A new mutation in the COL4A3 gene in eight families: phenotype and potential modifier genes.

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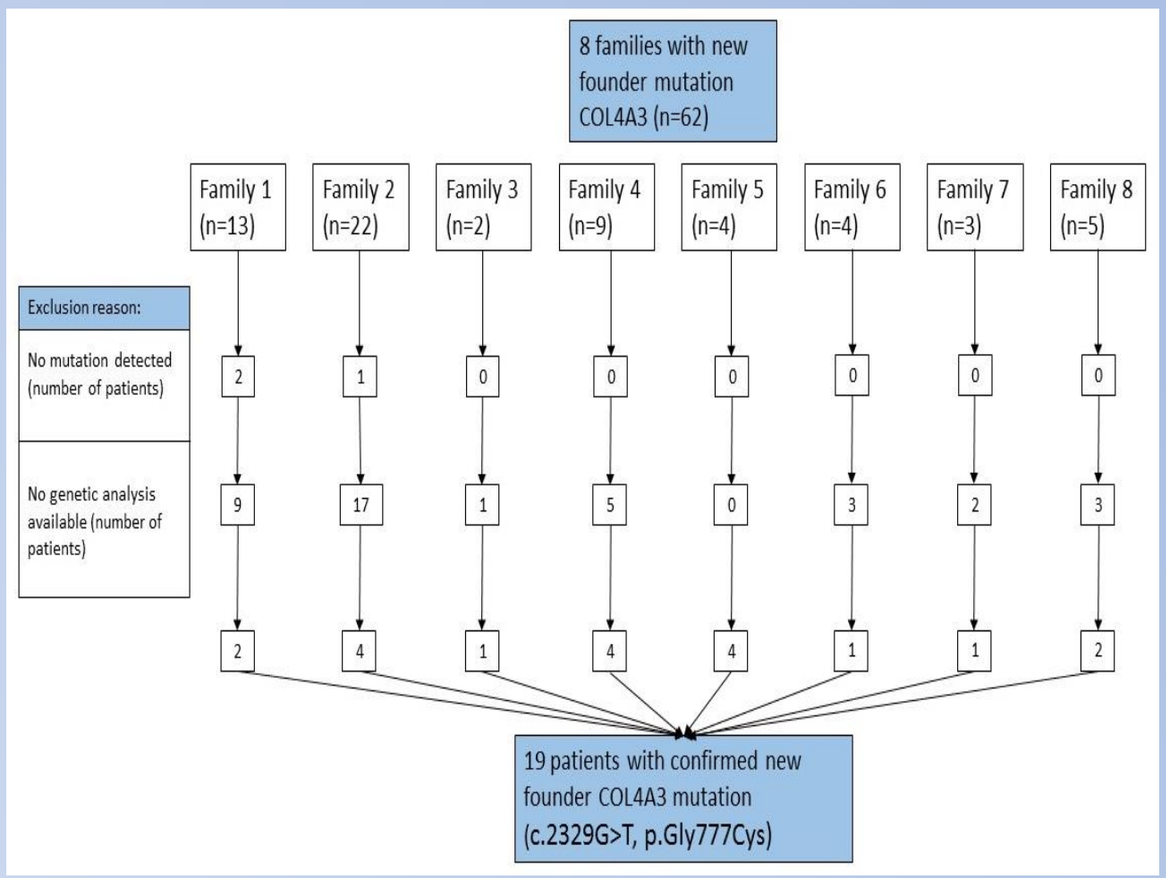
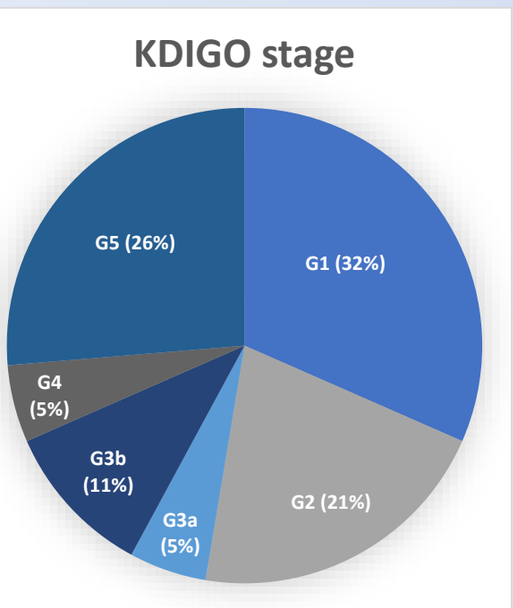
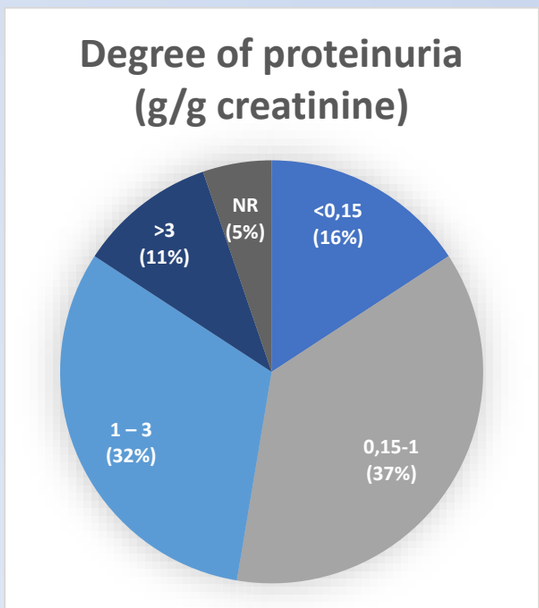
Objective: The spectrum of collagen IV nephropathies, comprises a clinically heterogeneous group of conditions with a phenotypic spectrum ranging from microscopic hematuria throughout life to early onset end-stage renal disease. Clinically and genetically, there is an overlap between thin basement membrane nephropathy and Alport syndrome. Although genotype-phenotype correlations exist, the phenotype is influenced by modifying factors, probably both environmental as genetic, which remain mainly undefined. We aimed to describe the phenotype of 8 families with a novel founder COL4A3 mutation and search for potential candidate modifier genes to explain the differences in phenotype.

