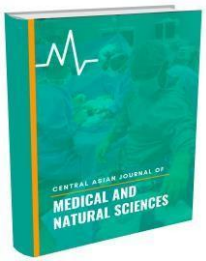

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Article

Rickets-Like Diseases in Children: Clinical Features, Molecular-Genetic Verification and Mutational Spectrum in The Uzbek Population

Abidova Malika Davron qizi*[1]

1. Assistant, Department of Neonatology, Tashkent State Medical University
* Correspondence: maly_sy@mail.ru

Abstract: The rickets-like diseases are a diverse group of hereditary disorders of phosphate-calcium metabolism with important diagnostic dilemmas for pediatricians. This is a prospective observational study carried out at the National children's medical center in Tashkent, Uzbekistan during 2024-2025. There were 46 children with rickets-like diseases (main group) and 30 apparently healthy age matched controls aged from 4 months to 16 years. Molecular-genetic diagnosis was confirmed in 82.6 % of the patients ($p<0.001$). In the genes VDR, CYP27B1, PHEX, and SLC34A3 five recurrent mutations were found, which could indicate a founder effect in the population of Uzbekistan. The results highlight the importance of implementing molecular-genealogic diagnosis in clinical care of rickets-like syndromes in Central Asian populations.

Keywords: Rickets-Like Diseases, Hereditary Hypophosphatemia, Vitamin D-Dependent Rickets, X-Linked Hypophosphatemia, Molecular Genetics, VDR, CYP27B1, PHEX, SLC34A3, Founder Effect, Uzbekistan, Children

1. Introduction

Rickets-like diseases (RLD) are a clinically and genetically heterogeneous group of disorders, which are united by some common features, namely impaired bone mineralization, skeletal deformities, growth retardation and disturbances of phosphate-calcium homeostasis. Hereditary forms of RLD are caused by mutations in genes that code for enzymes, receptors and transporters that are required for the metabolism of vitamin D and renal handling of phosphate, whereas nutritional rickets is mainly caused by vitamin D deficiency [1].

Global epidemiological burden. Nutritional rickets is a worldwide problem, affecting an estimated 1 billion vitamin D deficient people and clinically manifest rickets is reported in children from over 50 countries. Rickets prevalence ranged from 2.9 to 45 cases per 1,000 children in Africa and Asia in a multicountry consensus study published by Bone (Munns et al., 2016). Hereditary RLD is a significant diagnostic challenge as individual cases are rare, but the overall prevalence of hereditary rickets is estimated at one in twenty thousand for X-linked hypophosphatemia (XLH) which is associated with mutations in the PHEX gene. This is compounded by autosomal dominant and recessive hypophosphatemic rickets, vitamin D dependent rickets type 1 and type 2 and renal tubular disorders. In the Central Asian and Middle Eastern populations, the frequency of

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consanguineous marriages (20–60% in some areas) is a major risk factor for the occurrence of autosomal recessive forms of RLD. The prevalence of CYP27B1 and VDR mutations has been reported to be significantly higher in Iran, Turkey, and Saudi Arabia and is partly due to founder effects in geographically and genetically isolated communities [2].

However, the molecular genetic epidemiology of RLD is still limited in Uzbekistan and there is systematic data on it. Most children with biochemical abnormalities and/or skeletal deformities in whom rickets is suspected are treated empirically with vitamin D – most children with heritable forms are not genetically confirmed, and some children with potentially treatable forms such as phosphate supplemented XLH may be diagnosed late or not at all [3].

The lack of molecular diagnostics, high level of consanguinity in some areas of the country and a young population approximately 28% under 15 years (according to WHO 2023 data) makes the establishment of the local mutational spectrum of RLD an urgent scientific and clinical problem.

Aims and objectives

The main objective of this study was to find out the frequency of molecular-genetic verification of diagnosis in children with rickets-like diseases and describe the spectrum of mutations in the genes which cause them in the Uzbek population [4].

2. Materials and Methods

The study was a prospective observational study conducted in the National Children's Medical Center in Tashkent in the Republic of Uzbekistan from January 2024 to March 2025. The study was conducted following the principles of the declaration of Helsinki of the World Medical Association (revised 2013). All procedures were approved by the Local Ethics Committee of the National Children's Medical Center. Parents/legal guardians of all children enrolled in this study provided written informed consent and children ≥7 years of age provided assent [5].

