Identification of genetic variants of *PHEX* gene in a cohort of children with hereditary hypophosphatemic rickets in Sri Lanka

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Hereditary hypophosphatemic rickets (HHR) comprises a group of rare genetic disorders characterized by renal phosphate wasting leading to chronic hypophosphatemic rickets. The most common form, X-linked hypophosphatemic rickets (XLHR), arises from inactivating mutations in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene, which disrupts phosphate homeostasis through dysregulation of the phosphaturic hormone FGF23. Although more than 800 pathogenic *PHEX* variants have been reported globally, the genetic variants in Sri Lankan patients remain unexplored. This study aimed to identify the genetic variants of XLHR in Sri Lankan pediatric patients. Eleven children clinically diagnosed with hypophosphatemic rickets underwent comprehensive evaluation, including biochemical analyses, radiological assessments, and phenotypic characterization. PCR amplification followed by targeted Sanger sequencing was performed on *PHEX* exons 17, 19, and 22, along with flanking intronic regions. Pathogenicity predictions were conducted using MutationTaster and SpliceAI algorithms. The index patient (Male) harboring a novel variant was diagnosed at one year and five months of age and exhibited hypophosphatemia (0.9 mmol/L, approximately 25% below the normal lower limit for age), markedly elevated alkaline phosphatase (682 U/L, nearly twofold above normal range), serum calcium within normal limits (2.31 mmol/L), and elevated parathyroid hormone (8.06 pmol/L). Radiographs revealed classic rickets features. Genetic analysis identified a novel intronic deletion variant, c.1900-31_1900-30del, within the polypyrimidine tract 30 base pairs upstream of exon 19. This two-nucleotide deletion reduces a consecutive thymine stretch from 12 to 10 bases, potentially disrupting splice acceptor site recognition and pre-mRNA splicing. MutationTaster predicted the variant as disease-causing with possible cryptic splice site generation, while SpliceAI assigned low pathogenicity scores, illustrating the complexity of non-coding variant interpretation. This is the first report of an intronic polypyrimidine tract deletion in the *PHEX* gene in Sri Lankan patients. The variant's associated clinical phenotype supports its pathogenicity. Functional validation studies are needed to confirm these findings.

Keywords: *X-linked hypophosphatemic rickets, PHEX gene, Polypyrimidine tract, Splice site, Hypophosphatemia*