

P017 Disease-associated sequence variations congregate in a GAG recognition patch on human factor H revealed in 3D structure
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Mutations and polymorphisms in the complement regulator, factor H, are linked to atypical hemolytic uremic syndrome (aHUS), membranoproliferative glomerulonephritis, and age-related macular degeneration. aHUS is a thrombotic microangiopathy occurring primarily in the kidneys. It is characterised by hemolytic anemia, thrombocytopenia, and acute renal failure. Many aHUS patients carry mutations in the two C-terminal modules of factor H, which normally confers its ability to selectively recognise and protect self-surfaces. This host recognition process occurs through recognition of GAG markers on self surfaces. In this study, the 3D structure of the C-terminal module-pair of factor H has been determined. A binding site for a heparin-derived tetrasaccharide has been delineated using chemical shift mapping, and the C3d/C3b-binding site inferred from sequence comparisons and computational docking. The result allows assessment of the likely consequences of aHUS-associated amino acid substitutions in this region of factor H. Strikingly, excepting those likely to perturb the 3D-structure, aHUS-associated missense mutations congregate in the GAG binding site potentially disrupting a vital mechanism for regulating complement on self-surfaces in the microvasculature of the kidney.