Methods: After introducing targeted next generation sequencing of a fixed gene panel associated with kidney diseases, we identified 8 families with a novel founder COL4A3 mutation (c.2329G>T, p.Gly777Cys) in the University Hospitals of Leuven, presenting with an autosomal dominant form of Alport disease. Family trees were reconstructed. Only genetically confirmed cases were included. Phenotypic and genetic information was extracted from the electronic medical records after obtaining informed consent. The following clinical data were extracted: age, sex, degree of proteinuria, presence of hematuria and kidney function. A severe phenotype was defined as chronic kidney disease KDIGO stage 3A or more.

Results: Nineteen patients in 8 families had a confirmed mutation. Patients were predominantly female, and median age was 56 years old. All patients presented with hematuria and the majority of patients had proteinuria, with only a small portion of patients presenting with nephrotic range proteinuria. About half of the patients (53%) had normal kidney function, 47% had chronic kidney disease (16% KDIGO stage 3, 5% stage 4, 26% reached ESRD). Median age of patients reaching ESRD was 55 years old. In 5 of the 9 patients with a severe phenotype, exome sequencing was performed. The following variants of unknown significance were found mutations in NPHP1, NPHS1, INVS, COQ6, CUBN, EMP2, CFH, FAT1, ZMPSTE24, C3, NPHP4 and FAT1 genes.







Conclusion: The renal phenotype of patients with the autosomal dominant form of Alport is heterogeneous. Estimating prognosis for an individual patients therefore remains challenging. Further research remains necessary to determine if possible modifying genes could help to better predict prognosis in the future.

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VUS	Abbreviation	Plays a role in …
NPHP1	Nephrocystin 1	Nephronophthisis
INVS	Inversin	Nephronophthisis
NPHP4	Nephrocystin 4	Nephronophthisis
NPHS1	Nephrin	FSGS
ZMPSTE24	Zinc metallopeptidase STE24	FSGS
COQ6	Coenzyme Q6, monooxygenase	FSGS
FAT1	FAT atypical cadherin 1	Steroid resistant nephrotic syndrome
EMP2	Epithelial membrane protein 2	Childhood-onset nephrotic syndrome
C3	Complement C3	C3GN, aHUS
CFH	Complement factor H	C3GN, aHUS
CUBN	Cubilin	Isolated proteinuria