Complement factor H-related hybrid protein deregulates complement in dense deposit disease.

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Abstract

The renal disorder C3 glomerulopathy with dense deposit disease (C3G-DDD) pattern results from complement dysfunction and primarily affects children and young adults. There is no effective treatment, and patients often progress to end-stage renal failure. A small fraction of C3G-DDD cases linked to factor H or C3 gene mutations as well as autoantibodies have been reported. Here, we examined an index family with 2 patients with C3G-DDD and identified a chromosomal deletion in the complement factor H-related (CFHR) gene cluster. This deletion resulted in expression of a hybrid CFHR2-CFHR5 plasma protein. The recombinant hybrid protein stabilized the C3 convertase and reduced factor H-mediated convertase decay. One patient was refractory to plasma replacement and exchange therapy, as evidenced by the hybrid protein quickly returning to pretreatment plasma levels. Subsequently, complement inhibitors were tested on serum from the patient for their ability to block activity of CFHR2-CFHR5. Soluble CR1 restored defective C3 convertase regulation; however, neither eculizumab nor tagged compstatin had any effect. Our findings provide insight into the importance of CFHR proteins for C3 convertase regulation and identify a genetic variation in the CFHR gene cluster that promotes C3G-DDD. Monitoring copy number and sequence variations in the CFHR gene cluster in C3G-DDD and kidney patients with C3G-DDD variations will help guide treatment strategies.

Identifier

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