Pure microscopic hematuria, especially familial, in early life, resulting from heterozygous COL4A3/A4 mutations and CFHR5 C3 nephritis, may be responsible for many cases of CRF and ESKD in later life.

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INTRODUCTION AND AIMS: According to classical nephrology practice, pure microscopic hematuria of glomerular origin (GMH) is not considered a serious problem and up to date diagnostic studies, including renal biopsies, are not always carried out. Family urine studies to confirm or rule out a familial disease should always be carried out early and, if positive, molecular genetics should be used to study the whole family and establish the underlying genetic defect.

METHODS: During the last 30 years, we have searched systematically a homogeneous population of 650 000 people for familial GMH and some 120 such families are under study so far. Molecular genetic studies during the last 10 years have led to a genetic diagnosis in 59 such families. In particular, 30 families with a heterozygous COL4A3/A4 mutation and TBMN were identified, 23 families with the same mutation in the CFHR5 gene and C3 nephritis and 6 families with the Alport syndrome.

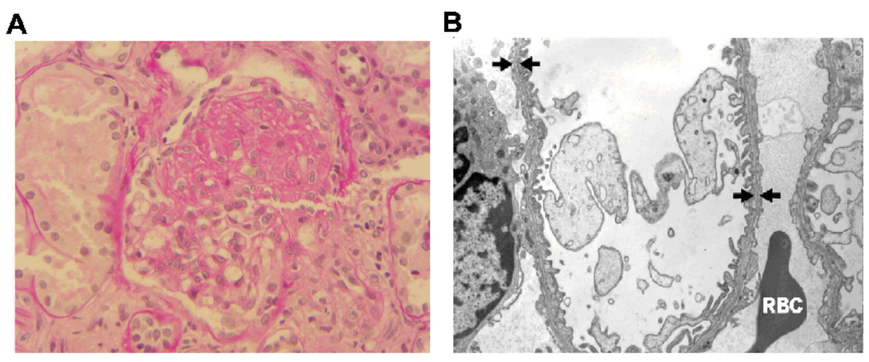

Figure 1:
Biopsy of a patient carrying the heterozygous COL4A3-G1334E mutation, the most frequent COL4 mutation in Cyprus. **A)** H&E X 220 showing classical segmental glomerulosclerosis. **B)** EM x12,000 showing diffuse thinning of GBMs measuring 200nm in thickness (arrows). An RBC is seen in the Bowman's space (x12,000) *[from Pierides et al, NDT, 2009]*

RESULTS: The most striking finding refers to the COL4A3/A4 heterozygous mutations that turn out to be the commonest cause of familial MH and have been identified in 249 carriers in 30 families. Some of these families are very big indeed and two of these mutations, COL4A3-G1334E and COL4A3-G871C, are particularly common **(Figure 1)**. Mutation COL4A3-G1334E was found in 174 patients coming from 15 families. C3 nephritis caused by the CFHR5 Cypriot mutation appears to be the second commonest cause of familial MH with 150 carriers in 23 families. Classical XLAS, caused by COL4A5 mutations, was identified in 3 families with 9 affected males and 8 female carriers, while ARAS was the diagnosis in 3 additional families, affecting 8 patients **(Figure 2)**. Among the 249 patients carrying a COL4A3/A4 heterozygous mutation and the 150 CFHR5 patients, 33 and 21 patients respectively have reached ESKD.

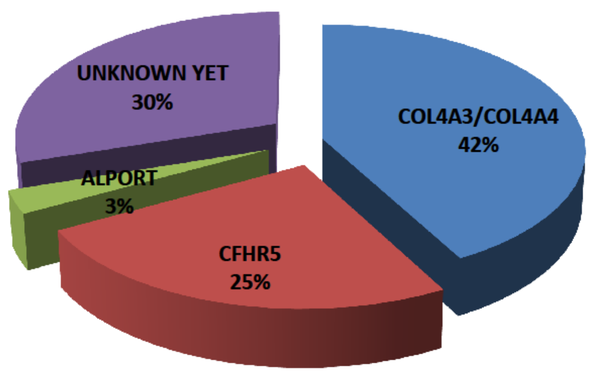

Figure 2:
Percentages of FMH causes in Greek-Cypriots. Our studies document FMH in 596 carrier members in 120 large families. 249 patients (42%) carry one *COL4A3/A4* mutation and 17 (3%) an X-linked COL4A5 mutation. 150 patients (25%) carry the new CFHR5 mutation, while 180 patients (30%), have as yet no definitive diagnosis.

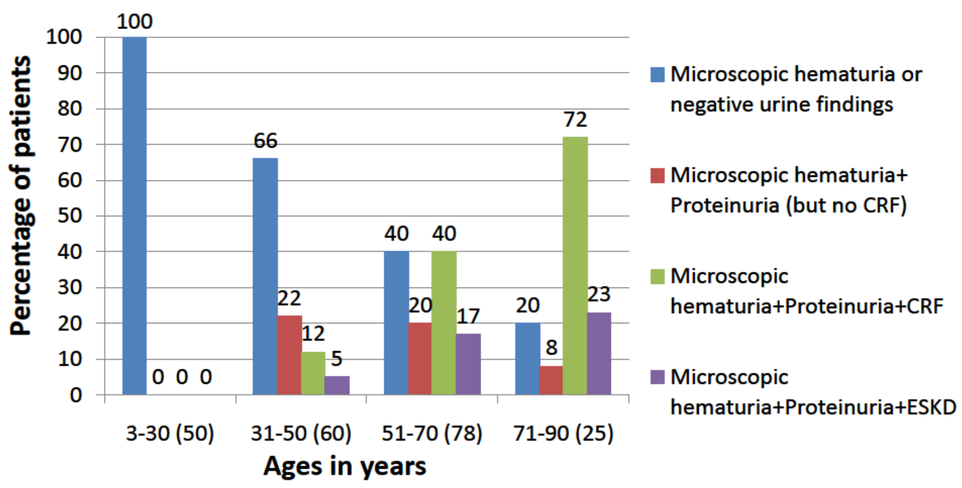

Figure 3:
Spectrum and distribution of findings/symptoms (%) according to age among 213 live patients with TBMN. The absolute numbers of patients are noted in parenthesis.
Note that until the age of 30 years, there is only isolated microscopic hematuria, while 40% of patients aged 51–70 years have developed chronic renal failure.

CONCLUSIONS: The results strengthen the great significance of the heterozygous COL4A3/A4 mutations, as a cause of ESKD in later life. These mutations that lead to TBMN are common and furthermore they represent the commonest cause of familial hematuria. More importantly, however, these mutations may lead much later in life to proteinuria, arterial hypertension, CRF and ESKD **(Figure 3)**, indicating the need for careful long term follow up. COL4A3/A4 heterozygous mutations, compared to classical XLAS and ARAS, are the cause of ESKD in twice as many patients but fortunately at a much older age. CFHR5 nephropathy, a new entity, is now part of the spectrum of familial hematuria, so this disease should be included in the differential diagnosis, especially in Cyprus where most cases are coming from.
Molecular genetics should be used more widely in order to establish a definite diagnosis of these entities causing familial MH. Long term follow up of these patients is mandatory for the early detection of evolving kidney disease and appropriate management to preserve kidney function.

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