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Case Report

A case with short stature and proteinuria: atypical presentation of a family with m.3243A>G mutation

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ABSTRACT

Background. The mitochondrial DNA (mtDNA) m.3243A>G mutation is one of the most common pathogenic mtDNA variants. The phenotypes associated with this mutation range from asymptomatic induviduals to well-defined clinical syndromes, or non-syndromic mitochondrial disorders. Variable clinical features in pediatric cases may cause difficulty in diagnosis. Kidney involvement in this mutation is uncommon and reported on a case-by-case basis. Here, we report on a patient with m.3243A>G mutation, who presented with short stature and proteinuria, and his family, who share the same genotype but exhibit different heteroplasmy levels in different tissues and variable phenotypes.

Case presentation. A 15-year-old male patient was admitted to the pediatric endocrinology department with short stature. His examinations revealed nephrotic range proteinuria, hearing loss, impaired glucose tolerance, and Wolf-Parkinson-White syndrome. From family history, it was learned that diabetes mellitus (DM) and progressive sensorineural hearing loss were common in this family. The patient's mother, who had chronic kidney disease, DM, and hearing loss, had died suddenly for an unknown reason. Considering the family history, a genetic analysis was performed for mitochondrial disease. Mitochondrial DNA analysis revealed a m.3243A>G mutation with 47% heteroplasmy in blood, 62% heteroplasmy in buccal cells, and 96% heteroplasmy in urothelial cells in our patient.

Conclusions. Short stature without any other complaint and renal involvement are rare findings in m.3243A>G mutation. In patients presenting with proteinuria, in the presence of conditions affecting many systems such as endocrine system pathologies, hearing loss, and cardiac pathologies, and in the presence of individuals with a similar family history of multiple organ involvement, mitochondrial diseases should be considered, and examined from this perspective. Our case illustrates the value of a detailed medical and family history.

Key words: maternally inherited diabetes and deafness, mitochondrial disease, m.3243A>G, proteinuria, short stature.

Short stature, one of the most common reasons for referral to pediatric clinics, resulting from reduced growth plate chondrogenesis may be due to growth plate-specific factors or factors elsewhere in the body that may affect the growth plate.[1] Therefore, patients with short stature should be carefully evaluated. Urinalysis is also recommended for evaluation.[2] Proteinuria is a common finding in primary care practice. Abnormal findings resolve in repeated tests in most children with proteinuria, but if proteinuria persists, further investigation is required. One of the important and rare causes of proteinuria is mitochondrial disease.[3]

Patients with mitochondrial diseases may present with a broad clinical spectrum. However, in mitochondrial diseases, some organs with a high energy demand, such as the nervous system, and skeletal and cardiac muscles are expected to be more affected as a result of insufficient ATP production to meet energy demands.[4] Mutations in mitochondrial DNA (mtDNA) or mitochondria-associated nuclear DNA (nDNA) genes can cause mitochondrial diseases. Thus, mitochondrial

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diseases can exhibit maternal inheritance attributable to mtDNA mutations; autosomal or X-linked inheritance associated with nDNA mutations, and a pattern of inheritance associated with de novo mutations that can occur in both genomes.[5] Pathogenic variants of mtDNA usually only affect a proportion of mtDNA molecules (heteroplasmy).[6] This means the presence of a mixture of mutated and wild-type mitochondrial genomes within individual cells. Since the range of heteroplasmy can vary from cell to cell, organ to organ, and individual to individual, clinical variability can be observed even with the same mtDNA mutation.[7] Although the mutant load at birth may be similar in different tissues, this changes with age progresses. Postmitotic cells, such as skeletal muscle or urinary epithelial cells, and mitotic cells, such as hair follicles and buccal mucosa, tend to have higher and more stable levels of heteroplasmy with age. Blood cells generally have the lowest levels of heteroplasmy.[8,9]

