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

Zehra Manav Yiğit[1], Mustafa Altan[2], Göksel Tuzcu[3], Gökay Bozkurt[1], Ahmet Anık[4]

[1]Aydın Adnan Menderes University Faculty of Medicine, Department of Medical Genetics, Aydın, Türkiye
[2]Ankara Bilkent City Hospital, Clinic of Medical Genetics, Ankara, Türkiye
[3]Aydın Adnan Menderes University Faculty of Medicine, Department of Radiology, Aydın, Türkiye
[4]Aydın Adnan Menderes University Faculty of Medicine, Department of Pediatric Endocrinology, Aydın, Türkiye

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### What is already known on this topic?

Mandibuloacral dysplasia (MAD) is associated with mutations in the *LMNA* gene, which plays an important 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 presentation, helping to improve the understanding of the genotype-phenotype relationship in MAD, it is hoped that more personalized diagnostic and therapeutic strategies will emerge.

## 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.

**Corresponding Author:** Prof. Ahmet Anık, Aydın Adnan Menderes University Faculty of Medicine, Department of Pediatric Endocrinology, Aydın, Türkiye
**E-mail:** ahmet.anik@yahoo.com **ORCID:** orcid.org/0000-0002-7729-7872
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**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:** Founder effect, *LMNA* gene, mandibuloacral dysplasia type A, partial lipodystrophy, progeroid syndrome

## 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 (1,2,3). Patients with MAD present either with partial lipodystrophy [type A; MADA; Online Mendelian Inheritance in Man (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* gene, encoding zinc metalloprotease (6), respectively. A third type of MAD progeroid syndrome [mandibular dysplasia progeroid syndrome (MDPB) 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 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). Furthermore, there are eight patients reported 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.

Therefore, 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 (78$^{th}$ percentile), a height of 140 cm (77$^{th}$ percentile), and a head circumference of 52 cm (72$^{nd}$ 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 (Figures 1, 2). Skinfold thickness measurements using a Holtain Skinfold Caliper were: 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 high-density lipoprotein (HDL) cholesterol (Table 1). 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.

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, she had a chronological age of 17 years, a height of 158 cm [-0.8 standard deviation score (SDS)], a weight of 51 kg (-1.2 SDS), a body mass index (BMI) of 20.2 kg/m$^2$ (-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 (normal range: 0-55); aspartate aminotransferase, 37 U/L (normal range: 0-34)], high insulin [77.50 µU/mL (normal range: 2-25)], high triglyceride [267 mg/dL (normal range: <150)], low HDL [22 mg/dL (normal range: >40)], and hyperandrogenism [total testosterone, 200 ng/dL (normal range: 0-50), free androgen index 25 (normal range: <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 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 (P3). Developmental milestones of P2 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 (<3$^{rd}$ percentile) and a head circumference of 53 cm

