# Thin Basement Membrane Nephropathy due to heterozygous *COL4A3/COL4A4* mutations is a more frequent cause of ESKD compared to Alport Syndrome

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## Abstract

**INTRODUCTION AND AIMS:** Alport syndrome (AS) is a severe hereditary hematuric nephritis, associated with deafness, eye defects and early progression to ESKD. About 85% of all AS cases are X-linked due to *COL4A5* mutations (**XLAS**) and the rest are autosomal recessive due to homozygous or compound heterozygous *COL4A3/COL4A4* mutations (**ARAS**). Thin basement membrane nephropathy (**TBMN**) is the leading cause of familial hematuria (FH) worldwide and is mostly explained by heterozygous *COL4A3/COL4A4* mutations. TBMN should no more be considered as a benign condition, since about half of these patients progress to chronic renal failure after the age of 50 years, and about 30% reach ESKD by the age of 70 years, according to our data in the Greek-Cypriot population. This study in a catchment area of ~600,000 people, aims to compare AS and TBMN in terms of ESKD cases.

**METHODS:** Since 1991 we identified more than 120 families with familial hematuria of different causes. We assessed and compared the number of ESKD cases in TBMN families (only for them that a heterozygous *COL4A3* or *COL4A4* mutation was found) and AS families.

**RESULTS:** We have identified nine AS families referred to our public hospitals: four XLAS families with nine living patients (71%) and five ARAS families with four living patients (29%). *COL4A5*-P628L was found in two of the XLAS families. Nine of these living patients reached ESKD. We have found a heterozygous *COL4A3* or *COL4A4* mutation in 213 living patients in 27 families. Mutation *COL4A3*-G1334E was found in 16 families and it accounts for 154 patients. Of these 213 patients, 21 have reached ESKD. Interestingly, we observe that Greek-Cypriots patients with ESKD due to TBMN (21 patients) outnumber by 2.3 times those who reach ESKD due to AS (9 patients).

**CONCLUSIONS**: This observation demonstrated again that TBMN is not a benign condition with excellent prognosis, as usually mentioned in the previous literature. Further investigations are needed in other populations to confirm this epidemiological finding, while work is in progress to identify putative genetic modifiers that are responsible for the adverse outcome in a subset of TBMN patients.

## Results

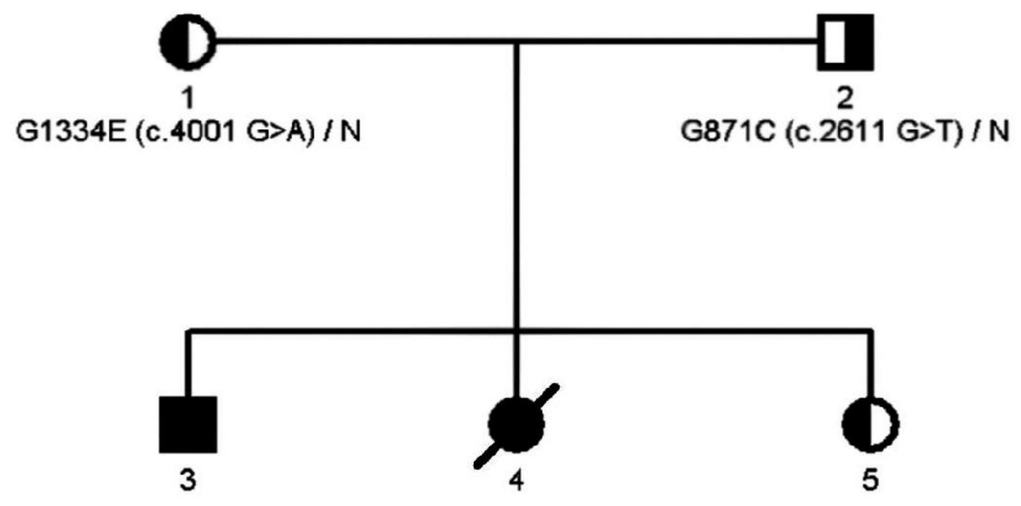


**Figure 1:** This pedigree shows two autosomal recessive Alport patients carrying the founder mutations COL4A3-G1334E and COL4A3-G871C. These mutations are found in many geographical regions of Cyprus.

