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Research Article

Founder Pathogenic Variant in *LMNA* and Its Diverse Phenotypic Manifestations in Mandibuloacral Dysplasia: Insights from a Turkish Cohort

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What is already known on this topic?
Mandibuloacral dysplasia (MAD) is associated with mutations in the *LMNA* gene, which plays a crucial role in maintaining nuclear structure. Previous research has documented various phenotypic manifestations of MAD, but the relationship between specific mutations and clinical variability remains poorly understood, particularly in diverse populations.

What this study adds?
This study identifies a common founder variant in the *LMNA* gene within a Turkish cohort and highlights the significant phenotypic variability observed among affected individuals. By correlating genetic findings with clinical presentations, the research enhances our understanding of the genotype-phenotype relationship in MAD, paving the way for more personalized diagnostic and therapeutic strategies.

Abstract
Objective: Mandibuloacral dysplasia (MAD) is a rare genetic disorder characterized by distinctive skeletal abnormalities, metabolic issues, and skin changes, often linked to pathogenic variants in the LMNA gene, which encodes lamin A/C. This study investigates a specific founder mutation within a Turkish cohort and explores its impact on phenotypic expressivity.
Methods: We conducted a comprehensive analysis involving genetic testing for LMNA variants in patients diagnosed with MAD. Clinical evaluations documented a wide range of phenotypic features, including facial dysmorphism, skeletal anomalies, and metabolic abnormalities. We also collected family histories to assess inheritance patterns and potential environmental influences.
Results: Our findings identified a common founder mutation in the LMNA gene among the cohort, which was present in a significant percentage of participants. Notably, phenotypic expressivity varied significantly, with some individuals exhibiting classic MAD features, while others showed atypical manifestations, such as additional endocrine disorders and variable severity of skeletal anomalies. This variability underscores the complexity of the genotype-phenotype relationship.
Conclusion: This study highlights the significance of the founder mutation in LMNA and its diverse phenotypic outcomes in MAD. Our results contribute to the understanding of how genetic mutations can lead to a spectrum of clinical presentations, emphasizing the necessity for personalized clinical approaches in managing this condition. Further research is warranted to elucidate the underlying mechanisms of phenotypic variability and to improve diagnostic and therapeutic strategies.
Keywords: *LMNA* gene, Mandibuloacral dysplasia Type A, Founder effect, Progeroid syndrome, Partial lipodystrophy

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INTRODUCTION

Mandibuloacral dysplasia (MAD) is a rare autosomal recessive progeroid disorder characterized by postnatal growth retardation, mandibular and clavicular hypoplasia, acro-osteolysis of the terminal phalanges, delayed cranial suture closure, joint contractures, lipodystrophy, skin atrophy, alopecia, and mottled skin pigmentation (1–3). Patients with MAD present either with partial lipodystrophy (type A; MADA; OMIM#248370) or generalized lipodystrophy (type B; MADB; OMIM#608612), resulting from biallelic variants in either the *LMNA* gene, encoding lamin A/C (4,5), or the *ZMPSTE24* genes, encoding zinc metalloprotease (6), respectively. A third type of mandibuloacral dysplasia progeroid syndrome (MDPS; OMIM #619127) due to biallelic variants in the *MTX2* gene encoding metaxin-2 (MTX2) has recently been described (7).

In addition to the cutaneous and skeletal manifestations, MAD patients are predisposed to metabolic complications, including insulin resistance, diabetes mellitus, and hypertriglyceridemia (4,6). While MAD type A (MADA) is rarely associated with hepatomegaly or hepatic steatosis, a few cases have been reported (1,4,8). To date, there are approximately 40 patients reported for MADA and 20 patients reported for MADB (9). There are 8 patients reported in the literature for the recently described MDPS (10). Information regarding genotype-phenotype correlations and the natural progression of MAD subtypes remains limited. Additionally, most existing literature focuses on children and young adults, resulting in a paucity of data on clinical manifestations and metabolic complications in older adults.

