Familial microscopic hematuria as a paradigm for a "multifactorial" Mendelian disease: A unique Cyprus experience

Professor Dr Constantinos Deltas
Director, Molecular Medicine Research Center, University of Cyprus, E-mail: Deltas@ucy.ac.cy

Summary

Familial microscopic hematuria (blood in urine) is a genetically heterogeneous group of autosomal dominant conditions that present with microscopic hematuria (MH) since childhood and may or may not be progressive on follow-up. Several genes are involved that include mainly collagen IV genes of the glomerular basement membranes (GBM), CFHR5, MYH9, and FN1. In Cyprus we have a unique experience with a large cohort of patients who inherit heterozygous mutations in the COL4A3/COL4A4 genes and develop a condition which is known as Thin Basement Membrane Nephropathy (TBMN) (basement membrane of the glomerulus is thinner than normal). In particular, among several other mutations, there is a wide founder effect for mutation COL4A3-p.G1334E, where there is a substitution of glutamate for glycine at aminoacid residue 1334 of the collagenous domain of the alpha 3 chain, of the trimer α3α4α5 in the GBM. Remarkably, this and the other mutations, result in a broad phenotypic spectrum. Specifically, on one end of the spectrum are patients who present with MH in childhood and will reach advanced age with either isolated MH or MH with added low grade proteinuria, without clinical significance. Importantly however, a significant percentage of the patients will progress to high grade proteinuria and chronic renal failure later in life, in the presence of focal and segmental glomerulosclerosis. According to our cohort with more than 250 patients, about 30% of all patients will reach end-stage renal failure by the age of 70 years, thereby coming into contrast with older literature, which considered this condition as benign, with excellent prognosis on long follow-up. Our group at the Molecular Medicine Research Center, in collaboration with many clinicians Cyprus wide, were the first to document these findings and alert the international community of this potential outcome of TBMN patients. Molecular genetic studies in our lab are focused on these patients and offer timely accurate diagnosis to patients with microscopic hematuria. In conclusion, the finding of familial MH with or without proteinuria of glomerular origin should be investigated further and the option for a genetic analysis be offered before a renal biopsy is considered. Also, the full spectrum of this monogenic condition behaves as a multifactorial trait, as additional genetic modifiers are implicated to play a crucial role in disease development.