The mtDNA *MT-TL1* m.3243A>G mutation, one of the most common pathogenic mtDNA variants, presents with complex genetic, pathogenic molecular mechanisms and phenotypes.[9] The first identified and best described m.3243A>G-associated phenotype is mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). In 1990, the m.3243A>G mutation was found in the *MT-TL1* gene that encodes mitochondrial leucine transfer RNA 1.[10] More than 16 in 100,000 individuals carry the m.3243A>G mutation. Carriers of the m.3243A>G mutation are clinically heterogeneous. Its phenotypes range from asymptomatic to well-defined clinical syndromes, or non-syndromic-mitochondrial disorders. Well-defined syndromes are MELAS, myoclonic epilepsy and ragged-red fibers (MERRF), maternally inherited diabetes and deafness (MIDD), and chronic progressive external ophthalmoplegia. Hearing loss, short stature, nephropathy, underweight, enteromyopathy, hypertrophic cardiomyopathy, and cluster headaches are non-syndromic-mitochondrial disorders.[9,11-15]

Sometimes, due to atypical presentation, diagnosis and classification may be difficult in mitochondrial diseases. Here, a patient with a *MT-TL1* m.3243A>G mutation, who presented with short stature and proteinuria, and his family, who have the same genotype with different heteroplasmy levels in different tissues and variable phenotypes, are reported.

Case Presentation

A 15-year-old male patient (III-2 in Fig. 1) was referred to our endocrine department with a complaint of short stature. The patient was born at term, with a birth weight of 3,000 g, from a nonconsanguineous marriage. His neuromotor development was consistent with his peers. His family history included individuals with diabetes mellitus (DM), sensorineural hearing loss, chronic kidney disease, stroke, psychosis, and sudden death from an unknown cause (Table I) (Fig. 1). When the patient applied to the endocrinology department, his body weight was measured as 38.4 kg (–2.94 standard deviation score [SDS]), his height was 154 cm (–2.3 SDS), and body mass index (BMI) was 16.1 kg/m² (–2.2 SDS). Bone age was 15 years. Blood pressure was 110/65 mmHg. The patient was Tanner stage V and other systemic examinations including the neurological system were normal. No edema was detected. The laboratory test results were compatible with impaired glucose tolerance, abnormal urinalysis with proteinuria, normal renal, and liver functional tests, and electrolytes (Table II). Thyroid function tests, insulin-like growth factor-1, and insulin-like growth factor binding protein-3 levels checked for short stature were normal. There was no acidosis or alkalosis. No pathology was detected in the examinations performed for short stature. No further examination was performed because the epiphyses were closed. When questioned about polyuria, polydipsia, and weight loss, it was learned that he had no additional complaints. The patient was negative for type-1 DM autoantibodies. Kidney ultrasonography and

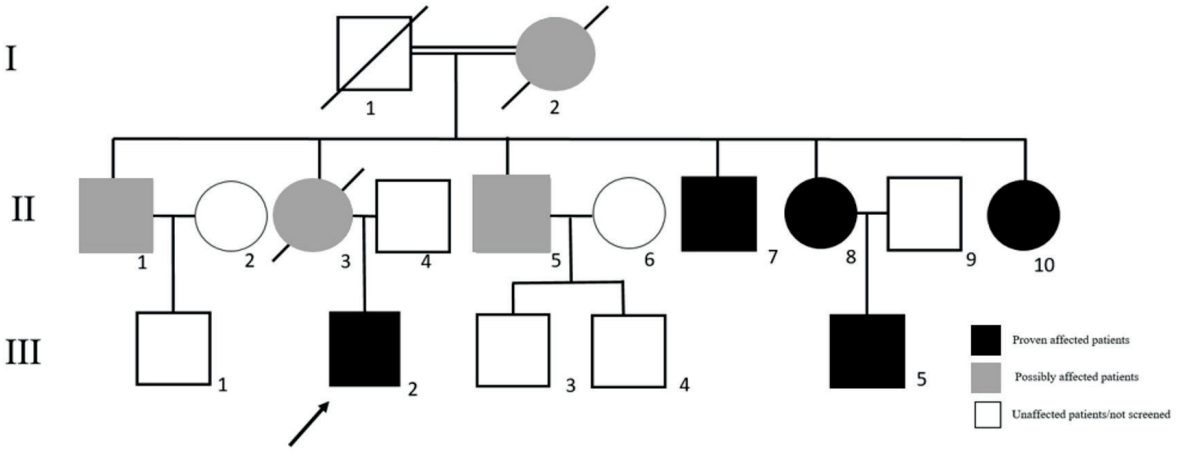

Fig. 1. Pedigree of this family with *MT-TL1* (NC_012920.1:3230_3304): m.3243A>G mutation. Circles, female patients; squares, male patients. Solid symbols represent individuals harboring the m.3243A>G mutation; shaded symbols represent individuals with a clinically suggestive history but no genetic confirmation; open symbols represent unaffected individuals. Roman numerals indicate the generation and the Arabic numerals indicate the individual. A line through the symbols indicates that the subject is deceased. Since the family history of the upper generations in the pedigree is not informative for the disease, it was not drawn. Maternal grandparents of the index case (individuals I-1 and I-2) were first-cousins.