In this context, we present a comprehensive characterization of four newly identified MADA patients from Türkiye, including a 61-year-old female, all carrying the same homozygous pathogenic variant in the *LMNA* gene.

PATIENTS AND METHODS

Patient 1 (P1): A 9-year-old female of Turkish descent presented with dysmorphic facial features, skeletal dysplasia of the hands, and a preliminary diagnosis of scleroderma. She was the second child born to healthy consanguineous parents. Her developmental milestones were reported as normal, and her older sister was healthy.

Anthropometric measurements revealed a weight of 36 kg (78th percentile), a height of 140 cm (77th percentile), and an head circumference of 52 cm (72nd percentile). She exhibited increased fat deposition in the periumbilical region and around the neck, with reduced subcutaneous fat in both upper and lower extremities. Additional features included microretrognathia, a bird-like nose, a bifid jaw, acral osteolysis, and increased radiolucency of the distal clavicle on chest X-ray (Figure 1,2). Skinfold thickness measurements using a Holtain Skinfold Caliper were as follows: biceps, 3.2 mm; triceps, 4.4 mm; subscapularis, 7 mm; and suprailiac, 3.2 mm.

Liver enzymes were elevated, and there was evidence of mild hypertriglyceridemia alongside low levels of HDL cholesterol. Fasting blood glucose levels were elevated, although glycated hemoglobin (HbA1c) remained within the normal range. Fasting serum insulin levels were notably high. A bone density assessment by dual-energy X-ray absorptiometry (DXA) revealed decreased bone density (Figure 1).
An abdominal ultrasound showed grade 1 hepatic steatosis (Table 1).
At the most recent follow-up of the patient who has been under surveillance for eight years, and taking metformin 2000 mg/day, omega-3, vitamin E 400 IU/day, and vitamin D 600 IU/day, had a chronological age of 17 years, a height of 158 cm (-0.8 SDS), a weight of 51 kg (-1.2 SDS), a BMI of 20.2 kg/m² (-0.7 SDS), and hirsutism was detected with a Ferriman-Gallwey score of 16. Laboratory tests revealed mild transaminase elevation [alanine aminotransferase, 67 U/L (0–55); aspartate aminotransferase, 37 U/L (0–34)], high insulin [77.50 µU/mL (2–25)], high triglyceride [267 mg/dL (<150)], low HDL [22 mg/dL (>40)], and hyperandrogenism [total testosterone, 200 ng/dL (0-50), free androgen index 25 (<5)]. Pelvic ultrasonography findings were consistent with polycystic ovary syndrome, with right and left ovarian volumes measuring 14 and 15 ml, respectively.
Patient 2(P2): This 13-year-old male of Turkish origin, the second child of healthy consanguineous parents (first cousins), was a dizygotic twin. He presented with an intellectual disability, skeletal dysplasia, and dysmorphic facial features. His birth weight was 2300 g and his physical appearance was unremarkable at birth. On the second day of life, he developed physiological jaundice, necessitating phototherapy for one week. Postnatally, he required umbilical cord surgery due to an infection and underwent inguinal hernia repair at three months of age. His twin sister was healthy, however his 25-year-old older brother exhibited similar dysmorphic features. His developmental milestones were delayed, particularly in gross motor skills. He had achieved independent sitting at 9 months, had ambulated independently at 18 months, and had spoken his first word at 18 months; however, he was unable to form complete sentences. Bladder and bowel control were attained at three years of age. Due to intellectual disability, he required special education. His pubertal development corresponded to Tanner stage 1.
