Case Report

Vitamin D Dependent Rickets Type 2A Due to a Rare Single Exon 3 Vitamin D Receptor Gene Deletion in oddly unfortunate Siblings Presenting with Alopecia and Refractory Rickets: A rare Case Report

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ABSTRACT

Vitamin D-dependent rickets type 2A (VDDR2A) is a rare autosomal recessive disorder caused by pathogenic variants in the vitamin D receptor (VDR) gene, resulting in resistance to calcitriol. Congenital alopecia is an important clinical clue to this disorder. We report two female siblings with VDDR2A who presented with progressive rickets, growth retardation, and congenital alopecia. Both had previously received conventional vitamin D and calcium therapy for presumed nutritional rickets, without significant clinical improvement. Biochemical evaluation showed hypocalcemia, hypophosphatemia, elevated alkaline phosphatase, normal 25-hydroxyvitamin D, and elevated 1,25-dihydroxyvitamin D concentrations. Molecular genetic testing identified a deletion involving exon 3 of the VDR gene in both siblings, confirming the diagnosis. Despite prolonged treatment, both children demonstrated limited clinical and radiological improvement. Congenital alopecia in a child with refractory rickets should prompt consideration of VDDR2A. Recognizing the characteristic biochemical profile and confirming it early with molecular testing can support accurate diagnosis, appropriate management, and genetic counselling.

Key words: Vitamin D-Dependent Rickets, Familial Hypophosphatemic Rickets, Alopecia.

Vitamin D-dependent rickets type 2A (VDDR2A), also known as hereditary vitamin D-resistant rickets (HVDRR), is a rare autosomal recessive disorder caused by pathogenic variants in the vitamin D receptor (VDR) gene, resulting in resistance to calcitriol's biological actions. Unlike nutritional vitamin D deficiency, affected children have adequate vitamin D stores but impaired tissue responsiveness to active vitamin D. The disorder commonly presents during infancy or early childhood with hypocalcemia, secondary hyperparathyroidism, hypophosphatemia, growth failure, and severe rickets [1,2,3]. The VDR gene, located on chromosome 12q13, encodes a nuclear receptor involved in calcium and phosphorus homeostasis. Defects affecting receptor structure or function impair vitamin D-mediated transcription despite elevated circulating concentrations of 1,25-dihydroxyvitamin D [4,5]. Reduced intestinal calcium absorption results in persistent hypocalcemia, secondary hyperparathyroidism, phosphate wasting, defective skeletal mineralization, and progressive rachitic deformities.

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A distinctive feature of VDDR2A is alopecia, ranging from patchy hair loss to alopecia totalis. Vitamin D receptor signaling has an important role in normal hair follicle function, and severe receptor dysfunction may therefore manifest with congenital or early-onset alopecia [6,7]. The combination of alopecia and refractory rickets is an important clinical clue to VDDR2A. As nutritional rickets remains a common cause of skeletal deformities in children, patients with VDDR2A may initially receive conventional vitamin D and calcium therapy. Failure to respond appropriately should prompt evaluation for hereditary forms of rickets using detailed biochemical assessment and molecular genetic testing.

Here, we report two female siblings with severe refractory rickets, congenital alopecia, and a homozygous single-exonic copy number deletion involving exon 3 of the VDR gene, classified as likely pathogenic. The cases emphasize the importance of recognizing alopecia as a clinical clue to VDDR2A and the role of molecular testing in establishing the diagnosis.

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CASE REPORT

Case 1

A 6-year-old female child, the first offspring of healthy non-consanguineous parents, presented with progressive bilateral lower-limb deformities, difficulty walking, and inability to stand without support. She was born at term by normal vaginal delivery with a birth weight of 3.0 kg following an uneventful antenatal and perinatal period. Developmental milestones were appropriate until approximately 3 years of age, after which she developed progressive difficulty in walking followed by impairment of standing and independent ambulation. Speech and cognitive development remained age-appropriate. Complete scalp alopecia had been present since birth. Progressive lower-limb deformity became evident at approximately 3 years of age and gradually worsened, accompanied by marked growth impairment. There was no history of recurrent fractures, chronic diarrhea, recurrent vomiting, polyuria, renal or liver disease, or prolonged drug exposure. Dietary intake and sunlight exposure were adequate. She had previously received therapeutic doses of vitamin D and oral calcium for presumed nutritional rickets according to standard treatment protocols, without significant clinical improvement. A similarly affected younger sibling had congenital alopecia and progressive skeletal deformities, whereas both parents and other family members were clinically unaffected. There was no history of consanguinity or known hereditary skeletal disease in the extended family.