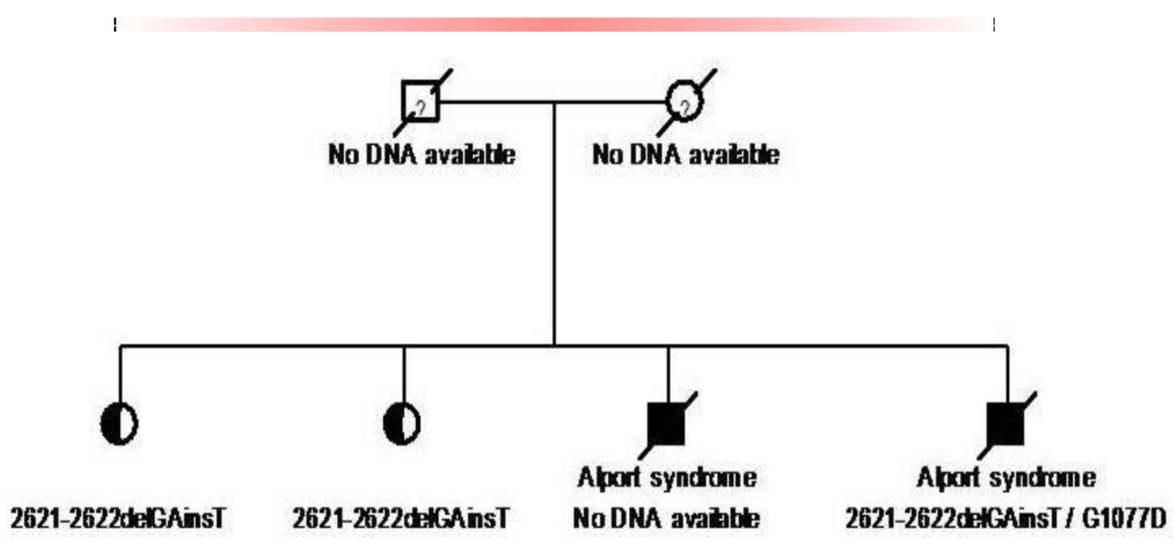


**Figure 2:** The above pedigree shows two autosomal recessive Alport patients carrying two COL4A3 mutations. These mutations were not found - in heterozygosity or compound heterozygosity - in any other patients in Cyprus. COL4A3-G1077D is a novel mutation, not registered in HGMD.