At 13 years of age, his physical examination revealed a height of 136 cm (< 3rd percentile) and a head circumference of 53 cm (3–10th percentile). His hand length was 15 cm, and the length of his third finger was 5.5 cm, ruling out brachydactyly or arachnodactyly. His father measured 185 cm tall and weighed 90 kg, while his mother was 165 cm tall and weighed 110 kg. His affected brother was 163 cm tall and weighed 75 kg, whereas his unaffected sister measured 170 cm in height and weighed 80 kg.
The patient exhibited dysmorphic features similar to those of P1, but additionally presented with dental anomalies, gynecomastia, diffuse mottled pigmentation on the trunk, and kyphosis. Cardiological assessments revealed grade 1 mitral insufficiency and dilated cardiomyopathy, with asymmetric left ventricular prominence on cardiac magnetic resonance imaging. Laboratory investigations demonstrated elevated plasma pro-brain natriuretic peptide (418 pg/mL; normal range: 0–100 pg/mL), troponin I (53.6 ng/mL; normal range: 0–36.6 ng/mL), creatine kinase (1118 U/L; normal range: 30–200 U/L), and lactate dehydrogenase (325 U/L; normal range: 125–243 U/L). Serum transaminase and glucose levels were also elevated, though lipid and lipoprotein profiles were within normal limits (Table 1). Abdominal ultrasonography demonstrated a thickened (5 mm) and trabeculated bladder wall, as well as hepatic steatosis. Bone density assessment by DXA showed decreased bone density (Figure 1). The patient was treated with enalapril (5 mg daily), digoxin (0.25 mg daily), and furosemide (40 mg every other day). Electromyography (EMG) findings were normal, and there was no evidence of muscle weakness. His karyotype was 46,XY, and an array comparative genomic hybridization (aCGH) study yielded normal results.
At 13 years of age, the patient developed cardiac symptoms and subsequently experienced sudden death.
Patient 3(P3): This 25-year-old male, the older brother of Patient 2, exhibited postnatal growth retardation. His dysmorphic features included bird-like facial features, full cheeks, prominent eyes, a pinched nose, joint stiffness, acroosteolysis of the distal phalanges, rounded fingertips, mottled pigmentation, skin atrophy, and partial lipodystrophy characterized by loss of subcutaneous fat from the extremities with increased fat deposition around the trunk and neck.
Radiographic studies confirmed acral osteolysis; however, the clavicles appeared normal (Figure 1,2). Despite these phenotypic abnormalities, his metabolic parameters remained within normal limits. Abdominal ultrasonography revealed grade 2 hepatic steatosis (Table 1). Bone density assessment by dual-energy X-ray absorptiometry (DXA) identified osteoporosis in the lumbar spine and osteopenia in the left hip (Figure 1). He did not exhibit cardiomyopathy or intellectual impairment.
At 20 years of age, he was diagnosed with polycythemia vera; however, JAK2 analyses was performed and the result was negative. At 21 years old, he developed nephrolithiasis. At 22 years, he underwent surgical excision of a pleomorphic adenoma of the parotid gland.
Patient 4(P4): This 61-year-old female of Turkish origin presented with short stature, skeletal dysplasia, and dysmorphic facial features. She weighed 33 kg, measured 134 cm in height, and had a body mass index (BMI) of 18.4 kg/m².
She exhibited dysmorphic features similar to those observed in affected individuals (Figure 1), including joint stiffness in the hands, knees, and elbows, along with prominent eyes, and she had previously been misdiagnosed with rheumatoid arthritis. She had marked irregularity and increased radiolucency of the distal clavicle on chest X-ray (Figure 2). Bone density assessment via DXA revealed osteoporosis in the lumbar spine and osteopenia in the left hip (Figure 1). Complete blood count and biochemical tests, including vitamin D, PTH, liver enzymes, and renal function tests, were within normal limits (Table 1).
She had no history of diabetes mellitus or coronary heart disease. Her parents were from the same small village, and she has one healthy brother and sister. She has no children.