On examination, she weighed 11.2 kg and measured 92 cm in height, with severe growth impairment. Head circumference was within normal limits. She was conscious, interactive, and hemodynamically stable. Examination revealed alopecia totalis, frontal bossing, rachitic rosary, Harrison sulcus, widening of the wrists and ankles, bilateral genu valgum, and a positive double-malleoli sign (Figure 1a). Dentition was appropriate for age without enamel defects or delayed eruption. Generalized muscular hypotonia, predominantly involving the proximal lower limbs, was present, and she was unable to stand independently. Spine and neurological examination were otherwise unremarkable.

Case 2

A 3-year-old female child, the younger sibling of Case 1, presented with progressive bilateral lower-limb deformities, difficulty walking, and inability to stand without support. She was born at term by lower-segment cesarean section with a birth weight of 2.7 kg following an uncomplicated antenatal and perinatal period. Developmental milestones were appropriate until approximately 3 years of age, after which progressive difficulty in walking and standing developed. Speech and cognitive development were normal for age. Partial scalp alopecia had been present since birth. Lower-limb deformity was first noted at approximately 3 years of age and progressively worsened. There was no history of recurrent fractures, chronic diarrhea, vomiting, renal or liver disease, or symptoms suggestive of malabsorption. Dietary intake and sunlight exposure were adequate. She had previously received therapeutic vitamin D and calcium supplementation for presumed nutritional rickets without appreciable clinical or biochemical improvement. On examination, she weighed 9.6 kg and measured 78 cm in height, both markedly below expected values for age. Head circumference was normal. She was alert and interactive. Examination revealed partial scalp alopecia, frontal bossing, rachitic rosary, Harrison sulcus, widening of the wrists and ankles, bilateral genu valgum, and a positive double-malleoli sign (Figure 1b). Dentition was normal for age. Generalized proximal muscular hypotonia was present, with inability to stand independently. Spine and neurological examination were otherwise unremarkable.

Radiographic features of rickets in the two siblings showed characteristic metaphyseal widening, cupping, and fraying, consistent with active rachitic changes. The radiographic findings of the siblings are shown in Figure 2. Both siblings demonstrated a biochemical pattern consistent with vitamin D receptor resistance, characterized by hypocalcemia, hypophosphatemia, elevated alkaline phosphatase, normal 25-hydroxyvitamin D, and elevated 1,25-dihydroxyvitamin D. Table 1 shows the investigations of the two cases. Molecular testing identified a homozygous single-exonic copy number deletion involving exon 3 of the VDR gene, with a copy number of zero and laboratory classification as likely pathogenic, supporting the diagnosis of VDDR2A (Figure 3).



Figure 1. a. Case 1. b. Case 2



Figure 2. Radiographs of two siblings.

Test Results and Interpretation

ON PHENOTYPE BASED ANALYSIS: SINGLE EXONIC CNV DETECTED.

CNV Variant

Nomenclature	Copy Number Variation	Disease	Copy Number	Classification
12:(?_48272560)_(48273071_?)	Deletion	Rickets, vitamin D-resistant, type IIA	0	Likely pathogenic

CNV Detail

Genes	–

CNV Region	Morbid Genes	Database	Previously reported	Variant references
Single exon VDR [Exon 3]	VDR	**Clinvar**: Not submitted	Yes [Homozygous]	Internal database (2 individuals)