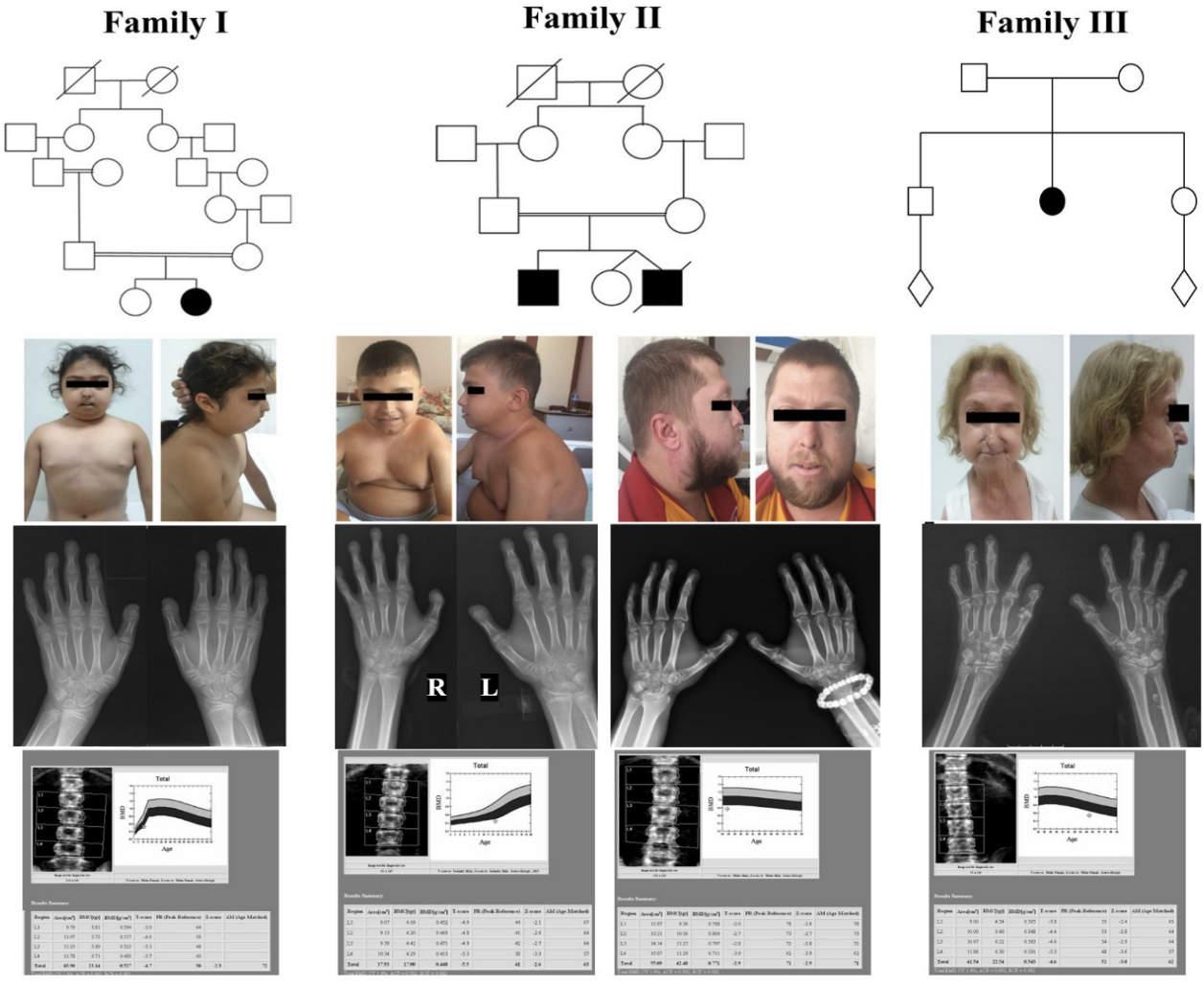


**Figure 1.** From top to bottom: pedigrees of three families, photographs of patients at the time of diagnosis, hand radiographs demonstrating acral osteolysis, and DXA scans indicating osteoporosis/osteopenia

*DXA: dual-energy X-ray absorptiometry*

(3-10$^{th}$ 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 (BMI SDS: 0.94), while his mother was 165 cm tall and weighed 110 kg (BMI SDS: 4.07). His affected brother was 163 cm tall and weighed 75 kg (BMI SDS: 1.39), whereas his unaffected sister measured 170 cm in height and weighed 80 kg (BMI SDS: 2.07).

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 findings were normal, and there was no evidence of muscle weakness. His karyotype was 46,XY, and an array comparative genomic hybridization 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 P2, 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, although the clavicles appeared normal (Figures 1, 2). Despite these phenotypic abnormalities, his metabolic parameters remained within normal limits. Abdominal ultrasonography revealed

**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/m2) | 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 |

SDS: standard deviation score, BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, HDL: high-density lipoprotein, LDL: low-density lipoprotein, USG: ultrasonography

grade 2 hepatic steatosis (Table 1). Bone density assessment by 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, Janus kinase 2 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 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 by DXA revealed osteoporosis in the lumbar spine and osteopenia in the left hip (Figure 1). Complete blood count and biochemical tests, including vitamin D, parathyroid hormone, 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 a 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 and sequenced in both directions. The amplicons were analyzed via direct sequencing using the ABI Genetic Analyse 3500 (Life Technologies, Waltham, MA,