Methods:

Written informed consent for the use of genetic information for research purposes was obtained from patients or their legal guardians who underwent genetic testing at Aydın Adnan Menderes University. Since this is a retrospective study ethical approval was obtained from the Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Evaluation Committee (Protocol No: 2025/96; Date: 20.03.2025).
Genomic DNA was extracted from the peripheral blood leukocytes of the probands. Sanger sequencing of the LMNA gene was performed on all patients who had been clinically diagnosed with MADA. The entire coding region, along with the highly conserved exon–intron boundaries, was amplified by polymerase chain reaction (PCR) and sequenced in both directions. The amplicons were analyzed via direct sequencing using the ABI Genetic Analyse 3500 (Life Technologies, Waltham, Massachusetts, USA). Results were interpreted using Mutation Surveyor software (Softgenetics, USA).
Whole body MRIs of 3 patients were performed with T1- and T2-weighted sequences using PHILIPS Achieva 1.5T, Milwaukee, USA.

Statistical Analysis:

Descriptive statistics were used to summarize clinical and laboratory findings across the four patients. For continuous variables such as age, height, BMI, insulin, triglyceride, HDL cholesterol, and liver enzyme levels, minimum, maximum, and mean values were calculated. Raw data were obtained from Table 1, and mean values were computed by summing individual patient data and dividing by the total number of patients (n=4). These calculations were performed manually to demonstrate phenotypic variability and to illustrate the range and average severity of metabolic and clinical findings within the cohort.

RESULTS

Among the four patients with MADA harboring the homozygous *LMNA* p.Ala529Val variant, clinical and metabolic parameters demonstrated notable variability. At diagnosis, ages ranged from 9 to 61 years (mean: 27 years), while heights varied between 134 cm and 163 cm (mean: 143.25 cm), and BMIs ranged from 18.37 to 27.8 kg/m² (mean: 21.82 kg/m²).

All affected patients were found to harbor the same homozygous variant on chromosome1:156137210 (GRCh38.p12) C>T; c.1586C>T; which is predicted to result in the substitution of alanine at position 529 with valine (p.Ala529Val) in *LMNA*. (Clinvar variation ID: 14513, dbSNP: rs60580541)

Whole-body MRI imaging revealed mandibular hypoplasia, acroosteolysis in the carpal bones, and regional fat accumulation in the gluteal and abdominal side walls in Patient 1. In Patient 3, acroosteolysis in the carpal bones, and focal fat accumulation in the submandibular region, chest, and abdominal side walls were observed. Patient 4 had mandibular hypoplasia, acroosteolysis of the carpal bones, focal fat accumulation in the bilateral submandibular region and gluteal regions, soft tissue calcifications, significant osteoporosis, and decreased corpus heights of the vertebrae. (Figure 2, Figure 3)

DISCUSSION

Several biallelic missense variants in *LMNA* have been reported in patients with mandibuloacral dysplasia type A. Among these, the most common variant is p.R527H, frequently identified in Italian patients in a homozygous state (11). This prevalence is attributed to a founder effect and the high rate of consanguinity among the parents. Similarly, four patients from Türkiye have previously been reported to harbor the homozygous p.A529V variant, suggesting a similar founder effect (3,12).

In this context, it is important to discuss the four patients presented in this report and their families. These individuals belong to a Turkmen community, who historically associated with woodworking. They are an insular society that has preserved its unique cultural and spiritual practices (13). According to the patients and their families, these cultural practices support the hypothesis of a founder effect for the *LMNA* mutation, as marriages have traditionally occurred exclusively within the community. This observation further reinforces the notion that a shared ancestor within this closed community likely explains why these three unrelated families, residing in different locations, carry the same pathogenic variant.

This study also provides an opportunity to compare the physical and metabolic profiles of patients from Türkiye with those of Italian patients carrying the homozygous p.R527H variant. Turkish patients exhibited similar skeletal manifestations but have milder metabolic complications (14). Notably, three out of four patients in this cohort showed hepatic steatosis and abnormal liver function tests; however none developed diabetes mellitus, and hypertriglyceridemia was observed in only one patient.

The occurrence of cardiomyopathy in the proband of pedigree P2 is noteworthy and appears to be unrelated to the *LMNA* variant, as his affected brother does not exhibit this phenotype. However, the absence of cardiomyopathy in the brother does not definitively rule out a connection, as cases of MADA with cardiomyopathy have been documented in the literature (14). Further insights into this question may emerge as additional MADA cases are reported and our understanding of the *LMNA* gene continues to advance.