Comparative IGV

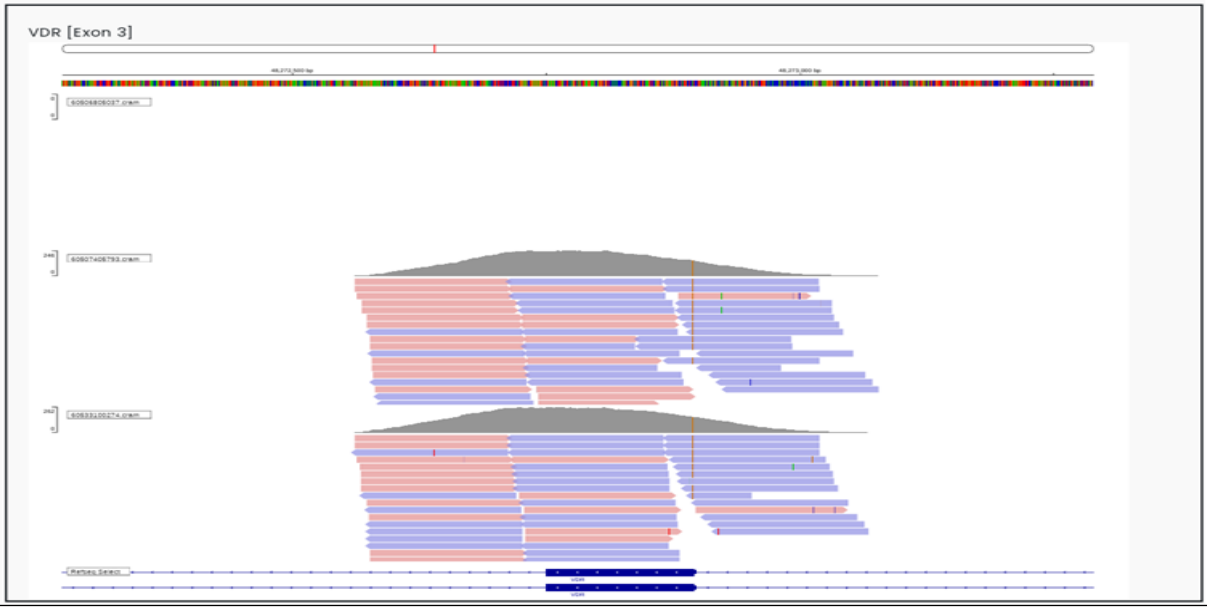


Figure 3. Molecular genetic findings of siblings

MANAGEMENT

Vitamin D 3000 IU/day + oral calcium 75 mg/kg/day was given to both the siblings initially, but there was no improvement in the clinical features. Hence, it was followed by Vitamin D 50 µg/day + oral calcium 1 g/day. The follow-up was done for around 3 years, yet there was no improvement despite the drug therapy (Table 2). The clinical course of the 2 siblings is shown in Table 3.

Table 1. Summary of Investigations in Both Siblings

Investigation	Case 1	Case 2
Haemoglobin	Normal	Normal
Serum Calcium	Low	Low
Serum Phosphorus	Low	Low
Serum Alkaline Phosphatase	Markedly elevated	Markedly elevated
Serum 25-Hydroxyvitamin D	Normal	Normal
Serum 1,25-Dihydroxyvitamin D	Elevated	Elevated
Renal Function Tests	Normal	Normal
Liver Function Tests	Normal	Normal
Serum Electrolytes	Normal	Normal
Wrist Radiograph	Metaphyseal widening, cupping, fraying, and splaying	Similar findings
Molecular Genetic Testing	Single exon 3 deletion in the *VDR* gene	Single exon 3 deletion in the *VDR* gene

Table 2. Treatment and Follow-up of the Two Siblings

Parameter	Case 1	Case 2
Initial therapy	Vitamin D 3000 IU/day + oral calcium 75 mg/kg/day	Vitamin D 3000 IU/day + oral calcium 75 mg/kg/day
Initial response	No clinical or biochemical improvement	No clinical or biochemical improvement
Final diagnosis	VDDR Type 2A	VDDR Type 2A
Current treatment	Vitamin D 50 µg/day + oral calcium 1 g/day	Vitamin D 50 µg/day + oral calcium 1 g/day
Duration of follow-up	3 years	1 year
Growth response	Negligible improvement	Negligible improvement
Biochemical response	No significant improvement	No significant improvement
Radiological response	Persistent rachitic changes without healing	Persistent rachitic changes without healing
Functional outcome	Unable to stand independently	Unable to stand independently
Alopecia at follow-up	Persistent alopecia totalis	Persistent partial alopecia

