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Genotype-Phenotype Correlation and Long Term Outcomes in a Large Cohort of Patients with Primary Distal Renal Tubular Acidosis from India

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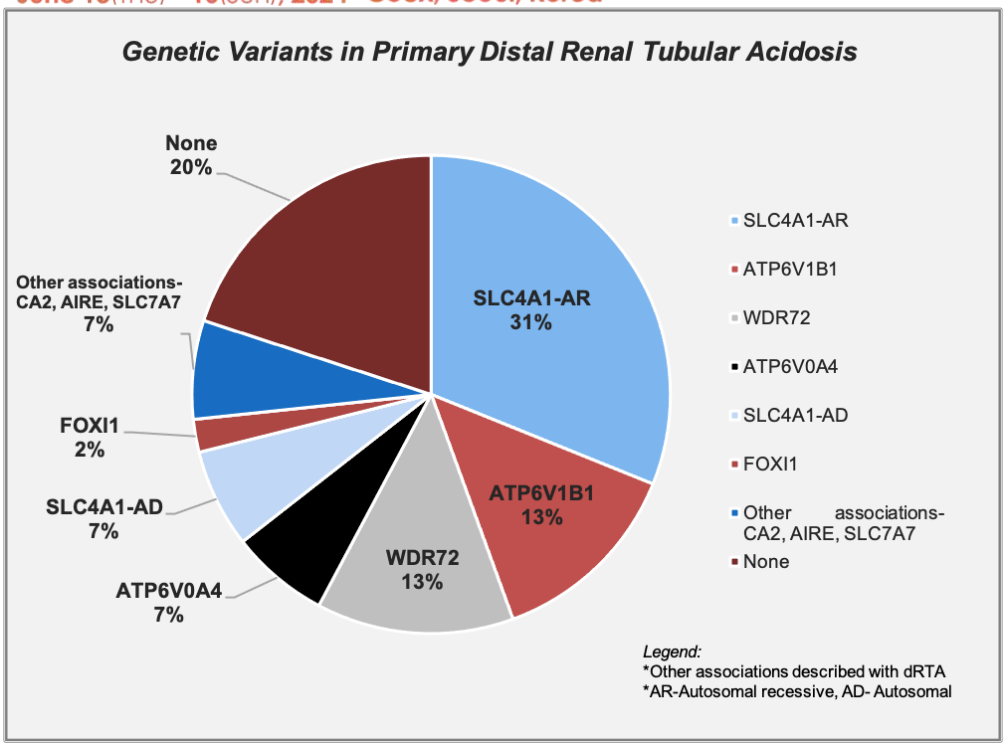
Objectives : Distal Renal Tubular Acidosis (dRTA) is a challenging renal tubulopathy in clinical practice. Clinical spectrum of dRTA ranges from an asymptomatic metabolic abnormality to severe metabolic bone disease, and life-threatening hypokalemia. dRTA is a relatively rare condition and data on genotype-phenotype correlation, and long-term outcomes are lacking. The present study comprehensively evaluated these aspects in a large cohort of primary dRTA.
Methods : From a dedicated Renal Tubulopathy Clinic established at a tertiary care referral nephrology centre in western India, 52 patients (45 families) with primary dRTA were enrolled in this study. Detailed history, clinical examination, laboratory data, treatment records, alkali requirement, and complications were reviewed. Next Generation Sequencing by Clinical Exome Sequencing was performed for 45 index cases.
Results : Mean ages at presentation and last visit were 6.58(SD-7.25) and 22.13(SD-13.51) years respectively. 23(51.1%) were males. Mean delay in diagnosis was 2.64 years. Growth failure and/or developmental delay were the commonest presenting features 32(71.1%), followed by hypokalemic paralysis 9(20.0%). Pathogenic mutations were detected in 33(73.3%) patients: SLC4A1-17(37.8%), ATP6V1B1-6(13.3%), WDR72 6(13.3%), ATP6V0A4 3(6.6%), and FOXI1 1(2.2%). The autosomal recessive SLC4A1 mutation [c.2573C>A (p.Ala858Asp)] causing South-Asian variant of dRTA with hemolytic anemia was detected in 14(82.4%). 6(100%) patients with WDR72 mutations had Amelogenesis Imperfecta. Sensorineural hearing loss was associated with ATP6 (V1B1 > V0A4) and FOXI1 mutations. Patients with homozygous ATP6 gene mutations had the most severe phenotype presenting in infancy, with 7(44.4%) having family history of early-life death of a sibling with failure to thrive. Patients with heterozygous ATP6 mutations 4(44.4%) had a muted phenotype. 7(15.5)% had eGFR <60ml/min/1.73m2 at last follow-up.
Conclusions : Our study shows that novel mutations account for substantial proportion of cases of primary dRTA. Delayed diagnosis leads to significant impairment in growth and development. Distinct phenotypes can serve as strong pointers towards underlying genetic defects, helping in timely diagnosis and prognostication.

APCN Figure 1.png


Genetic Variants in Primary Distal Renal Tubular Acidosis
None 20%
Other associations- CA2, AIRE, SLC7A7 7%
FOXI1 2%
SLC4A1-AD 7%
ATP6V0A4 7%
WDR72 13%
ATP6V1B1 13%
SLC4A1-AR 31%
SLC4A1-AR
ATP6V1B1
WDR72
ATP6V0A4
SLC4A1-AD
FOXI1
Other associations- CA2, AIRE, SLC7A7
None
Legend:
*Other associations described with dRTA
*AR-Autosomal recessive, AD- Autosomal