Intellectual impairment has not been previously reported in MADA cases associated with *LMNA* variants. This observation suggests that the intellectual disability in this patient may result from the co-inheritance of another undetermined rare genetic variant. Unfortunately, further investigations could not be conducted due to the patient's demise.

When reviewing reports of patients diagnosed with MADA and found to have biallelic variations in the *LMNA* gene to date, only one case has not been reported to exhibit micrognathia or mandibular hypoplasia (15). Although patient 3 did not present signs of micrognathia, mandibular hypoplasia was also not observed in radiographic examinations. This phenomenon may be attributed to phenotypic expressivity. The etiology of polycythemia vera in P3 also remains unclear. Additional genetic studies are required to further clarify the findings observed in these patients.

Finally, P4, the oldest MADA patient to date, offers valuable insights into the long-term complications of MADA due to the p.A529V variant. Despite her advanced age, she has not developed diabetes, dyslipidemia, abnormal liver function tests, coronary heart disease, or cardiomyopathy. The absence of metabolic complications despite the patient's advanced age may be attributed to her nutritional habits and environmental factors.

To date, two studies from Turkey have reported cases of MADA patients who are homozygous for the *LMNA* p.Ala529Val variant (3,12). These earlier cases presented with the classic skeletal and cutaneous features consistent with those observed in our cohort. However, certain findings observed in our patients, such as cardiomyopathy, polycythaemia vera and intellectual disability, have not previously been described in association with this specific variant. Additionally, mandibular hypoplasia is considered a hallmark of MADA; however, it was absent in one of our patients, further illustrating phenotypic variability. Previous studies have consistently noted the absence of breast development in female patients, suggesting that this may be a frequent manifestation of the A529V genotype. However, this finding was not observed in our female patients. These inter-individual differences, despite an identical *LMNA* variant, highlight the possible influence of genetic modifiers or environmental factors on disease expression.

The clinical phenotype associated with the p.Ala529Val variant appears to represent a distinct, potentially milder form of MADA compared to other *LMNA* variants, such as Val440Met, Arg471Cys, Arg527Leu, Thr528Met, Ala529Thr, Met540Ile and Met540Thr (11). While core findings such as acroosteolysis and lipodystrophy were consistently observed in all patients with the Ala529Val variant, dermatological and metabolic features were notably less prominent. Notably, none of the patients exhibited alopecia, and only one showed insulin resistance without progression to diabetes, contrasting with variants such as Lys542Asn and Ala529Thr, which have been associated with more frequent metabolic disturbances. Furthermore, clavicular hypoplasia varied, and the overall severity of lipodystrophy was moderate. Most strikingly, one individual was diagnosed at the age of 61, marking the latest reported onset among MADA cases to date. The presence of intellectual disability and polycythemia vera, which have not previously been described in association with LMNA-related MADA, may suggest novel, variant-specific manifestations. However, it remains unclear whether these features are directly attributable to the p.Ala529Val variant or whether they arise from unrelated aetiologies. Further research is needed to establish whether these findings broaden the phenotypic spectrum of MADA or represent coincidental comorbidities. Overall, these findings suggest that the p.Ala529Val variant may contribute to a late-onset, less penetrant, and clinically atypical subgroup within the broader MADA spectrum.

Study Limitations:

This study has several limitations. Firstly, the sample size is small, as MADA is an extremely rare disorder, limiting the generalizability of the findings. Secondly, functional studies were not conducted to further investigate the molecular mechanisms of the *LMNA* p.A529V variant. Thirdly, due to the retrospective nature of the study, some clinical and metabolic parameters were not consistently available across all patients.