Table I. General characteristics of the family members.

Patient no (see Fig. 1)	Sex	Age at diagnosis (years)	Short stature	Malnutrition	Proteinuria	Chronic kidney disease	Diabetes mellitus	Wolf Parkinson White syndrome	Muscle cramps	Stroke and seizures	Progressive sensorineural hearing loss	Psychosis	Other features
I-2	F	Death at 66				+	+				+		
II-1	M	48					+				+		
II-3	F	Death at 46				+	+				+		
II-5	M	45					+						
II-7	M	42						+					
II-8	F	41									+	+	
II-10	F	40	+	+			+		+	+	+		
III-2	M	15	+	+	+			+			+		IGT
III-5	M	17	+	+								+	

IGT: impaired glucose tolerance

Doppler ultrasonography were normal. Hearing test revealed mild bilateral sensorineural hearing loss. The ophthalmic examination was normal. It was learned that the genetic analysis ordered with the preliminary diagnosis of Alport due to hearing loss and proteinuria was normal.

Considering the family history, the mitochondrial whole genome was sequenced via next generation sequencing system (Myseq, Illumina®) with the DNA extracted from peripheral lymphocytes. A missense known variant on *MT-TL1* gene, m.3243A>G was found with a 47% heteroplasmy level in blood.

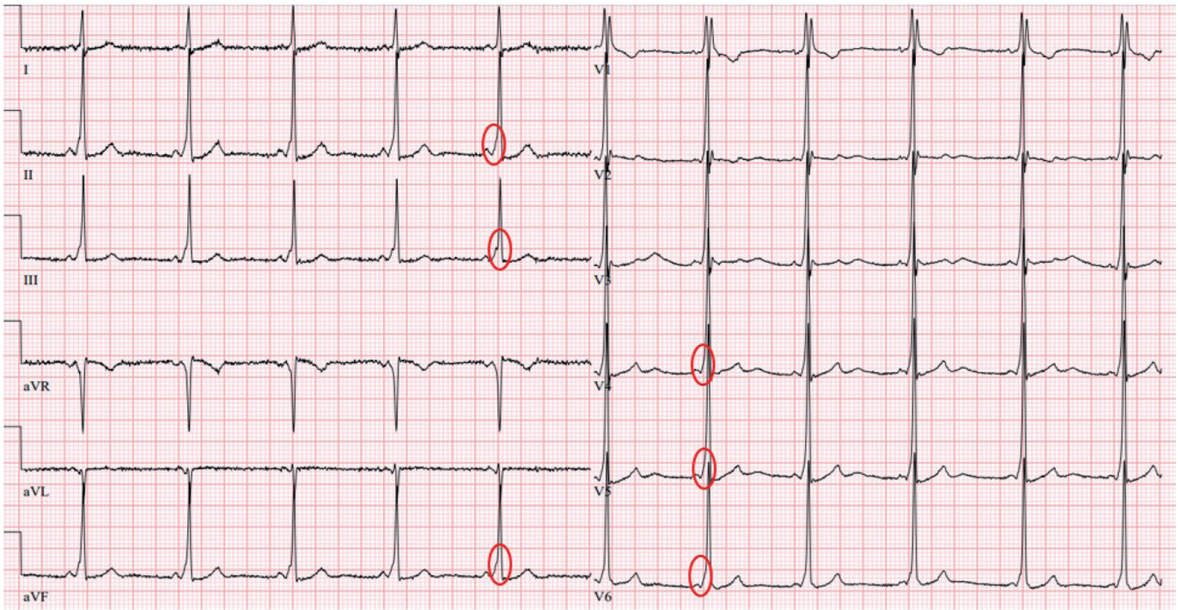

Fig. 2. Electrocardiogram of index case (III-2) with Wolf-Parkinson-White pattern. Elliptical red markings highlight the delta waves.

