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Functional Reclassification of a COL4A5 Splice-site Variant by Urine mRNA Analysis: Phenotypic Spectrum in Seven Unrelated Families

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Objectives : Splice-site variants of uncertain significance (VUS) in COL4A5 pose a diagnostic challenge in X-linked Alport syndrome (XLAS), as standard sequencing cannot determine their functional impact. We aimed to functionally reclassify a COL4A5 VUS using urine mRNA analysis and characterize its phenotypic spectrum.
Methods : A COL4A5 splice-site VUS (c.991-7T>A) was identified in a 73-year-old male with hematuria and proteinuria and kidney pathology suggestive of Alport syndrome. Urine-derived mRNA analysis was performed to evaluate aberrant splicing and support ACMG/AMP-based variant reclassification. Additional carriers were identified through a retrospective query of two institutional sequencing databases. Clinical data included proteinuria, eGFR trajectory, age at ESKD.
Results : Urine mRNA analysis of COL4A5 c.991-7T>A confirmed aberrant splicing with partial intron 17 retention, resulting in a frameshift (p.Gly331Asnfs*17) in approximately 80% of transcripts, supporting reclassification from VUS to likely pathogenic. This variant has been reported only in Koreans, and database searches identified six additional probands. Across seven families, 14 individuals (7 males) were genetically confirmed and 13 (6 males) were clinically suspected; confirmation used Sanger sequencing (78.6%) or targeted NGS panels (21.4%). Most individuals presented with asymptomatic urinary abnormalities, with a mean detection age of 10.0 years in males. At last follow-up, male phenotypes ranged from isolated hematuria (23.1%; median age 16.3 years), proteinuria with preserved kidney function (30.8%; 26.3 years), CKD stage 3–4 (23.1%; 77.1 years), and ESKD (23.1%; 45.0 years). Notably, disease severity varied widely: one male underwent kidney transplantation in his twenties, whereas the proband aged 77 years remained ESKD-free.
Conclusions : Urine mRNA analysis established the pathogenic splicing consequence of the previously uncharacterized COL4A5 c.991-7T>A, enabling its reclassification as likely pathogenic and revealing a broad phenotypic across seven families. There findings support incorporating urine mRNA testing into the diagnostic work up for COL4A5 splicing variants, particularly when DNA sequencing yields VUS results.