

P037

P037 -Large scale whole-genome sequencing reveals the genetic architecture of primary membranoproliferative glomerulonephritis and C3 glomerulopathy

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Primary Membranoproliferative glomerulonephritis and C3 Glomerulopathy (PMG) is a rare, untreatable kidney disease characterized by glomerular complement deposition. Familial C3 glomerulopathy (a subtype of PMG) can be caused by complement gene mutations and rare variants in such genes have also been reported in people with non-familial PMG. We performed whole-genome sequencing in 165 PMG cases, recruited via the Rare Renal Disease Registry (RaDaR), alongside over 10,000 individuals participating in the National Institute of Health Research BioResource-Rare Diseases Study. We observed no significant enrichment of rare variants in cases, either in the candidate complement genes or exome-wide. However, two significant common variant loci were identified: 6p21.32 overlapping the major histocompatibility complex, and 12q14.1. Imputation of HLA types mapped the chromosome 6 signal to a specific haplotype ($p = 2.75 \times 10^{-9}$, OR 2.28), a finding that was replicated by analysis of HLA serotypes in 338 individuals with membranoproliferative glomerulonephritis and 15,614 individuals with non-immune renal failure undergoing renal transplantation in the UK over the past 25 years ($p = 1.4 \times 10^{-4}$, OR 1.44). These findings challenge the paradigm of causative complement gene mutations in non-familial PMG and imply a causal role of autoimmune mechanisms in the disease.