The total number of children enrolled was 76 children ranging from 4 months to 16 years old, subdivided into two groups:

A total of 46 children (group I) were clinically and/or biochemically suspected of having rickets-like diseases. Apparently healthy children of the same age range but no history of skeletal, renal, or metabolic disease were selected as control group (Group II), consisting of 30 children. The inclusion criteria for Group I: (1) age 4 months to 16 years, (2) having ≥2 clinical signs of rickets (skeletal deformities, growth retardation, muscle hypotonia, rachitic rosary, Harrison's groove); and/or (3) biochemical signs (hypophosphatemia, elevated alkaline phosphatase (ALP), elevated parathyroid hormone (PTH) despite regular doses of vitamin D).

Exclusion criteria: acquired bone metabolic diseases, malabsorption syndromes, chronic kidney disease stage ≥3 or refusal to participate [6].

Standardized clinical examination was performed in all patients, which included anthropometric measurements (height, weight, BMI) and the calculation of Z scores based on the WHO (2006/2007) growth standard. Serum calcium (Ca), inorganic phosphorus (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] were measured in biochemical analysis, along with urine phosphate reabsorption (tubular reabsorption of phosphate, TRP). In all patients of group I, a radiographic examination of wrists and knees was conducted [7].

Peripheral blood leukocytes were used for genomic DNA extraction, which was performed by a standard salting-out method. Targeted next-generation sequencing (NGS) of a designed gene panel (PHEX, FGF23, DMP1, ENPP1, SLC34A1, SLC34A3, SLC9A3R1, VDR, CYP27B1, CYP2R1, and CLCN5) was used for molecular-genetic analysis. Libraries

were generated according to the Illumina TruSeq Custom Amplicon protocol, and sequenced using the Illumina MiSeq platform with an average coverage depth of ≥100×. [8]

The variant calling and annotation was done by the GATK pipeline and ANNOVAR software. Pathogenicity of identified variants was determined based on ACMG/AMP 2015 guidelines. All pathogenic and probable pathogenic variants were confirmed by Sanger sequencing. The statistical analysis was done through IBM SPSS Statistics v.26.0 and GraphPad Prism v.9.0. Data are shown as mean ± standard deviation (M ± SD) or median with interquartile range (Me [IQR]) as appropriate for distribution normality determined by the Shapiro-Wilk test. Student's t-test, or Mann-Whitney U test was used for group comparisons as appropriate. Chi-square (χ^2) test or Fisher's exact test was used for the analysis of categorical variables. The differences were deemed to be statistically significant when $p < 0.05$ [9], [10].

3. Results

Table 1. Demographic and baseline clinical characteristics of study groups

Parameter	Group I (n=46)	Group II (n=30)	p-value
Age (months), Me [IQR]	38.5 [14–96]	42.0 [18–102]	0.612
Male sex, n (%)	27 (58.7%)	17 (56.7%)	0.855
Height Z-score, M ± SD	−2.41 ± 1.18	−0.22 ± 0.74	<0.001
Weight Z-score, M ± SD	−1.87 ± 1.02	−0.15 ± 0.68	<0.001
Consanguinity, n (%)	19 (41.3%)	2 (6.7%)	<0.001

Patients in Group I demonstrated significantly lower height and weight Z-scores compared to healthy controls ($p<0.001$). The rate of consanguineous parentage was markedly higher in the main group (41.3% vs. 6.7%, $p<0.001$), which is consistent with the autosomal recessive inheritance pattern predominant in several RLD subtypes [11], [12].

Table 2. Comparative biochemical parameters between study groups

Parameter	Group I (n=46)	Group II (n=30)	p-value
Serum P (mmol/L), M ± SD	0.81 ± 0.24	1.42 ± 0.18	<0.001
Serum Ca (mmol/L), M ± SD	2.18 ± 0.31	2.37 ± 0.15	0.003
ALP (U/L), Me [IQR]	487 [312–764]	198 [155–241]	<0.001
PTH (pg/mL), Me [IQR]	86.4 [42.1–194.6]	28.3 [22.1–36.5]	<0.001
25(OH)D (ng/mL), Me [IQR]	22.3 [11.8–38.7]	29.6 [24.1–41.2]	0.048
$1,25(OH)_2D$ (pg/mL), Me [IQR]	31.2 [18.4–56.7]	44.8 [36.2–58.9]	0.031
TRP (%), M ± SD	72.4 ± 11.3	88.6 ± 6.2	<0.001

Patients with RLD exhibited significantly lower serum phosphorus, calcium, and tubular phosphate reabsorption, alongside elevated ALP and PTH levels compared to controls (all $p<0.05$), confirming the characteristic biochemical phenotype of the study population. Molecular-genetic diagnosis was confirmed in 38 of 46 patients (82.6%) of the main group. This proportion was significantly higher than in the group without genetic confirmation (17.4%), $\chi^2 = 41.3$, $p<0.001$. The distribution of causative genes is presented in Table 3.

