brother (passed away because of lung cancer), one child carried both mutations. The laboratory test results of the proband

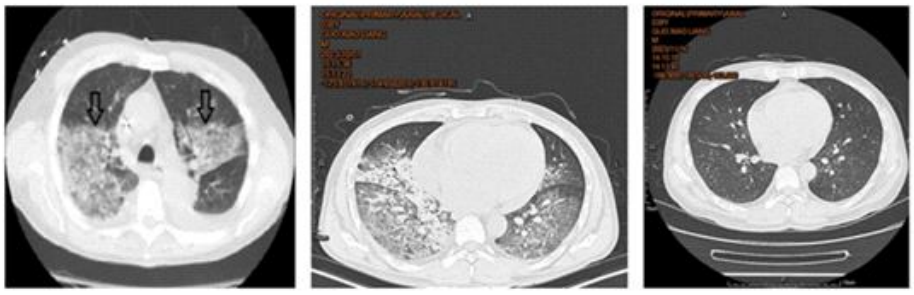

Fig. 1. Lung imaging features of diffuse alveolar haemorrhage in aHUS
(A) Chest computed tomography (CT) from a previously reported aHUS case with DAH, showing diffuse patchy alveolar infiltrates centred around the pulmonary hilum (adapted from Al-Shyoukh et al. 2019)
(B) Chest CT image of the present case, revealing bilateral diffuse ground-glass opacities and increased parenchymal density consistent with diffuse alveolar haemorrhage.
(C) Follow-up CT scan of the present patient one month after treatment, demonstrating marked resolution of pulmonary infiltrates following plasma exchange and corticosteroid therapy

and his mutation-carrying son are compared in Table 1. Co-segregation without recombination confirmed tight linkage inheritance, consistent with cis-configuration within the CFH/CFHR cluster (1q32.3, ~7.5 kb apart).

Bioinformatic Analysis

The CFH variant has been previously reported in aHUS and affects protein function (Ferreira et al. 2009; Ueda et al. 2018; Martín Merinero et al. 2021; Gastoldi et al. 2023). REVEL: 0.667; ClinPred: 0.9986. The CFHR1 variant has not been reported in East Asians, with REVEL: 0.136 and ClinPred: 0.6705. SIFT and PolyPhen-2 both indicated damaging effects (Table 2). In a literature review, five variants of the CFH-CFHR1 gene were identified in the CFH/CFHR cluster (Table 2, Fig. 3).

DISCUSSION

CFH is part of a complement regulatory gene cluster on chromosome 1q32, along with the factor H-related genes CFHR1, CFHR2, CFHR3, CFHR4, and CFHR5. Through two distinct alternative splicing events, the 23-exon CFH gene yields both the 22-exon factor H (FH) and the 10-exon factor H-like protein 1 (FHL-1) (Piras et al. 2022). Each gene produces proteins characterised by short consensus repeats (SCRs), which are approximately 60 amino acids in length. FH consists of 20 SCRs, with the N-terminal SCR1-4 mediating complement regulation as a cofactor for factor I to accelerate C3 convertase decay. SCR6-7 and the C-terminal SCR19-20 domains mediate interactions with C3b, glycosaminoglycans, heparan sulfate, and sialic acid present on cell surfaces, thereby providing cellular protection. The CFHR1 gene comprises six exons encoding five SCRs. Unlike FH, the N-terminal domain of FHRs lacks SCR1-4 and thus does not exert direct complement regulatory activity, a function that remains controversial (Krid et al. 2012; Medjeral-Thomas and Pickering 2016; Banerjee et al. 2022; Márquez-Tirado et al. 2022; Sugawara et al. 2023; Sándor et al. 2024). Owing to the pronounced homology of their C-terminal domains with those of FH, specific FHR proteins can engage in competitive binding with FH for C3b and other surfaces. This interference indirectly fosters complement activation, a process referred to as FH deregulation. Deposition of C3 fragments, factor B, and properdin is enhanced following the binding of FHR-1, FHR-4, and FHR-5 to vascular endothelial cells and the extracellular matrix, facilitat-

