

## Genetic, Clinical, and Pathologic Backgrounds of Patients with Hereditary COL4A3/COL4A4/COL4A5 variants: Single Centre Experience

Dr Vishnu Jeyalan<sup>1</sup>, Dr Michelle Chong<sup>1</sup>, Dr Shaw Liew Kang<sup>1</sup>, Dr Arvind Ponnusamy<sup>1</sup>

<sup>1</sup>Renal Department, Royal Preston Hospital, Preston, United Kingdom

### Background

Alport syndrome is a nephropathy related to mutations in the COL4A3/COL4A4/COL4A5 genes and is inherited in a dominant, recessive and x-linked pattern. The clinical phenotype and histological finding varies between each mutation, timing, and renal risk factors which can mislead physicians. To confound matters further there can be further noncollagen/podocyte modifier genes that may have impact in altering the expected clinical course especially in those with TBM nephropathy.

Here we present a single centre experience of 5 cases with a varied presentation of a col4a disorders.

### Methods:

We conducted a retrospective analysis of 5 patients with a genetically proven col4A disorder. Clinical, laboratory, genetic and pathologic data were collected from medical records. Genetic analysis was performed by next generation DNA sequencing of podocyte-related and Alport-related collagen genes, to make a diagnosis of COL4A disorder and identify possible modifier genes.

### Results:

Amongst our series, we present a case that was initially diagnosed and treated as FSGS for several years in a different renal unit. On transfer of care to our centre due to relocation, a good clinical history revealed that his offspring had been having microscopic haematuria. This prompted the diagnosis to be reviewed and genetic testing performed revealed an X linked col4a5 mutation. Patient has recently been transplanted uneventfully last year at the age of 53.

We also present a case of a patient presenting with preserved renal function and haematoproteinuria. Renal biopsy at initial presentation revealed thin basement membrane only. However as renal function started to dwindle, genetic testing done revealed a COL4a3 recessive mutation. This prompted the expectation of an unfavourable renal trajectory and after almost 2 decades of follow-up, patient now has an eGFR of 17ml/min at the age of 56.

Lastly, we present 3 cases of a heterozygous COL4a3/COL4a4 disorder or TBM. However, on genetic panel testing each of these patients revealed a further non-pathogenic (modifier gene) NPHS2 variant. One patient was labelled as TBM based on family history alone at the age of 18 and was lost to follow-up. Patient represented now at age of 35 with hypertension and advanced CKD which prompted genetic testing. The 2 other patients had biopsies showing thin basement membrane nephropathy with an added element of foam cells and element of FSGS changes separately. Clinical course so far revealed preserved kidney function but with worsening proteinuria approaching nephrotic range despite RAAS inhibition.; see below table 1

### Conclusion:

There is a varied presentation to COL4a disorders, therefore this diagnosis must not be overlooked. An extensive genetic panel screening will aid in giving clarity to the underlying mutation and associated modifier mutations which will have different projected clinical courses. The presence of these modifier gene is thought to impact functionality of already altered GBM and be a risk factor for CKD progression in patients with TBM.

Good clinical history corroborated with the biopsy and genetic testing is key in accurately diagnosing and managing these patients. It will aid in future planning with renal replacement therapy, transplantation and familial screening