Table 3. Distribution of causative genes in patients with confirmed RLD (n=38)

Gene	Inheritance	n (%)	Diagnosis
PHEX	X-linked recessive	10 (26.3%)	X-linked hypophosphatemia
VDR	AR	9 (23.7%)	VDDR type II
CYP27B1	AR	9 (23.7%)	VDDR type I
SLC34A3	AR	6 (15.8%)	Hereditary hypophosphatemia with hypercalciuria (HHRH)
FGF23	AD	2 (5.3%)	Autosomal dominant hypophosphatemic rickets (ADHR)
Other genes	Various	2 (5.3%)	Other RLD forms

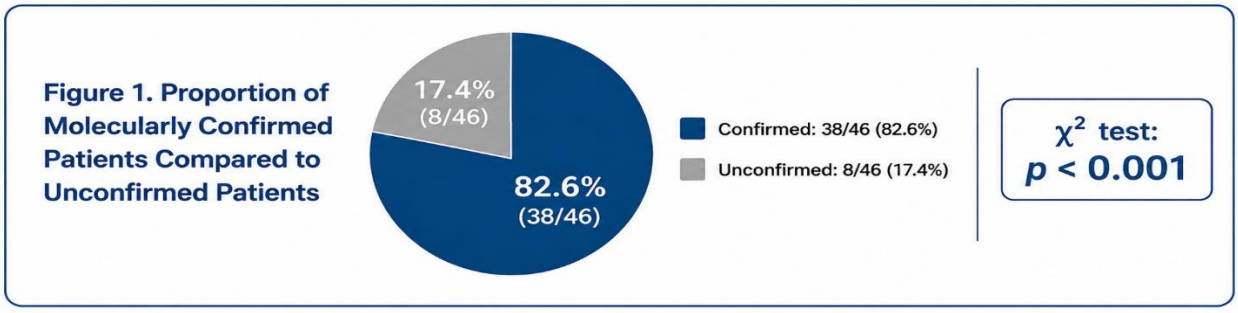
AR = autosomal recessive; AD = autosomal dominant; R = recessive

Five recurrent mutations - each identified in two or more unrelated patients - were detected in the cohort (Table 4). The high frequency of specific variants within individual genes strongly suggests a founder effect in the Uzbek population [11].

Table 4. Recurrent mutations identified in unrelated patients (n=38)

Gene	Variant	Frequency Among Gene-Specific Mutations (%)	ACMG Class	Predicted Effect
VDR	c.374C>T (p.Pro125Leu)	66.7%	Pathogenic	p.Pro125Leu (ligand-binding domain)
CYP27B1	c.1166G>A (p.Arg389His)	66.7%	Pathogenic	p.Arg389His (enzymatic activity ↓)
PHEX	c.1045C>T (p.Arg349Cys)	20.0%	Likely pathogenic	p.Arg349Cys
PHEX	c.2179_2180delAG	20.0%	Pathogenic	Frameshift / premature stop
SLC34A3	c.1565T>C (p.Leu522Pro)	50.0%	Pathogenic	p.Leu522Pro (transporter dysfunction)

The variant c.374C>T in _VDR_ was identified in 6 of 9 patients with VDDR-II (66.7%), all of whom originated from the Fergana Valley and Kashkadarya regions. Similarly, c.1166G>A in _CYP27B1_ was detected in 6 of 9 patients with VDDR-I (66.7%), predominantly from southern Uzbekistan. The c.1565T>C in _SLC34A3_ was found in 3 of 6 patients with HHRH (50.0%). The geographic clustering of these variants and their occurrence in patients from non-consanguineous families provide additional support for a founder effect rather than independent mutational events [13].



VDDR-II – Vitamin D-dependent rickets type II; VDDR-I – Vitamin D-dependent rickets type I; HHRH – Hereditary hypophosphatemic rickets with hypercalciuria.

The proportion of molecularly confirmed patients compared to those remaining unconfirmed is shown in Figure 1 (descriptive):

- Confirmed: 38/46 (82.6%)
- Unconfirmed: 8/46 (17.4%)
- χ^2 test: $p<0.001$

4. Discussion

The molecular-genetic verification rate reached to 82.6 % in this study, which is quite high, and indicates the sensitivity of the NGS-based gene panel used and relatively limited genetic structure of RLD in the Uzbek group. This is in line with the published diagnostic yields in European cohorts (60–75%), and such cohorts have higher consanguinity rates, a higher proportion of recessive disorders, and a higher likelihood of pathogenic variants being detected by targeted panels [14].

Five recurrent mutations across four key RLD genes, especially the predominance of c.374C>T (VDR) and c.1166G>A (CYP27B1) mutations have direct clinical implications. Recognition of population-specific mutations allows for the development of first tier genetic screening strategies that can involve Sanger sequencing of the most common mutations before more extensive panel testing, at least for the time being, as genetic testing becomes more widespread.