Table 1: Comparison of test results between the proband and his son

Testing items	*Proband*	*Period of disease stable period*	*Son*	*Reference range*	*Detection method*
Haemoglobin (g/L)	74	146	211	130-175	Electrical impedance method
Platelets (×10y /L)	37	134	328	125-350	Electrical impedance method
Creatinine (umol/L)	690.3	1167	79	57-97	Oxidase method
Complement C3 (mg/dl Immunoturbidimetry	Ÿ	51	91	103	90-180
Complement C4 (mg/dl)	19.2	20.4	16	10-40	Immunoturbidimetry
Human complement factor H (ug/ml)	1850.1	1550.1	745.98	300-800	ELISA
Human complement factor H antibody (ng/ml)	/	>2000	>2000	0-1425	ELISA
Human complement factor I (ug/ml)	/	135.31	107.47	12.5-125.0	ELISA
Human complement factor B (ng/ml)	/	7.669	153.876	25.35-219.64	ELISA
Soluble complement membrane attack complex (ng/ml)	/	256.318	261.088	12-252	ELISA
Blood immune electrophoresis	IgA-LAM	IgA-LAM	Negative	Negative	Electrophoresis method
Urine immunoelectrophoresis	IgA-LAM	IgA-LAM	Negative	Negative	Electrophoresis method

Abbreviations: IgA-LAM: Immunoglobulin A Lipid Arabino-Mannan; ELISA: enzyme linked immunosorbent assay

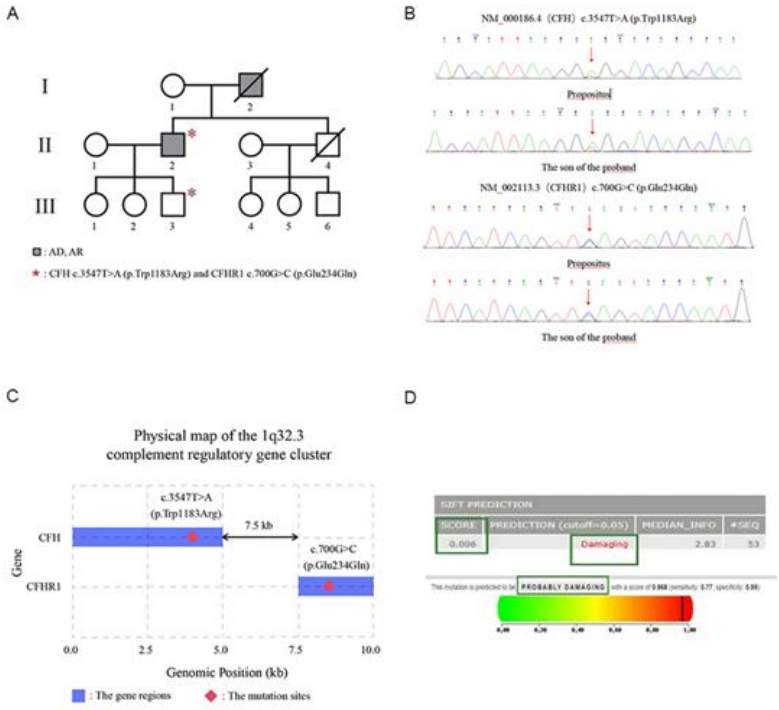

Fig. 2. Genetic findings in the patient and his family
(A) Pedigree chart showing the proband (II-2) and his son (III-3), both carrying heterozygous mutations in CFH and CFHR1 genes.
(B) Sanger sequencing results of the proband and his son, showing heterozygous mutations at NM_000186.4: c.3547T>A (p.Trp1183Arg) in the CFH gene and NM_002113.3: c.700G>C (p.Glu234Gln) in the CFHR1 gene
(C) The genetic physical map shows that CFH and CFHR1 are only approximately 7.5 kb apart in the genomic distance
(D) Functional prediction of the CFHR1 mutation using SIFT and PolyPhen-2 software, with scores indicating likely damaging effects on protein function (SIFT: 0.006; PolyPhen-2: 0.968)

Table 2: Case reports of patients with atypical HUS

Author	*Gender*	*Age at onset*	*Remedy*	*Genetic variation*
Yuko Tasaki (Tasaki et al. 2024)	female	8 months	Eculizumab+PE	CFH::CFHR1 fusion gene
Yuka Sugawara (Sugawara et al. 2023)	female	36y	PE	CFH::CFHR1 fusion gene
Yuka Sugawara (Sugawara et al. 2023)	male	55y	PE	CFH-CFHR1 gene deletion
Elisabetta Valoti (Valoti et al. 2015)	male	52y	MP+PE+HD	CFH::CFHR1 fusion gene
Krid S (Krid et al. 2012)	female	4 y	PE+HD	CFH-CFHR1 gene deletion
Present case	male	38y	MP+PE+HD+PD	CFH-CFHR1 gene linkage

Abbreviations: PE plasmapheresis, MP methylprednisolone, HD haemodialysis, PD Peritoneal dialysis, Gray box Extra copy, Dotted box: Missing