On cardiac examination, the patient had normal echocardiographic findings but was found to have Wolff-Parkinson-White syndrome (Fig. 2). He underwent radiofrequency ablation (RFA) for Wolff-Parkinson-White syndrome. ECG findings resolved after RFA and no any residual ECG abnormalities were detected again during the follow-up.

The patient was also evaluated by the Divisions of Pediatric Neurology and Metabolism. Metabolic investigations involving very long-chain fatty acids, free carnitine, urinary organic acids, urinary and plasma amino acids, pyruvic acid, and ammonia levels were normal. The laboratory analyses revealed intermittently mildly elevated lactate (27.9-28.9 mg/dL, controls < 19.8), and the creatine kinase (CK) level was found to be high once, but the repeat tests were found to be within the normal range (Table II). Brain magnetic resonance imaging (MRI) showed that the 4th ventricle was larger than normal, cerebellar folia were enlarged incompatible with the patient's age, and perimedullary-pericerebellar extra-axial cerebrospinal fluid spaces were enlarged. Magnetic resonance spectroscopy was found normal. As a result of all these evaluations, a treatment consisting of enalapril and coenzyme Q_{10} as well as thiamine, riboflavin, and carnitine was initiated. The patient, who has been followed for 2 years, has had no additional complaints, and the latest laboratory values are given in Table II. During follow-up, nephrotic-range proteinuria was detected in the patient.

Other family members were referred to relevant departments for clinical and genetic assessment. The same m.3243A>G heteroplasmic pathogenic variant in the *MT-TL1* gene was detected with the mitochondrial genome sequencing from peripheral lymphocytes in some family members whereas some did not have it (Table III). Some family members could not be evaluated because they were either deceased or unwilling to participate in the study. It was learned that the aunt's (II-10) hearing loss became apparent at the age of 18 and a cochlear implant was placed at the age of 25. She was diagnosed with DM at the age of 18 and ordered for genetic analysis for maturity-onset diabetes of the young (*HNF1A, HNF4A, HNF1B* and *GCK* gene), which was found to be normal. The aunt (II-10) had a stroke and seizure at the

Table II. The laboratory findings of the case

Parameters	On admission	Second visit	Latest visit	Reference ranges
Fasting plasma glucose (mg/dL)	89	75	72	<100
2. hour glucose during an OGTT (mg/dL)	151	NA	NA	<140
HbA1c (%)	5.6	5.1	5.2	<5.7
Total cholesterol (mg/dL)	NA	159	NA	107-202
HDL (mg/dL)		50		>40
LDL (mg/dL)		89		<100
TG (mg/dL)		102		47-210
CK (U/L)	553	123	108	32-294
Na/K/Cl (mEq/L)	137/4.7/100	138/4/99	138/4.1/101	132–146/3.5–5.5/98–109
Urea (mg/dL)	39	34	39	17-43
Creatinine (mg/dL)	0.66	0.67	0.63	0.67-1.25
eGFR (ml/min/1.73 m²)	97	95	102	>90
Uric acid (mg/dL)	5.2	5.2	4.7	3.7-9.2
Albumin (g/L)	48	45	46	32-48
Blood pH	7.35	7.35	7.38	7.35-7.45
Bicarbonate (mmol/L)	26.3	24.3	23.8	21-26
Lactate (mg/dL)	27.9	23.3	28.9	4.5-19.8
Urine pH	6	5.5	5.5	4.5-8
Urine protein	3+	3+	3+	Negative
Spot urine protein/creatinine (mg/mg)	1.7	2.3	3.5	<0.2
24-hour urinary protein (mg/m²/hour)	21	42	44.1	<4
24-hour urine microalbumin (mg/day)	422	810	882	<30
Spot urine beta-2 microglobulin (mg/L)	NA	0.19	0.16	0-0.2
24-hour urinary beta-2 microglobulin (mg/day)	0.36	NA	NA	0.03-0.37

CK, creatine kinase; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; TG, tryglyseride. e-GFR was calculated using the modified Schwartz formula.

age of 39. In laboratory results, renal functional tests, electrolytes, urinalysis, lactate, and CK were found to be normal. HbA1c was 6.7% (normal: <5.7%). The cardiological evaluation was normal. Our patient's cousin (III-5) was 17 years old and was evaluated in our clinic. His height was 159 cm (–2.4 SDS), and his BMI was 17.4 kg/m² (–2.3 SDS). Systemic examinations including the neurological system were normal. In laboratory results, renal functional tests, electrolytes, urinalysis, lactate, CK, and cardiological evaluation were normal.