Conclusion:

This study enhances the clinical and molecular understanding of MADA caused by the homozygous p.A529V variant in *LMNA*. The identification of a founder effect within the patients's community underscores the significance of cultural and genetic factors in the epidemiology of rare diseases. The reported cohort provides unique insights into the metabolic, skeletal, and other atypical complications of MADA, including the first description of intellectual disability associated with *LMNA* mutations. These findings highlight the necessity for comprehensive and multidisciplinary approaches to improve diagnosis, management, and genetic counseling for affected patients.

Author Contributions: Z.M.Y., G.B., and A.A. participated in the design of the study. Z.M.Y., M.A., and G.T. analyzed and interpreted the data. Z.M.Y., G.B., and A.A. revised the article and gave final approval for the version to be published. G.B. and A.A. critically reviewed the data for important intellectual content. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate: This study was performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest: The authors declare no conflicting interest in this study.

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Table 1. Clinical and Laboratory Characteristics of the Patients at the Age of Diagnosis

	Patient 1	Patient 2	Patient 3	Patient 4
Age (year)	9	13	25	61
Weight (kg)	36	42	75	33
Weight-SDS	0,71	-0,08	-	-
Height (cm)	140	136	163	134
Height-SDS	0,67	-1,84	-	-
BMI (kg/m^2)	18,37	22,71	27,8	18,4
BMI-SDS	0,58	1,02	-	-
Glucose (mg/dL)	81	94	81	88
Insulin (µU/mL)	42,2	25,1	22,9	8,5
HbA1c (%)	5	5,6	5,6	5,2
ALT (U/L)	190	70	40	12
AST (U/L)	134	47	31	24
Total cholesterol (mg/dL)	207	176	200	214
Triglyceride (mg/dL)	206	108	63	133
HDL cholesterol (mg/dL)	27,8	41,1	46,2	53,8
LDL cholesterol (mg/dL)	138	113	141	134
Creatine kinase (U/L)	72	1118	-	87
Abdominal USG	grade 1 hepatic steatosis	grade 1 hepatic steatosis	grade 2 hepatic steatosis	normal