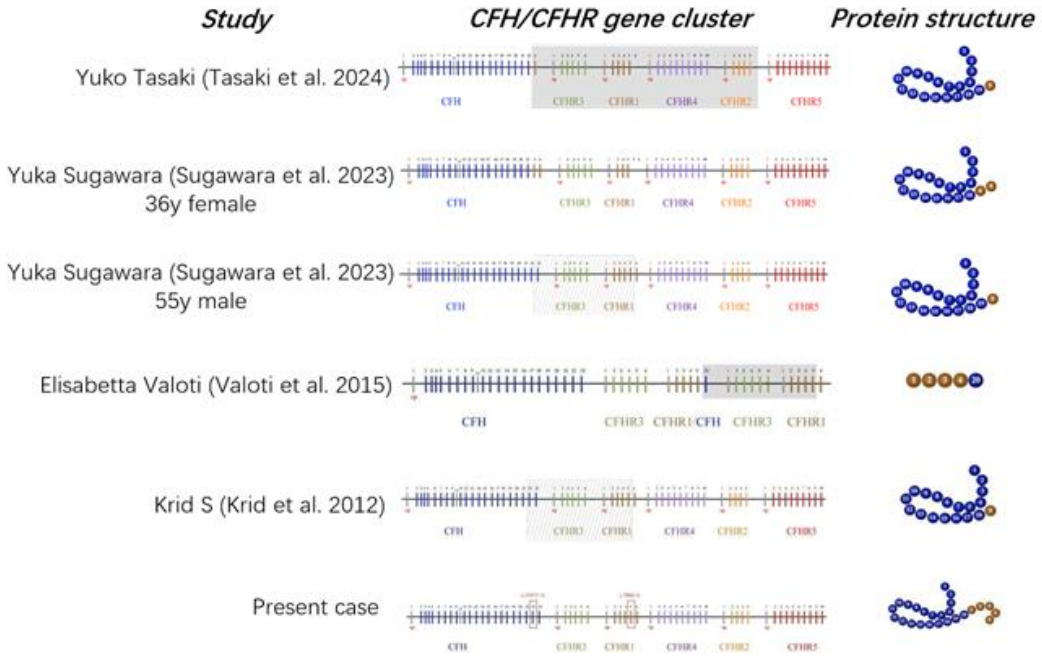

Fig. 3. The CFH/CFHR gene cluster and protein structure, based on case reports of patients with atypical HUS

ing the assembly of an active C3 convertase (Sándor et al. 2024). Evidence points to a bifunctional nature of FHR proteins, which facilitate early-stage complement activation while simultaneously curbing the terminal pathway and associated inflammation, thereby maintaining complement activity within a safe range (Sándor et al. 2024). Inhibition of C5 convertase may occur when FHRs bind densely deposited C3b, preventing C5 convertase formation (Mannes et al. 2021).

Compared with previously reported CFH::CFHR1 fusion genes (three of which also had extra gene copies or deletions), the case presents a unique inheritance pattern of linked inheritance. Specifically, the proband carried co-inherited point mutations in CFH and CFHR1, likely due to their close physical proximity within the CFH/CFHR gene cluster at chromosome 1q32. This produced a non-recombining linked inheritance pattern. As shown in Table 2, previously reported cases often involved structural variants (fusion or deletion), but their inheritance models were unclear. In contrast, the case provides clear evidence of co-segregation of two point mutations across two generations, confirming linked inheritance as a novel pathogenic mechanism (Krid et al. 2012; Valoti et al. 2015; Sugawara et al. 2023; Tasaki et al. 2024).

Clinically, this case is also distinctive due to the concurrent presence of severe DAH and MGR, features rarely observed together in aHUS. DAH is especially rare in aHUS. Only three cases of Campylobacter-associated HUS with DAH have been reported (Delans et al. 1984; Bowen et al. 2016; Al-Shyoukh et al. 2019), none of which included genetic complement analysis. In one report, the diagnosis of aHUS was retrospectively inferred from the clinical response to eculizumab, underscoring the diagnostic challenges and rarity of this phenotype (Piras et al. 2022). In this case, chest CT demonstrated bilateral patchy ground-glass opacities centred around the pulmonary hilum, consistent with DAH. Previous reports emphasised the efficacy of high-dose intravenous corticosteroids in Campylobacter-associated HUS with DAH, which rapidly improved patient outcomes.