Finally, considering the heteroplasmic distribution of the mitochondrial variants among different tissues, mitochondrial genome analyses for the known pathogenic variant were repeated using the DNA extracted from buccal swabs and urine in the patients who accepted to give samples. The variant was detected with a 72% heteroplasmy level from the urine sample of the 42-year-old uncle (patient II-7) with a history of Wolff-Parkinson-White syndrome, whose blood and buccal samples were normal (Table III).

Table III. Heteroplasmy levels at different tissues of the *MT-TL1* gene m.3243A>G variant in family members

Patient number	Blood (%) / Reading depth	Buccal cells (%) / Reading depth	Urothelial cells (%) / Reading depth
II-7	Normal	Normal	71 / 452
II-8	30 / 2736	NA	NA
II-10	36 / 1756	35 / 341	55 / 162
III-2 (index)	47 / 955	62 / 596	96 / 999
III-5	52 / 1273	NA	NA

NA, not available.

Discussion

The mutation m.3243A>G in the mitochondrial *MT-TL1* gene results in a heterogeneous disorder due to its significant overlap and diverse spectrum of clinical presentations. We describe the phenotypic features and molecular diagnosis of a family with *MT-TL1* m.3243A>G mutation. The presenting symptoms of the proband in the family were short stature and proteinuria, which were reported less frequently. In contrast, the symptoms were distributed in a wide range of DM, chronic kidney disease, Wolff-Parkinson-White syndrome, sensorineural hearing loss, psychosis, stroke to sudden death history in the current family. It was learned that although there were multiple affected individuals in the family and they were followed up in different departments, and they were never examined for mitochondrial disease. This case highlights the atypical presentation of *MT-TL1* gene m.3243A>G mutation in children, the importance of detailed family history, and the possibility of metabolic disease in cases of unexplained multisystem involvement.

The nervous system is the most affected system in patients with m.3243A>G, and the other affected tissues or organs are skeletal muscles, heart muscles, ears, eyes, kidneys, liver, and the endocrine system.[16] The clinical features of m.3243A>G mutation have been described in several reports. Xia et al.[17] evaluated one hundred pediatric patients with symptomatic mitochondrial disease harboring the m.3243A>G mutation. They found that seizure (76%) and short stature (73%) were the most common symptoms. They also showed that elevated plasma lactate (70%), weight loss (69%), abnormal MRI changes (68%), vomiting (55%), decreased vision (52%), headache (50%), and muscle weakness (48%) were other symptoms. In their study, they reported that while most of the patients were multi-symptomatic, only two patients had one symptom, and five patients manifested two symptoms.[17] In another study evaluating 35 patients with the m.3243A>G mutation, short stature was detected in 22.9% of the cases.[18] Short stature is frequently observed in individuals who carry the m.3243A>G mutation. Nevertheless, our case, who presented no symptoms and was identified only based on short stature during the investigation, has not been documented in the literature. Abnormally low body weight and stunting have also been observed in individuals with mitochondrial diseases.[19] Although the etiology of growth retardation is not fully known, it is thought that it may be related to many medical comorbidities such as central nervous system, cardiac, gastrointestinal and renal diseases beyond endocrinopathies. It should also be noted that it may be due to growth hormone deficiency.[18]

The other endocrine system involvements in the m.3243A>G mutation include the pancreas, thyroid, parathyroid, pituitary, and gonads.[20] MIDD is the most common phenotype involving the endocrine system.[21] Clinical characteristics related to MIDD include early onset DM with short stature, a normal or low BMI, and bilateral hearing impairment that occurs at about the same time as the onset of DM.[22] Although patients may present differently, insulin-dependent DM and sensorineural

hearing loss usually occur by the age of 30-40.[23] Cardiomyopathy, neuropsychiatric disorders, myopathy, and renal dysfunction are other clinical comorbidities associated with this disease.[23] Another study showed that the m.3243A>G mutation may be a contributing genetic factor in the development of end-stage kidney disease in patients with diabetes.[24] DM, kidney disease, and hearing loss were common in the family who had never been evaluated for mitochondrial disease. Our case illustrates the value of a detailed medical and family history as it can help in the diagnosis of mitochondrial diseases on clinical suspicion alone.

