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Pathophysiology of familial microscopic hematuria (FMH) with thin basement membranes and/or progressive kidney disease. *COL4A3/A4* heterozygous mutations are the commonest cause but Alport *COL4A5* hypomorphic, missense mutations are also a possibility.

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INTRODUCTION: Familial Microscopic Hematuria diagnosis & molecular genetics

Molecular genetics (MG) allows now for accurate diagnoses and elimination of uncertainties based on electron microscope (EM) findings alone in patients with familial microscopic hematuria (FMH) and especially the Alport syndrome (AS). AS used to be diagnosed only if thickened and lamellated glomerular basement membranes were present, while thinning was thought characteristic of benign FMH due to heterozygous *COL4A3/A4* mutations. This may not always be the case.

METHODS

Long term clinical follow up, laboratory studies to include renal biopsies with EM and MG since 1991, are used to study patients with FMH. PCR-RFLP or direct DNA re-sequencing is used to identify carriers of previously found mutations.

RESULTS – ANALYSIS

1. Thin Basement Membrane Nephropathy & Autosomal Recessive Alport Syndrome (*COL4A3/COL4A4* mutations)
This most common entity, relates to heterozygous *COL4A3/A4* mutations that account for 28 large families in our center, with 213 live carriers having inherited one out of nine detected mutations. The initial phenotypic expression is isolated microscopic hematuria (MH) starting in childhood. Most families however, include members (65%), who later develop additional proteinuria, hypertension and CRF, usually after the age of 50. Presently, 21 patients [10%], have reached ESRD. On the opposite, 20% of carriers reached 70 yo with only MH. Ocular abnormalities are absent. The histopathology is Thin Basement Membrane Nephropathy (TBMN) with superadded FSGS in members who develop proteinuria, CRF and ESRD. In homozygosity or compound heterozygosity, these nine *COL4A3/A4* mutations have been responsible for five patients with classical autosomal recessive AS, reaching ESRD in late adolescence with deafness and ocular changes.

2. Mild form of X-linked Alport syndrome (*COL4A5* mutations)
46 other carriers with FMH, belonging to 8 different families proved to be caused by one of two missense, X-linked, *COL4A5* AS mutations. These were: G624D in six families and P628L in two families. CRF developed in hemizygous males and 11 such males reached ESRD between 31 and 61 yo. Several other affected males exhibiting TBMN, remain well in their late 50's. Affected heterozygous females show only MH. In more detail:
P628L mutation (Cyprus): In the first family (Figure 1A), 5 males and 4 females have been identified so far and all exhibit microhematuria. All 5 affected males reached ESRD at 30, 31, 34, 44 and 56 years of age. At the second family (Figure 1B), 9 mutation carriers, 4 males and 5 females have been identified so far and all exhibit microhematuria. The 4 AS males also developed proteinuria and 2 patients CY-1111 and CY-1137 progressed to ESRD at ages 52 and 45 and died at 60 & 57 years of age respectively. The remaining 2 affected male patients are currently 51 and 57 year old and only show mild renal insufficiency, (creatinine: 1.6 & 1.5 mg/dl respectively). These 2 patients had renal biopsies that had shown well-preserved glomeruli with widespread thinning of the GBM on electron microscopy.
G624D mutation (Greece): Altogether 75 family members, 28 males, (12 positive) and 47 females (25 positive) from 6 Greek families were genetically tested. Of the 12 hemizygous males in these 6 hellenic families, only 4 have reached ESRD at ages 61, 51, 50 and 39. This mutation has been also refereed by others as a mild one.

Figure 2A

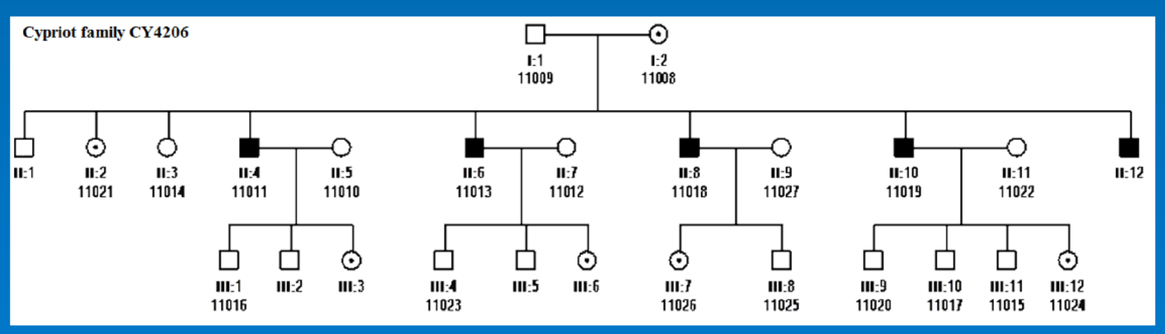

Figure 2B

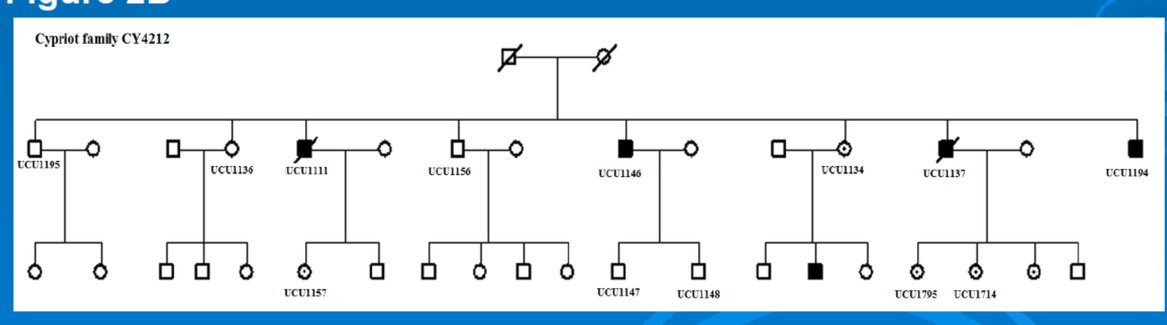

Figure 2A & 2B: Pedigrees of the two Cypriot microhematuric families with mild X-linked AS, resulting from the *COL4A5*-P628L hypomorphic mutation.

CONCLUSIONS

Molecular genetics studies confirm that some COL4A5 AS mutations may be expressed with TBMN and variable degrees of CRF. It should therefore be known that X-linked *COL4A5* AS mutations show a wide phenotypic spectrum with a) classical AS, characterized by early onset ESRD, neurosensory deafness and ocular defects from serious nonsense *COL4A5* mutations, b) males who develop late onset ESRD and late onset deafness and c) hypomorphic, missense, *COL4A5* mutations, such as G624D and P628L that in hemizygous males exhibit MH, TBMN, mild CRF or late onset ESRD. Therefore, when investigating "benign FMH", these two and other similar X-linked COL4A5, mutations should always be looked for. X-linked *COL4A5* hypomorphic mutations G624D & P628D may exhibit PHENOCOPIES OF THIN MEMBRANE NEPHROPATHY WITH BENIGN MICROHEMATURIA.

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