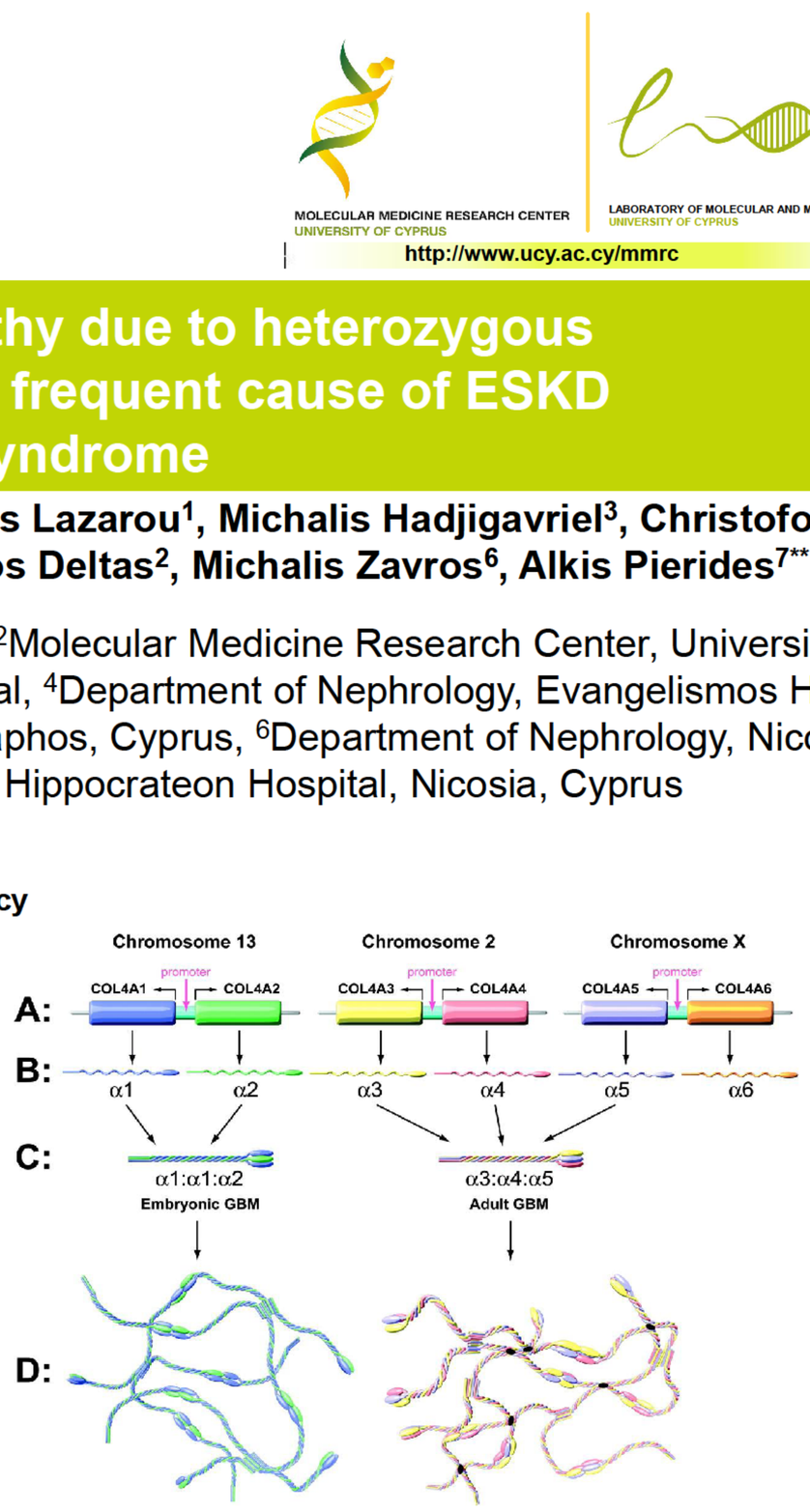


**Figure 3: A.**The six collagen IV genes (*COL4A1* to *COL4A6*) located pairwise in a head-to-head manner on three different chromosomes generate six different α chains that have a globular noncollagenous domain at their C-terminus **B.** Three chains form triple-helical molecules that can have different combinations. **D** Extracellularly, the triple-helical type IV collagen molecules form a network by associating with each other at their ends so that two molecules are cross-linked through their C-terminal globular domain (NC1) and for trimers associated with each other at the N-termini.
**(Tryggvason K , Patrakka J JASN 2006;17:813-822)**

**Table 1:** This table indicates the mutations in COL4A3, COL4A4, COLA45, found so far in Cyprus in living patients. Cypriots patients with ESKD due to TBMN are nearly four times more than those with AS.

| MUTATION | DISEASE | Number of living patients | Number of living patients who have reached ESKD |
|---|---|---|---|
| COL4A3-G1334E | TBMN | 154 | 14 |
| COL4A3-G871C | TBMN | 24 | 1 |
| COL4A3-3854delG | TBMN | 15 | 3 |
| Other mutations found | TBMN | 20 | 3 |
| *SUM FOR TBMN CASES* | | 213 | 21 |
| COL4A5-P628L | XLAS | 6 (hemiz. men) | 4 |
| COL4A3-G1334E COL4A3-G871C | ARAS | 1 | 1 |
| COL4A3-3533delC | ARAS | 1 | 1 |
| Other AS cases not genetically studied | | 5 | 3 |
| *SUM FOR ALPORT CASES* | | 13 | 9 |

## Discussion

**Alport Syndrome is a hereditary nephropathy that results in irreversible, progressive renal failure. This syndrome is often associated with sensorineural hypoacusis and ocular abnormalities. TBMN is the most common cause of persistent hematuria in children and adults, the other main causes being IgA nephropathy and Alport Syndrome. Mutations in *COL4A5* gene cause X-linked AS, while mutations in *COL4A3* and *COL4A4* genes are responsible for autosomal recessive AS. Interestingly, we observed that Greek-Cypriots patients with ESKD due to TBMN (21 patients) are nearly 2,5 times more than those due to AS (9 patients). This observation shows once again that TBMN is not benign and most probably is the cause of more ESKD cases than AS. Further investigations are needed in other populations to confirm this epidemiological finding.**

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