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COMMENTARY

Increasing evidence that genetic variation in Complement factor H related 5 (CFHR5) causes disease: A commentary on 'Atypical haemolytic uremic syndrome and genetic aberrations in the complement factor-H-related 5 gene'

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The complement pathway was first recognised over a century ago in 1890. It is composed of a cascade of proteins and is one of the major arms of our innate immune defence system.[1] Complement activation can be initiated by a number of different events, which include direct activation by microorganisms (the alternate pathway) and by antibody binding to antigen (the classical pathway). A striking feature is the potential for massive amplification, which is regulated by intricate control mechanisms. Activation of the complement pathway has been implicated in self-injury in a very diverse range of disease processes, with examples including ischaemic tissue injury, age-related macular degeneration and neurodegeneration. Understanding how the complement pathway operates is important because it will enable us to make specific molecular diagnoses in the (relatively rare) disorders that are directly due to disturbed complement activation, and to develop precise therapeutic interventions for these patients. More broadly, manipulating complement activation may be useful in other settings where complement activation contributes to the disease process. The article by Westra *et al.*[2] suggests that variations in one of the complement regulatory proteins, complement factor-H-related 5 (CFHR5), cause some cases of atypical haemolytic uremic syndrome (aHUS).

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HUS was first recognised in 1955. Most cases are triggered by infection with *E coli* that produce Shiga-like toxin. It involves profound dysfunction of the microvascular endothelium with intravascular coagulation, destruction of red blood cells, consumption of platelets and renal failure. About 10% of cases are classified as 'atypical', because they are not associated with an obvious infectious trigger.[3] These cases are more often familial and have a higher likelihood of recurrence and chronicity. Molecular genetic analyses have shown that many cases of aHUS are associated with mutations in complement regulatory proteins as shown in Table 1. The most frequent mutations are in *CFH*, which encodes complement factor H, a protein that accelerates decay of the active C3 convertase complex, and also acts as a cofactor for factor-I-mediated cleavage of C3b. Recently, the FDA has approved eculizumab, a monoclonal antibody directed against complement C5, for the treatment of aHUS, based on very encouraging phase II studies.

Like *CFH*, *CFHR5* is a gene in the Regulator of Complement Activity cluster on chromosome 1. It encodes a protein homologous to CFH, which is able to regulate components of the alternative pathway in *in vitro* assays. In Westra *et al.*'s[2] study, they screened a collection of 65 individuals with aHUS for genetic variation in *CFHR5*. They found three novel single amino acid substitutions in CFHR5, which are strong candidates for disease-causing mutations: Ser195Thr, Leu 105Arg and Trp436Cys. As is often the case in human genetics, the available evidence falls short of proof that these variants are indeed causing the disease. But it suggests that heterozygosity for a single amino acid substitution in CFHR5 can lead to aHUS. Importantly, an independent study of another aHUS cohort found three other nonsynonymous coding variants in CFHR5,

Table 1 Genetic abnormalities in aHUS

Gene	*Main effect of mutations*	*Percentage of cases (%)*
CFH	Disturbs binding of CFH to endothelium	20–30
CFHR1/3	Development of anti-factor H antibodies	6
MCP	No surface expression of MCP	10–15
CFI	Low level of CFI/low cofactor activity	4–10
CFB	Abnormally stable C3 convertase	1–2
C3	Resistance to C3b inactivation	5–10
THBD	Reduced C3b inactivation	5
CFHR5	Unknown	3–5

Abbreviations: aHUS, atypical haemolytic uraemic syndrome; CFH, complement factor-H; CFHR5, complement factor-H-related 5.
Adapted from Noris and Remuzzi.[3]

Glu75Xaa, Val277Asn and Val379Leu, which were not present in controls.[4]

For patients with mutations in *CFHR5* and aHUS, one consequence is that there is likely to be a substantial risk of recurrence following renal transplantation, as CFHR5 (like CFH) is made in the liver. The association of missense mutations in *CFHR5* with aHUS adds to an emerging literature, implying that CFHR5 is a critical regulator of the alternate pathway in humans, and that subtle variations can cause disease. A duplication of two exons of the gene results in a C3 glomerulonephritis (CFHR5 nephropathy) in which there is deposition of complement in the kidneys and progressive renal failure without systemic complement depletion or thrombotic microangiopathy.[5] Dense deposit disease (membranoproliferative glomerulonephritis type II) is another C3 glomerulopathy caused by uncontrolled alternative pathway activation, and there is some evidence that single-nucleotide polymorphisms in *CFHR5* may be associated with the condition.[6] Most recently, a child with persistent C3 glomerulopathy (histologically type I membranoproliferative glomerulonephritis) was found to be heterozygous for a single insertion causing a premature stop codon and reduced circulating CFHR5.[7] Interestingly, in kindreds with the duplication of exons 2 and 3 of *CFHR5*, and in those with a frameshift and premature stop codon, there are individuals (especially women) with the mutation, who do not have significant renal disease, establishing that this change is not sufficient to cause disease, and implying that other genetic and environmental factors are required.

A number of important questions remain to be addressed. It will be interesting to determine whether the type of mutation reliably predicts whether individuals are at risk of aHUS or C3 glomerulopathy, and understanding why this is the case. An intriguing issue is why alterations in CFHR5 have any effect, given that the circulating concentration of CFHR5 is much lower than CFH and that it seems to be a less potent regulator in *in vitro* assays. What these studies in humans imply is that CFHR5 is not redundant with CFH, and challenge us to understand its precise role in regulating complement activation.

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