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Investigation of Hellenic families with microscopic hematuria reveals the frequency of collagen IV mutations and evidence for activation of the unfolded protein response

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Familial hematuria(s) comprise a genetically heterogeneous group of conditions which include heritable glomerulopathies, such as Alport Syndrome (AS) and thin basement membrane nephropathy (TBMN). AS is rare and is caused by X-linked *COL4A5* or autosomal recessive *COL4A3/A4* mutations (ARAS), while TBMN is frequent with an estimated population prevalence of 1%. About 40% of TBMN is caused by heterozygous *COL4A3/A4* mutations. Genetics studies in the Hellenic population revealed that 12-16% of families with microscopic hematuria harbor mutations in the *COL4A3/A4* genes. Specifically, 9 mutations were found in the *COL4A3/A4*/A5 genes of 15 Greek families and 10 mutations in 30 Greek-Cypriot families. Focusing on 228 TBMN patients of Greek-Cypriot ancestry with known *COL4* mutations, shows that by the age of 70-years nearly half of patients develop chronic renal failure and 30% reach end-stage kidney disease (ESKD). These findings clearly challenge the formerly thought benign nature of TBMN. In our cohort, although at later age at onset, twice as many patients reach ESKD because of TBMN than patients with AS. Two founder mutations in *COL4*A3 (G1334E & G871C) account for 84% of all patients. Mutation G1334E was found in 174 patients of 15 families. We have evidence that the adverse outcome of a subset of TBMN patients is attributed to co-inheritance of modifier genes with negative impact. One such modifier is the podocin variant NPHS2-R229Q, while we are in the process of searching for more, taking advantage of our genetically more homogeneous population. Functional studies showed that mutant *COL4* chains expressed in podocytes are preferentially retained in the cells, compared to WT chains. Also, mutant chains differentially triggered activation of the unfolded protein response (UPR) pathway. Importantly, UPR activation was shown in biopsies of patients with TBMN who carried mutation *COL4*A3-G1334E, as well as in homozygous knockin mice presenting with AS-like nephritis. The UPR maladaptive activation is part of an intracellular phenotype that probably contributes to disease development. If so, it may prove to be a target for novel therapies through the use of chemical chaperones.

Biography

Constantinos Deltas received his Pharmacy degree from the University of Athens, Greece and his PhD in Biochemistry from Rutgers-The State University of New Jersey, USA, in a joint program with the Robert-Wood Johnson Medical School. He engaged in research of the connective tissue and osteogenesis imperfecta. He returned to his home country, Cyprus in 1991, where he developed diagnostic and research programs on inherited renal conditions, such as polycystic kidney disease and medullary cystic kidney disease, and more recently on collagen IV nephropathies such as Alport Syndrome and thin basement membrane nephropathy (TBMN). His group was involved in pioneering work relating to the mapping (*PKD2, MCKD1*) and cloning of genes (PKD2), the two-hit hypothesis for cyst formation in polycystic kidney disease and the demonstration that TBMN may progress to severe renal failure due to the likely role of genetic modifiers. His most recent work demonstrated the activation of the unfolded protein response pathway in collagen IV nephropathies.

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