Table 3. Clinical Timeline of the Two Sibling

Age/Time Point	Case 1	Case 2
Birth	Term female, birth weight 3.0 kg, normal vaginal delivery, complete scalp alopecia noted since birth	Term female, birth weight 2.7 kg, LSCS, partial scalp alopecia noted since birth
Birth–3 years	Normal growth and developmental milestones	Normal growth and developmental milestones
Around 3 years of age	Progressive bowing of both lower limbs noticed with gradual difficulty in walking.	Progressive bowing of both lower limbs noticed with gradual difficulty in walking.
Subsequent months	Progressive worsening of lower limb deformities with inability to stand without support	Progressive worsening of skeletal deformities with inability to stand without support

Initial evaluation	Diagnosed as nutritional rickets and treated with therapeutic vitamin D and oral calcium	Similar diagnosis of nutritional rickets with standard vitamin D and calcium therapy
Response to therapy	No clinical or biochemical improvement despite adequate treatment	No clinical or biochemical improvement despite adequate treatment
Further evaluation	Persistent hypocalcemia, hypophosphatemia, elevated alkaline phosphatase, normal 25-hydroxyvitamin D, elevated 1,25-dihydroxyvitamin D	Similar biochemical profile suggestive of vitamin D receptor resistance
Radiological assessment	Wrist radiographs showed metaphyseal widening with cupping, fraying, and splaying consistent with active rickets.	Similar rachitic changes on wrist radiographs
Genetic testing	Single exon 3 deletion in the *VDR* gene confirming Vitamin D-dependent rickets type 2A	Identical single exon 3 deletion in the *VDR* gene confirming Vitamin D-dependent rickets type 2A
Definitive treatment	Vitamin D 50 µg/day with oral elemental calcium 1 g/day	Vitamin D 50 µg/day with oral elemental calcium 1 g/day
Follow-up	Three years of follow-up with persistent skeletal deformities, absent biochemical and radiological response, negligible growth improvement, persistent alopecia totalis	One year of follow-up with persistent skeletal deformities, absent biochemical and radiological response, poor growth, persistent partial alopecia

DISCUSSION

The present cases highlight the diagnostic importance of congenital alopecia in children with refractory rickets. The coexistence of congenital alopecia, severe rickets, and failure to respond to conventional vitamin D and calcium therapy should therefore prompt early evaluation for VDDR2A. Recognition of this clinical phenotype may prevent prolonged empirical treatment and progression of skeletal deformities and functional disability.

Our findings are consistent with previous reports identifying alopecia as a characteristic feature of VDDR2A. A systematic review of 119 probands reported alopecia in 81.5% of patients and demonstrated associations between specific VDR genotypes, alopecia, disease severity, and treatment response [8]. Similar biochemical and skeletal manifestations, including hypocalcemia, hypophosphatemia, elevated alkaline phosphatase, and increased 1,25-dihydroxyvitamin D, have been reported in affected children [9]. However, treatment response is variable and may depend on the underlying VDR defect and residual receptor activity. Some reported patients have shown poor response to oral calcium and calcitriol and required intensive or intravenous calcium therapy [10,11], whereas others have demonstrated satisfactory improvement with high-dose calcium and active vitamin D therapy [12]. Thus, the limited response in our patients is compatible with the recognized therapeutic variability of VDDR2A, but treatment response should not be attributed solely to the location of the identified deletion without functional evidence.

The principal limitations of this report are the small sample size and the inclusion of two siblings, which limits generalizability to the broader clinical and genetic spectrum of VDDR2A. Functional studies assessing the effect of the exon 3 deletion on VDR expression or activity were not available. In addition, longer-term follow-up with standardized biochemical, radiological, growth, and functional assessments would provide a better understanding of disease progression and treatment response. Future multicenter studies and registries incorporating detailed VDR genotypes, functional characterization, phenotype, and longitudinal treatment outcomes may improve genotype-phenotype correlations and facilitate individualized management.

CONCLUSION

These cases emphasize that congenital alopecia in a child with refractory rickets should prompt early consideration of VDDR2A, enabling timely biochemical evaluation and molecular confirmation for appropriate management and genetic counselling.

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