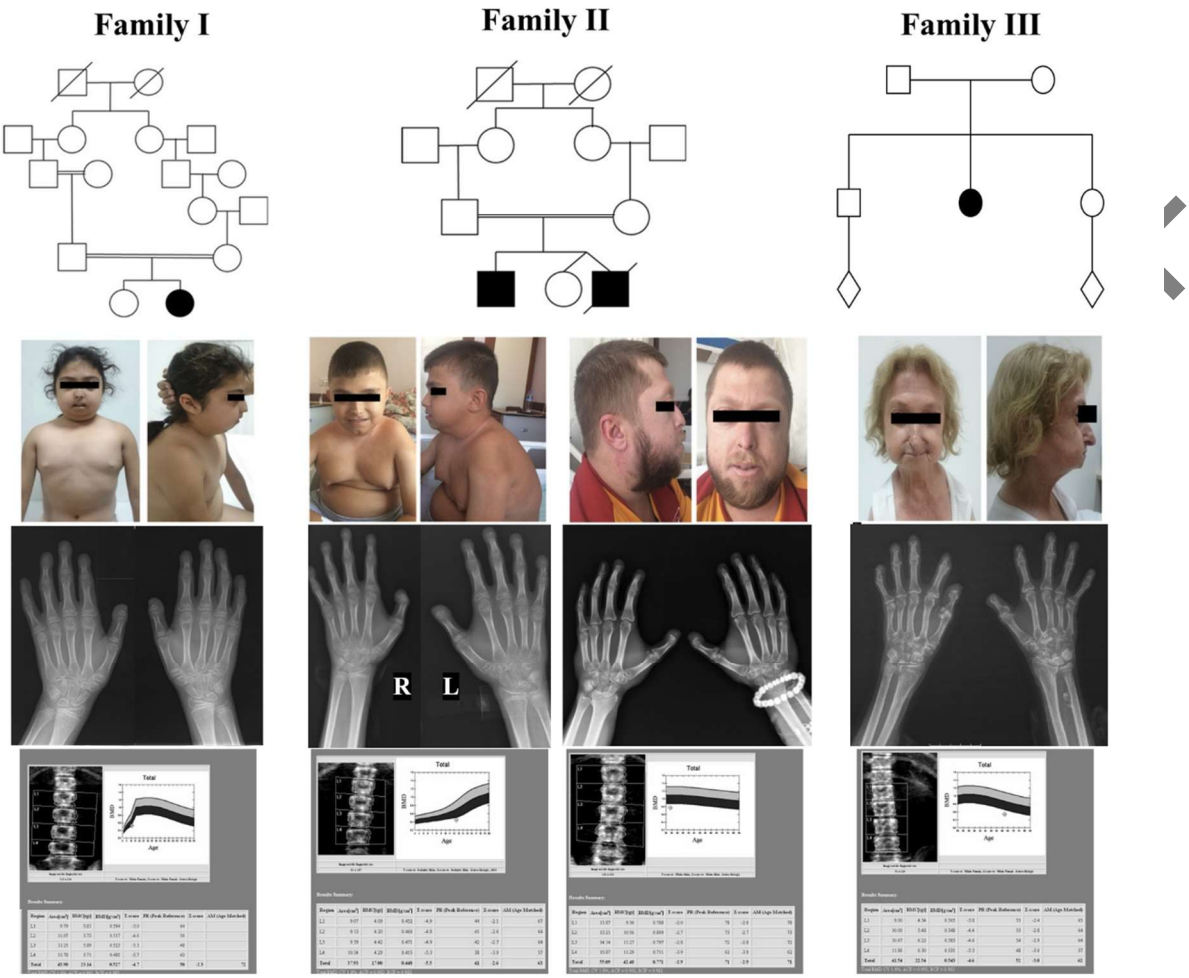

Figure 1. From top to bottom: pedigrees of three families, photographs of patients at the time of diagnosis, hand radiographs demonstrating acral osteolysis, and DEXA scans indicating osteoporosis/osteopenia.

