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PHOSPHATE DISORDERS AND TUBULAR DYSFUNCTION AS CLINICAL MANIFESTATION OF RICKETS-LIKE DISEASE IN DIABETES IN CHILDREN: CLINICAL ASPECTS AND MOLECULAR MECHANISMS

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PHOSPHATE DISORDERS AND TUBULAR DYSFUNCTION AS CLINICALMANIFESTATION OF RICKETS-LIKE DISEASE IN DIABETES INCHILDREN: CLINICAL ASPECTS AND MOLECULAR MECHANISMS

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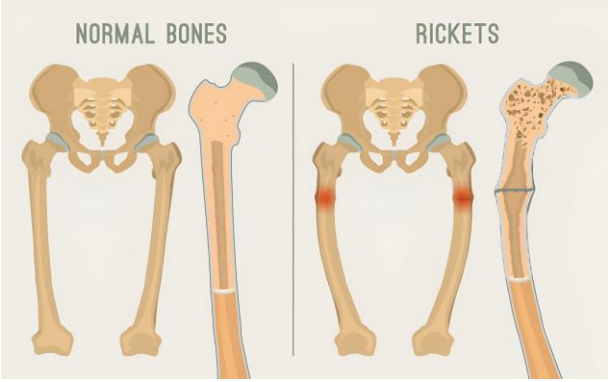
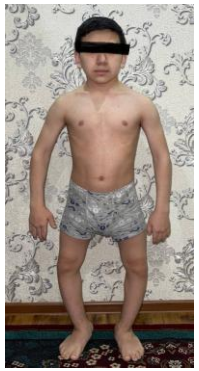
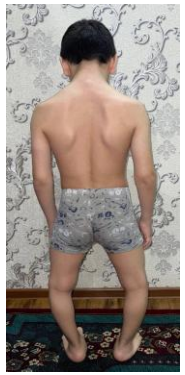
Research Relevance: Rickets-like diseases are rare hereditary disorders affecting phosphate-calcium metabolism and bone mineralization, often challenging to diagnose due to overlapping symptoms and genetic diversity. Advances in molecular genetics enable precise diagnosis and personalized treatment, yet data on their prevalence and genetic features in Uzbekistan are limited. Understanding the molecular basis of rickets-like diseases in the Uzbek population will contribute to improved diagnostic algorithms and therapeutic strategies for affected children.



The aim of the study: To investigate the molecular-genetic characteristics and mutational spectrum of rickets-like diseases in children in the Republic of Uzbekistan.

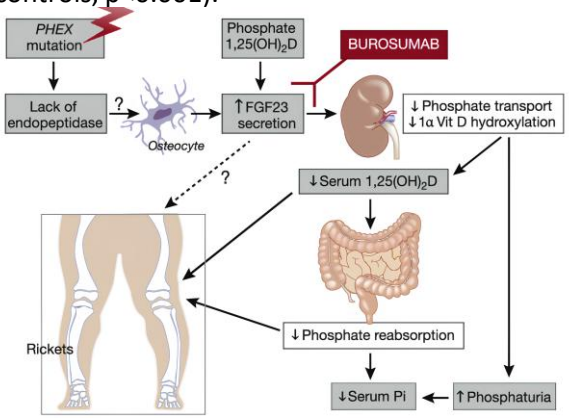
Materials and Methods: A comprehensive examination of 78 children was conducted at the National Children's Medical Center of the Ministry of Health of the Republic of Uzbekistan during 2023-2025. The study population comprised 48 patients with rickets-like diseases (main group) and 30 healthy children of the same age range (control group). Next-generation sequencing (NGS), polymerase chain reaction (PCR), biochemical, enzyme-linked immunosorbent assay, and hormonal investigations were employed. Genetic analysis included screening of genes associated with hereditary rickets-like disorders: PHEX, CYP27B1, VDR, SLC34A3, CLCN5, and ALPL. Biochemical parameters included serum phosphate, calcium, alkaline phosphatase, 25(OH)D3, 1,25(OH)2D3, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23) levels.





“11-year-old child with rickets”
Diagnosis : Unspecified chronic tubulointerstitial nephritis. Latent course

Results: Pathogenic mutations were identified in 48 children with rickets-like diseases, with PHEX gene mutations being the most prevalent (18 cases, 37.5%), followed by CYP27B1 mutations (10 cases, 20.8%), VDR mutations (7 cases, 14.6%), SLC34A3 mutations (6 cases, 12.5%), CLCN5 mutations (4 cases, 8.3%), and ALPL mutations (1 case, 2.1%). Seven previously undescribed pathogenic variants were identified, expanding the known mutational spectrum of rickets-like diseases. X-linked hypophosphatemic rickets associated with PHEX mutations represented the most common form, characterized by significantly reduced serum phosphate levels (0.65±0.12 mmol/L vs. 1.45±0.18 mmol/L in controls, $p<0.001$) and elevated FGF23 concentrations (156.3±45.7 pg/mL vs. 32.1±8.4 pg/mL in controls, $p<0.001$). Patients with CYP27B1 mutations demonstrated severe vitamin D deficiency with 1,25(OH)2D3 levels of 18.2±6.3 pg/mL compared to 45.8±12.1 pg/mL in controls ($p<0.001$) and secondary hyperparathyroidism (PTH: 187.4±52.6 pg/mL vs. 28.5±7.2 pg/mL, $p<0.001$). Strong genotype-phenotype correlations were established, with PHEX mutations showing the highest correlation with growth retardation ($r=0.78$, $p<0.001$) and skeletal deformities ($r=0.82$, $p<0.001$). Biochemical markers revealed distinct patterns: alkaline phosphatase levels were significantly elevated across all genetic subtypes (ranging from 245±67 to 398±89 U/L vs. 156±34 U/L in controls, $p<0.001$).



Conclusion: This study provides the first comprehensive molecular-genetic analysis of rickets-like diseases in Uzbek children, revealing a diverse mutational spectrum with PHEX mutations predominating, including seven novel pathogenic variants. Strong genotype-phenotype correlations and distinct biochemical profiles offer valuable insights for diagnosis, prognosis, and potential biomarkers. These findings support the development of population-specific diagnostic algorithms and personalized therapies, enabling earlier diagnosis and improved clinical outcomes.

Proshlyakova, T. Yu, T. S. Korotkaya, and S. Yu Kuznetsova. "COMPARATIVE CHARACTERISTICS OF RICKETS-LIKE DISEASES." *Rossiyskiy Vestnik Perinatologii i Pediatrii (Russian Bulletin of Perinatology and Pediatrics)* 63.3 (2018): 19-25.

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