In most aHUS patients, CFH variants are clustered in the C-terminal region (Piras et al. 2022). The CFH mutation in the patient was located in exon 22 (SCR19), while the CFHR1 mutation was in exon 5 (SCR4), both affecting C-terminal domains essential for ligand binding. As shown in Table 2, cases 1, 2, 3, and 5 with gene fusions or deletions disrupted FH-C and FHR1-C terminal domains. Loss of these normal domains impairs ligand recognition, leading to excessive early complement activation, while FHR1-C terminal damage further reduces its ability to inhibit terminal complement activation.

In case 4, FHR1-SCR5 was replaced by FH-SCR20, producing a hybrid CFHR-CFH protein that is competitively bound with FH, reducing FH's ligand binding capacity. Two specific amino acid variations (L290, A296), which distinguish FHR1-SCR5 from FH-SCR20, affected the structure and function of the FHR1 C-terminal region. Impairment of the FHR-1 C-terminal domain compromised its competitive capacity against factor H (FH) for ligands such as C3b, diminishing its contribution to early-stage complement activation. As Table 2 shows, in six cases CFH mutations were found, although serum FH levels were normal, most variants resulted in functional deficiency, leaving early complement activation uncontrolled. Similarly, mutated FHR proteins showed reduced C3b binding and impaired ability to promote C5 convertase formation, leading to uncontrolled complement activation.

Unlike previous reports, both the proband and his son in this study tested positive for anti-FH antibodies, though their role remains unclear. As shown in Table 1, during the proband's remission and in his asymptomatic son with the same mutations, haemoglobin, platelet count, and complement levels were normal, with only mildly elevated soluble MAC (C5b-9). This suggests that genetic predisposition alone may not trigger aHUS, and environmental or physiological stressors (for example age, infection, pregnancy, drug exposure) may serve as necessary cofactors.

Pulmonary-renal syndrome is typically seen in anti-GBM disease, ANCA-associated vasculitis, or lupus, but these conditions were excluded serologically in the patient. Although bronchoscopy was not performed due to clinical risk, imaging and clinical features strongly indicated DAH. Although pulmonary hemorrhage is rarely seen in aHUS, it may result from complement-mediated endothelial injury (Martins et al. 2022). Excessive endothelial deposition of the membrane attack complex (MAC) C5b-9, driven by alternative pathway dysregulation due to CFH/CFHR1 mutations, initiates a cascade of thrombosis, microvascular damage, and DAH (Raina et al. 2022).

The key pathogenic mechanism lies in dysfunction of complement regulators. Normally, CFH serves as an essential cofactor for factor I (CFI) and exerts decay-accelerating activity against the C3 convertase (C3bBb). CFHR1, though lacking direct regulatory domains, may modulate FH activity or compete for ligand binding. In this scenario, genetic alterations affecting the C-terminal SCR regions result in defective binding to C3b and cell surfaces, which undermines the regulation of the complement system. Loss of this control promotes complement overactivation and endothelial injury in kidneys and lungs (Józsi et al. 2008). The GBM, a key component of the glomerular filtration barrier, due to its unique structure and lack of membrane cofactor protein (MCP, a key surface-bound regulator), is particularly vulnerable to complement-mediated damage (Poon et al. 2021).

Although the patient also presented with MGRS and anti-FH antibodies, their roles remain unclear and require further study. CFHR1 mutations may promote autoantibody production via epitope exposure or molecular mimicry, though this hypothesis requires functional validation. Importantly, prior studies have shown anti-FH autoantibodies in aHUS are most often associated with CFHR1 deletions, alone or in combination with CFHR3/CFHR4 deletions, rather than point mutations as in this case (Valoti et al. 2019; Piras et al. 2022).

CONCLUSION

This case illustrates a rare presentation of aHUS with DAH and MGRS, associated with combined CFH and CFHR1 mutations. These genetic abnormalities likely drive uncontrolled complement activation, leading to concurrent renal and pulmonary microvascular injury. Where eculizumab is unavailable, plasma exchange combined with corticosteroids remains effective. Comprehensive genetic testing is essential in suspected aHUS, particularly with atypical manifestations such as DAH.

COMPETING INTERESTS

No conflict of interest is declared by the authors.

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This work lacked targeted funding from any source.

AUTHORS' CONTRIBUTIONS

All listed authors have made substantial contributions to this work and fulfill all established criteria for authorship. The study was designed and the manuscript drafted by XLS. QTZ performed the data acquisition, while XPW conducted the literature review. JHZ was responsible for data analysis and correspondence. All authors read and approved the final manuscript.

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DATA AND MATERIAL AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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