

P044

P044 -X-linked Alport syndrome in the genomic medicine era - uncovering unusual clinical phenotypes of COL4A5 variants

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Introduction

Next generation sequencing technology has revolutionised genetic testing of hereditary renal disorders. In 2017, NHS England Board developed a national genomic medicine service strategy and in our region, genomic and renal medicine services have been early adopters of the new changes. We present six cases/families with pathogenic COL4A5 variants illustrating unusual clinical presentations of X-linked Alport syndrome.

Methods

Retrospective case review of subjects identified from the regional clinical genetics service.

Results

- Hair root analysis detects deep intronic COL4A5 variant:**
14-year-old boy with progressive proteinuria on a background of microscopic haematuria and renal biopsy supportive of Alport syndrome. Analysis of COL4A3/4/5 on DNA from blood was negative but cDNA sequencing from hair roots showed a deep intronic COL4A5 variant (at -468 position) resulting in abnormal splicing of transcripts.
- De novo COL4A5 variant in adult female with FSGS:**
28-year-old woman identified with heavy proteinuria (urine PCR 300mg/mmol Cr) but no haematuria; renal biopsy showed FSGS. Her 6-year-old son had just been seen in hospital for microscopic haematuria. She has a Gly missense substitution in COL4A5.
- Mild phenotype in older male with COL4A5 multiexonic duplication:**
53-year-old man with >20 years history of microscopic haematuria and progressive proteinuria. His eGFR was 58 ml/min/1.73m²; no renal biopsy done. A maternal aunt had history of FSGS and had transplant in her 60s. He is hemizygous for a duplication of exons 10-24 of COL4A5.
- Milder presentation in male with mosaic COL4A5 variant:**
30-year-old man with microscopic haematuria from 18 years, moderate proteinuria (latest urine ACR 46mg/mmol Cr) but eGFR >90 ml/min/1.73m². No significant family history. Renal biopsy showed FSGS. Focal areas of GBM thinning and lamellation were also noted but collagen subunit immunostaining was normal. A mosaic Gly missense substitution in COL4A5 was identified explaining his milder phenotype.
- Mother and daughter with haematuria but apparent de novo COL4A5 variant in daughter:**
14-year-old girl presented with recurrent macroscopic haematuria at the age of 5 years. Renal biopsy showed thin GBM. Mother has persistent microscopic haematuria but no proteinuria so presumed thin basement membrane nephropathy. Daughter has a COL4A5 splicing variant, but mother's saliva and blood DNA did not detect the same variant, suggesting possible maternal mosaicism in renal tissue.

6. Severe childhood phenotype in female siblings – possible modifier effect:

Two sisters, aged 10 and 7 years respectively, presented with reported history of Alport syndrome in their estranged father. They have significant proteinuria (urine PCR 292mg/mmol and 119mg/mmol) at a young age. A COL4A5 splicing variant was detected and, in addition, R229Q NPHS2 variant, a known modifier increasing the severity of renal disease in Alport syndrome.

Discussion

Absence of family history should not preclude consideration of X-linked Alport syndrome, and the index of suspicion should be high even in females.

FSGS on biopsy can suggest Alport syndrome and patients with milder or atypical presentation may have a mosaic or deep intronic variant.

A high quality renal genomic medicine service can be developed through multidisciplinary cooperation between pathology, genomics and renal teams.