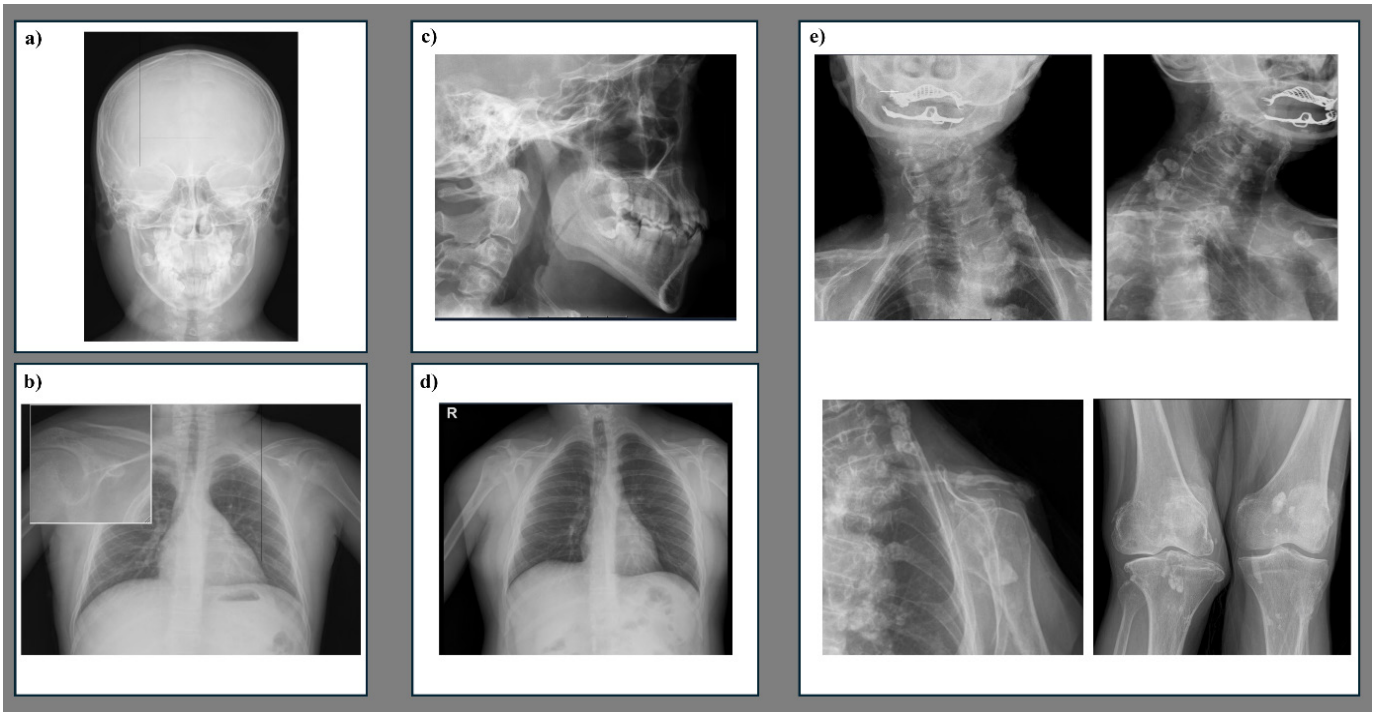


**Figure 2.** a) Patient 1; skull X-ray demonstrating mandibular hypoplasia. b) Patient 1; increased radiolucency of the distal clavicle. c) Patient 3; lateral skull X-ray demonstrating the absence of mandibular hypoplasia. d) Patient 3; normal clavicle. e) Patient 4; mandibular hypoplasia, soft tissue 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

USA). Results were interpreted using Mutation Surveyor software (Softgenetics, USA).

Whole body magnetic resonance imaging scans (MRIs) of 3 patients were performed with T1- and T2-weighted sequences using PHILIPS Achieva 1.5T, (Philips Inc., Milwaukee, WI, 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 median 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

All affected patients were found to harbor the same homozygous variant on *LMNA* gene; chr1:156137210, LMNA (NM_170707.4) c.1586 C>T; which is predicted to result in the substitution of alanine at position 529 with valine (p.Ala529Val). (Clinvar variation ID: 14513, dbSNP: rs60580541).

Among the four patients from three families 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 (median: 19 years), while heights varied between 134 cm and 163 cm (median: 138 cm), and BMIs ranged from 18.37 to 27.8 kg/m² (median: 20.56 kg/m²).

Whole-body MRI imaging revealed mandibular hypoplasia, acroosteolysis in the carpal bones, and regional fat accumulation in the gluteal and abdominal side walls in P1. In P3, acroosteolysis was evident in the carpal bones, and focal fat accumulation was observed in the submandibular region, chest, and abdominal side walls. P4 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 MAD 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.


**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

*MRI: magnetic resonance imaging*

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 necessary to discuss the social circumstances of 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 suggestion 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 had 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 reported previously (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 been reported in which the patient did not exhibit micrognathia or mandibular hypoplasia (15). It is therefore noteworthy that P3 did not present with signs of micrognathia and mandibular hypoplasia was not observed on radiographic examination. 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. According to her medical history, she has maintained a traditional diet characterized by a low intake of processed foods and refined sugars, regular consumption of home-cooked meals, and limited excess calories. Additionally, she has led a physically active life, maintaining sustained daily mobility without prolonged sedentary periods. She has also not been exposed to known cardiometabolic risk factors, such as smoking or chronic occupational stress. These observations, though anecdotal, suggest that favorable dietary habits and a low-risk living and working environment may have mitigated the development of metabolic complications in this patient. This highlights the potential role of environmental modifiers in the phenotypic expression of MADA.

To date, two studies from Türkiye 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. Furthermore, mandibular hypoplasia is considered a hallmark of MADA but 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 as 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. Remarkably, 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 years, which appears to be the latest age at diagnosis reported for MADA in the available literature. 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 etiologies. 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 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 expands the clinical and molecular understanding of MADA caused by the homozygous p.A529V variant in *LMNA*. The identification of a probable founder effect within the patients' 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.

**Ethics**

**Ethics Committee Approval:** 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).

**Informed Consent:** 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.

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**Footnotes**

**Authorship Contributions**

Concept: Zehra Manav Yiğit, Ahmet Anık, Design: Zehra Manav Yiğit, Gökay Bozkurt, Ahmet Anık, Data Collection or Processing: Zehra Manav Yiğit, Mustafa Altan, Göksel Tuzcu, Analysis or Interpretation: Zehra Manav Yiğit, Mustafa Altan, Göksel Tuzcu, Literature Search: Zehra Manav Yiğit, Mustafa Altan, Göksel Tuzcu, Gökay Bozkurt, Ahmet Anık, Writing: Zehra Manav Yiğit, Göksel Tuzcu, Gökay Bozkurt, Ahmet Anık.

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