SIGNIFICANCE STATEMENT

Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy associated with complement genetic abnormalities. A retrospective genetic analysis in our aHUS cohort (n=513) identified nine unrelated patients carrying a novel genetic abnormality that causes the transfer of DNA fragments between two complement genes. This genetic abnormality, which escapes detection by currently-used next-generation massive parallel DNA (NGS) sequencing, generates a strong competitor of factor H, the main complement regulator that prevents complement-mediated damage to host tissues. The result is complement dysregulation and endothelial damage. The data advance understanding of the genetic complexities underlying aHUS and illustrate the importance of functional assays to disclose genetic abnormalities not revealed by current NGS analysis.