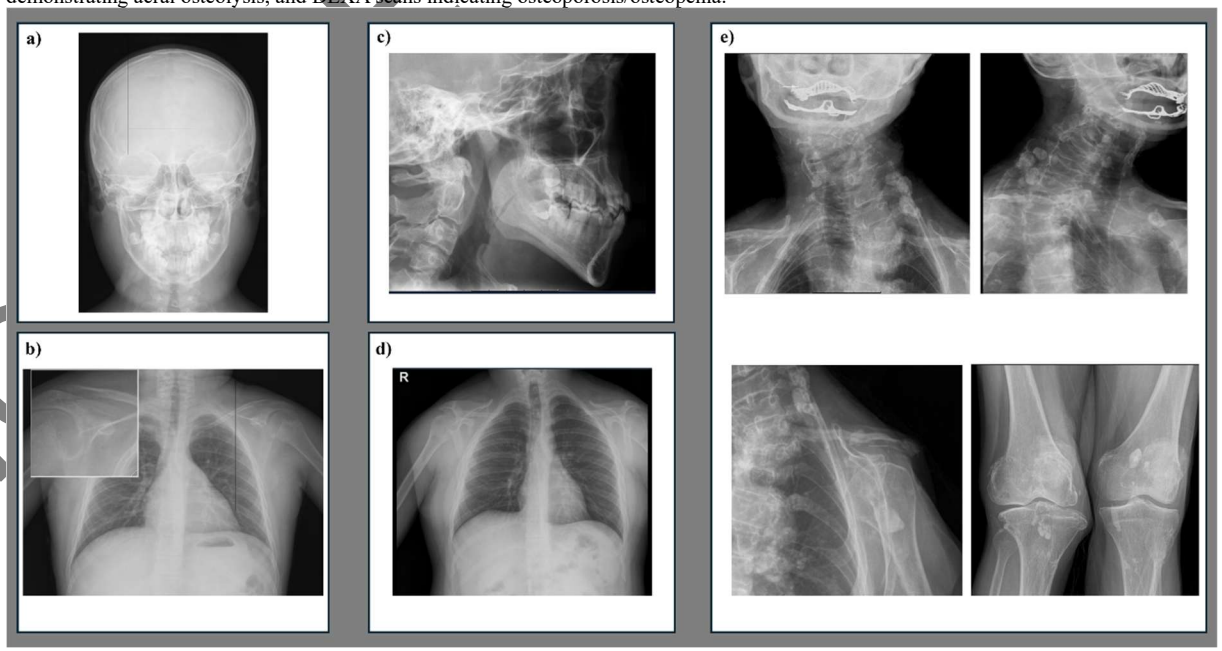

Figure 2. a) Patient 1; skull X-ray demonstrating mandibular hypoplasia. b) Patient 1; increased radiolucency of the distal clavicle. c) Patient 3; lateral skull X-ray demonstrating the absence of mandibular hypoplasia. d) Patient 3; normal clavicle. e) Patient 4; mandibular hypoplasia, soft tissue calcifications, marked irregularity and increased radiolucency of the distal clavicle, advanced degeneration of joint-facing bone surfaces, osteoporosis in bone structures, and vertebral height loss.

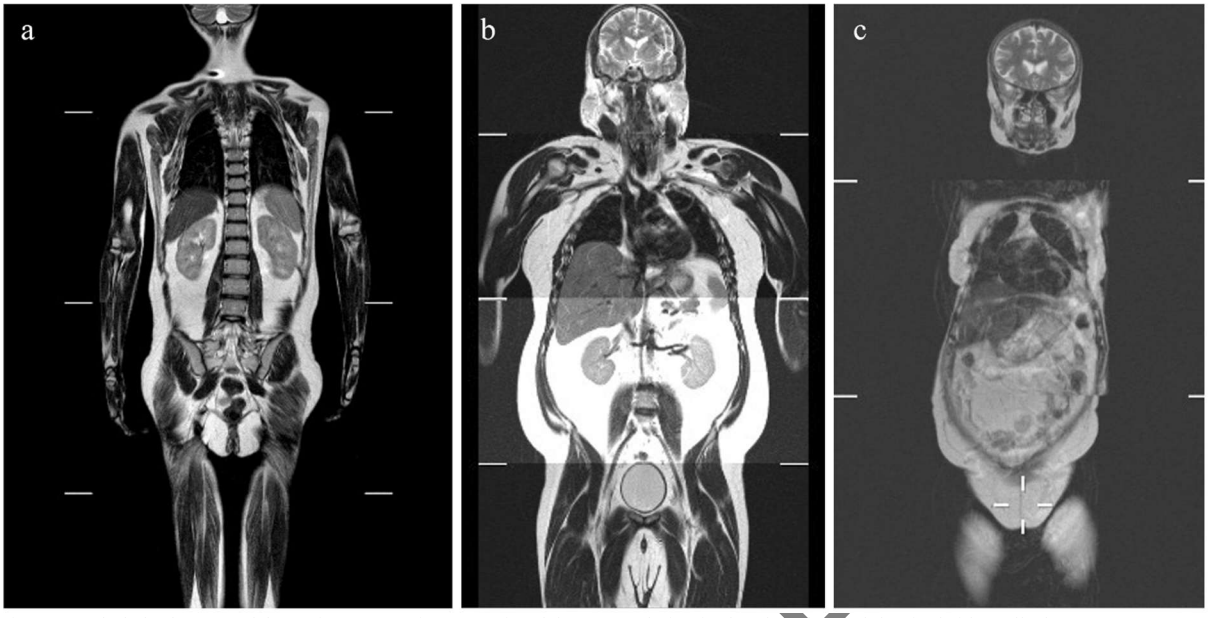

Figure 3. Whole body MRI of the patients. a) Patient 1; regional fat accumulation in the gluteal and abdominal side walls. b) Patient 3; focal fat accumulation in the submandibular region, chest, and abdominal side walls. c) Patient 4; focal fat accumulation in the bilateral submandibular region and gluteal region.