Since mitochondria are also abundant in the kidneys, mitochondrial dysfunction can also cause renal damage. Kidney involvement should not be overlooked as it has a potential impact on morbidity and mortality.[25] Patients with MELAS have been reported to have worsening renal function and progression into end-stage renal disease.[26] Yang et al. found the prevalence of nephropathy to be 13% in their study.[14] Previous reports have shown that kidney involvement in carriers of the m.3243A>G mutation is usually in the form of Fanconi syndrome or focal segmental glomerulosclerosis (FSGS).[26,27] These patients usually present with signs of proximal tubular dysfunction and nephrotic-range proteinuria. Since tubular function has a high energy demand, tubular dysfunction is the most common renal symptom in mitochondrial diseases.[28] Fanconi syndrome is believed to be caused by impaired activity of ATP-dependent sodium-potassium pumps, which are essential in the tubular reabsorption process.[25] Previous studies have found abnormal mitochondrial build-up in podocytes in the kidneys of patients with FSGS-associated mitochondrial disease. These findings have been attributed to a compensatory increase in mitochondria due to mitochondrial dysfunction. Mitochondrial dysfunction in podocytes leads to damage in glomerular epithelial cells, resulting in proteinuria and ultimately glomerulosclerosis.[28] Accurate identification of the mitochondrial origin of renal disease in these patients is essential for the selection of adequate treatment and appropriate supportive care. Although genetic analysis could not be performed because our patient's mother and grandmother died, it is thought that their chronic kidney disease may have been due to the m.3243A>G mutation. Kidney function tests and blood pressure monitoring of this family should be performed regularly.

Our patient had bilateral mild sensorineural hearing loss in addition to proteinuria. Sensorineural hearing loss that accompanies renal disease initially suggests Alport syndrome. But haematuria is a key feature of Alport syndrome in contrast to m.3243A>G associated nephropathy. Sensorineural hearing loss in patients with m.3243A>G mutation often begins gradually, occurs bilaterally, and may become severe over time and men are affected more than women.[29] In a study 238 cases of m.3243A>G were evaluated, and hearing impairment was detected in 81% of the cases.[30]

Another system affected in our patient was the cardiovascular system. Cardiac manifestations in m.3243A>G mutation patients are common and serious. Although hypertrophic cardiomyopathy is the most commonly reported cardiovascular disease in patients with m.3243A>G mutation, cardiac conduction disorders such as Wolff-Parkinson-White syndrome have also been reported.[31] Sudden adult death syndrome is a frequent occurrence in patients with m.3243A>G[32] so it is important to conduct regular cardiac arrhythmia surveillance and cardiac echocardiography in m.3243A>G mutation carriers.

In our case report, mutation load was also investigated in different tissues in some family members. We found that the proportion of mutant genomes was markedly higher in the DNA from urothelial cells than in the DNA from blood and buccal cells. While the uncle (patient II-7) had no detectable mutant genomes in blood and buccal cells, these were present in urothelial cells. This is related to the fact that, as we have emphasized before, urine

epithelial cells tend to have higher and more stable heteroplasmy levels than blood cells with increasing age.[8] This finding suggests that when the index of suspicion for a mitochondrial DNA mutation is high, DNA from multiple tissues should be screened.

In conclusion, the current family showed intra-familial clinical diversity. Maternal family history of chronic kidney disease, DM, stroke, psychosis, and hearing loss in some of the family members led to a suspicion of mitochondrial disease. While patients without typical findings are generally diagnosed with mitochondrial diseases based on screening results due to their relatives, in our family, the entire family was diagnosed after the patient who presented with atypical findings was diagnosed. It should be remembered that only short stature may be the first clinical symptom at presentation in these patients. Our case illustrates the value of a detailed medical and family history.

Ethical approval

We have obtained informed consent from the patient's parent or guardian and family members to publish this case report as it includes a detailed family history.

Author contribution

Study conception and design: GB, Mİ, BÇ; data collection: GB, Mİ, BÇ; analysis and interpretation of results: GB, Mİ, BÇ; draft manuscript preparation: GB, Mİ, BÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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