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P048 -A large family kindred with CFHR5 Nephropathy

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CFHR5 nephropathy (OMIM:614809) is a recently described autosomal dominant complement mediated renal disease; characterised by persistent microscopic haematuria, with episodes of macroscopic haematuria associated with pyrexial illness and appearances of predominant C3 deposition on renal biopsy. Progression to end stage renal disease is common in males with the condition, whilst this is rare in women, the reason for this is unclear. The pathogenesis of CFHR5 nephropathy remains unclear.
The alternative complement system is constitutively active and therefore requires tight regulation to prevent inappropriate complement mediated damage to healthy host tissues. Located on chromosome 1 in the regulators of complement activation (RCA), complement factor H (CFH) is one of the key regulators of the alternative complement cascade; Pathogenic variants in CFH result in atypical haemolytic uraemic syndrome and C3 glomerulopathy. Within the RCA there are five CFH related genes (CFHRs); the roles of the CFHRs (including CFHR5) are less clear.
CFHR5 nephropathy was originally described in multiple patients of Cypriot origin. These patients were found to have a founder mutation resulting in a common internal duplication of exon 2 and 3. Subsequently this disease has been described in patients without Cypriot ancestry, these patients were found to have a novel intronic variant resulting in duplication of exon 2 and 3. The resultant CFHR5 is thought to result in a protein that is not able to regulate complement.

Method
We describe a large kindred (figure 1), without Cypriot ancestry, in which eight generations have evidence of persistent haematuria and renal disease. Renal biopsy in two affected individuals demonstrated C3 glomerulopathy. We therefore undertook analysis of the complement system assessing copy number with MLPA. This demonstrated 3 copies of CFHR5 exons 2-3. Breakpoint analysis with Sanger sequencing identified the same breakpoint as identified in the previous non-Cypriot families. Serum was available from selected individuals and Western blotting analysis demonstrated an aberrant CFHR5 molecule.
Discussion
We describe a large family with persisted microscopic haematuria, biopsy evidence of C3 glomerulopathy and progression to end-stage renal failure in selected individuals. Using MLPA we have identified a known pathogenic internal duplication in CFHR5. This case highlights the importance complement analysis in patients with a family history of persistent microscopic haematuria to identify patients with CFHR5 nephropathy.