The high consanguinity rate (41.3%) in the main group is in line with that of other populations from the central Asian countries, and is related to the high proportion of autosomal recessive cases, particularly VDDR-I and VDDR-II, in this group. These results suggest the need for specific genetic counselling program in areas of high consanguinity [15].

5. Conclusion

An NGS-based targeted panel sequencing has a high diagnostic efficacy (MOG82.6%, far superior to non-genetically confirmed children, $p<0.001$).

Five recurrent mutations were identified in VDR (c.374C>T, 66.7%), CYP27B1 (c.1166G>A, 66.7%), PHEX (c.1045C>T and c.2179_2180delAG, 20.0% each), and SLC34A3 (c.1565T>C, 50.0%), consistent with a founder effect in the Uzbek population. In Uzbekistan, genealogy (consanguinity) is very high (41.3%) in patients with RLD, and the majority of RLD are autosomal recessive, which requires targeted genetic counseling and population level screening strategies.

Molecular-genetic diagnosis is strongly recommended to incorporate into the routine clinical assessment of children with vitamin D resistant rickets to ensure that children receive the correct treatment and prevention of irreversible complications of skeletons..

REFERENCES

[1] C. F. Munns, N. Shaw, M. Kiely, et al., "Global consensus recommendations on prevention and management of nutritional rickets," Journal of Clinical Endocrinology & Metabolism, vol. 101, no. 2, pp. 394–415, 2016.

[2] T. O. Carpenter, N. J. Shaw, A. A. Portale, et al., "Rickets," Nature Reviews Disease Primers, vol. 3, Art. no. 17101, 2017.

[3] F. H. Glorieux and J. M. Pettifor, "Vitamin D/dietary calcium deficiency rickets and pseudo-vitamin D deficiency rickets," BoneKEy Reports, vol. 3, Art. no. 524, 2014.

[4] M. D. Ruppe, "X-linked hypophosphatemia," in GeneReviews®, Seattle, WA, USA: University of Washington, 2012, updated 2023.

[5] S. Richards, N. Aziz, S. Bale, et al., "Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the ACMG and AMP," Genetics in Medicine, vol. 17, no. 5, pp. 405–424, 2015.

[6] K. Dahir, M. S. Roberts, S. Krolczyk, et al., "X-linked hypophosphatemia: A new era in management," Journal of the Endocrine Society, vol. 4, no. 12, Art. no. bvaa151, 2020.
[7] K. P. Schlingmann, J. Ruminska, J. Kaufeld, et al., "Autosomal-recessive mutations in SLC34A3 cause hereditary hypophosphatemic rickets with hypercalciuria," New England Journal of Medicine, vol. 374, pp. 1112–1122, 2016.
[8] M. P. Whyte, "Hypophosphatasia and disorders of mineral metabolism," in Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 9th ed., C. J. Rosen, Ed. Hoboken, NJ, USA: Wiley-Blackwell, 2018, pp. 541–550.
[9] A. Linglart, M. Biosse-Duplan, K. Briot, et al., "Therapeutic management of X-linked hypophosphatemia from infancy to adulthood," Endocrine Connections, vol. 3, no. 1, pp. R13–R30, 2014.
[10] E. A. Imel, A. Biggin, A. Schindeler, and C. F. Munns, "FGF23, phosphate and vitamin D regulation: Lessons from genetic diseases," Bone, vol. 121, pp. 121–133, 2019.
[11] D. Haffner, F. Emma, D. M. Eastwood, et al., "Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia," Nature Reviews Nephrology, vol. 15, no. 7, pp. 435–455, 2019.
[12] I. Endo, S. Fukumoto, K. Ozono, et al., "Nationwide survey of fibroblast growth factor 23-related hypophosphatemic diseases in Japan," Endocrine Journal, vol. 62, no. 9, pp. 811–816, 2015.
[13] G. I. Baroncelli, S. Bertelloni, and F. Sodini, "Genetic forms of vitamin D-dependent rickets and osteoporosis," Journal of Endocrinological Investigation, vol. 44, no. 12, pp. 2511–2525, 2021.
[14] Y. Kinoshita and S. Fukumoto, "X-linked hypophosphatemia and FGF23-related hypophosphatemic diseases: Prospects for precision medicine," Endocrine Reviews, vol. 39, no. 3, pp. 274–291, 2018.
[15] R. Padidela, O. Nilsson, and O. Mäkitie, "New insights into the pathogenesis and management of inherited rickets," Frontiers in Endocrinology, vol. 11, Art. no. 606, 2020.