Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis


Summary

Background Complement is a key component of the innate immune system, and variation in genes that regulate its activation is associated with renal and other disease. We aimed to establish the genetic basis for a familial disorder of complement regulation associated with persistent microscopic haematuria, recurrent macroscopic haematuria, glomerulonephritis, and progressive renal failure.

Methods We sought patients from the West London Renal and Transplant Centre (London, UK) with unusual renal disease and affected family members as a method of identification of new genetic causes of kidney disease. Two families of Cypriot origin were identified in which renal disease was consistent with autosomal dominant transmission and renal biopsy of at least one individual showed C3 glomerulonephritis. A mutation was identified via a genomewide linkage study and candidate gene analysis. A PCR-based diagnostic test was then developed and used to screen for the mutation in population-based samples and in individuals and families with renal disease.

Findings Occurrence of familial renal disease cosegregated with the same mutation in the complement factor H-related protein 5 gene (CFHR5). In a cohort of 84 Cypriots with unexplained renal disease, four had mutation in CFHR5. Overall, we identified 26 individuals with the mutation and evidence of renal disease from 11 ostensibly unrelated kindreds, including the original two families. A mutant CFHR5 protein present in patient serum had reduced affinity for surface-bound complement. We term this renal disease CFHR5 nephropathy.

Interpretation CFHR5 nephropathy accounts for a substantial burden of renal disease in patients of Cypriot origin and can be diagnosed with a specific molecular test. The high risk of progressive renal disease in carriers of the CFHR5 mutation implies that isolated microscopic haematuria or recurrent macroscopic haematuria should not be regarded as a benign finding in individuals of Cypriot descent.

Funding UK Medical Research Council and Wellcome Trust.