**Genomic Rearrangement Events in the RCA Cluster as a Cause of aAypical Haemolytic Uraemic Syndrome**

**Introduction**

Atypical Haemolytic Uraemic syndrome (aHUS) is a triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury. Familial aHUS most commonly occurs as a result of inherited mutations in the complement regulatory protein (CFH), resulting in uncontrolled alternative complement activation. *CFH,* along with five highly homologousgenes (*CFHR1-5*), is located within the Regulators of Complement Activation cluster. Due to the high degree of homology*,* this region is prone to genomic recombination events, resulting in hybrid genes (*CFH::CFHR1* and *CFHR1::CFH*), which fail to regulate complement activation thus predispose to aHUS.

**Method**

Patients referred to the National Renal Complement Therapeutic Centre with a diagnosis of aHUS (*n=984*) underwent both direct sequencing of known aHUS genes,to identify point mutations and MLPA of *CFH* and *CFHR*s to investigate copy number*.* Genomic rearrangement events generating CFH::CFHR1 hybrid were identified using copy number analysis demonstrating loss of sequence underlying the probes covering *CFH* Ex.22/23 and gain of the corresponding sequence of *CFHR1* (Ex.5/6). CFHR1::CFH hybrids were identified due to loss of *CFHR1* Ex.5/6 and gain of *CFH* Ex.22/23.

**Results**

Direct sequencing identified 77 cases with pathogenic variants in *CFH*. Copy number analysis revealed an additional 46 patients with either *CFH::CFHR1* or *CFHR1::CFH* hybrids, which could then be subdivided in to gene conversions, single crossovers and double crossover events, based on the copy number of CFHR3 and CFHR1 Ex.1-4.

**Discussion**

Genomic rearrangement events within *CFH* are responsible for one third of pathogenic variants in *CFH* in aHUS. These events will not be identified by Sanger or whole exome sequencing techniques, as the correct sequence is present, but in the wrong genomic location. Copy number analysis is therefore essential to ensure patients with these variants are not missed.