

Project title:

Genetic modifiers predisposing to CKD in Alport and thin basement membrane nephropathy

Lay Title:

Let's find out why some Alport patients do better than others (COL4Alport)

Length of the project:

from March 1, 2016 to August 31, 2019

Principal Investigator:

Constantinos Deltas

Proposed research and aim of the research:

Alport Syndrome (AS) and thin basement membrane nephropathy (TBMN) are inherited glomerulopathies presenting with familial microscopic hematuria (MH) since childhood. AS follows X-linked (COL4A5) or autosomal recessive inheritance (COL4A3/COL4A4) and patients usually progress to end-stage renal disease (ESRD) by the fourth decade of life. About 40-50% of TBMN cases are caused by heterozygous COL4A3/A4 mutations and most patients follow mild course with isolated MH; however recently we and others published work showing that a subset of patients develop focal segmental glomerulosclerosis and progressive kidney function decline while 15-30% of TBMN patients progress to ESRD, usually after the sixth decade. The clinical presentation can be complex and the full phenotypic spectrum behaves as a multifactorial condition, implicating primary genes, modifier genes and environmental factors.

A key unanswered question is why some patients follow a mild course with isolated MH or low-grade proteinuria, but others with the same primary mutations develop progressive renal dysfunction. Using a candidate gene approach, we and others described evidence of modifier genes, but much remains unexplained. To address this we will use unbiased Whole-Exome-Sequencing in a large population of patients harboring a limited number of pathogenic heterozygous COL4A mutations. The size and relative homogeneity of our cohort, both in terms of the shared Cypriot genetic background and the small number of COL4A mutations, will maximize power to identify common and rare variants associated with disease progression and we will seek replication of findings in patients from other European populations. Candidate genetic modifiers will be recapitulated on Alport mice models in order to provide proof-of-principle for their contributory effect. We anticipate that such functional modifiers may play a similar role in the general population as factors predisposing to renal impairment by aging. This, in turn may pave the way for new therapeutic approaches.

List of the papers published in peer review journals:

none

List of the presentations done at major congresses/meetings:

- *Familial microscopic hematuria as a paradigm for a "multifactorial" Mendelian disease:*

A unique Cyprus experience

Croatian Society for Human Genetics and University of Zagreb Medical School. Invited by Prof. Danica Galesic Ljubanovic, Department of Histopathology. February 21, 2017, Zagreb, Croatia.

- *Collagen IV glomerulopathies: An underdiagnosed phenotypic chameleon?*

54th European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress. Part of the CME Course "Diagnosis and management of inherited kidney diseases: What's New?" (Organised by WGIKD, the ERA-EDTA Working Group on Inherited Kidney Disorders)". June 3-6, 2017, Madrid, Spain.

- *Collagen IV nephropathies and the search for genetic modifiers*

The 2017 International Workshop on Alport Syndrome. In collaboration with the 50th Anniversary Meeting of the European Society for Paediatric Nephrology. September 4-6, 2017, The Lighthouse, Glasgow, Scotland, UK.