The Application of Clinical Genetics

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CASE SERIES

Variable Expressivity in Type 2 Familial Partial Lipodystrophy Related to a Pathogenic *LMNA* Variant R482: Maternal Transmission to Non-Identical Twins

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Abstract: Familial partial lipodystrophy type 2 (FPLD2), or Dunnigan syndrome, is a rare autosomal dominant disorder caused by mutations in the lamin A (*LMNA)* gene, most frequently involving the p.R482W variant. It is characterized by regional loss of subcutaneous fat and severe metabolic abnormalities, particularly dyslipidemia, insulin resistance, and hepatic steatosis. We report a family with three individuals -mother and two siblings- carrying the same pathogenic *LMNA* c.1444C>T (p.R482W) variant but exhibiting distinct clinical and biochemical profiles. The proband (patient 1) is a 29-year-old male, presented with moderate metabolic disturbances, including hypertriglyceridemia, low levels of high density lipoprotein-cholesterol (HDL-C), and hepatic steatosis, accompanied by physical features such as dorsocervical fat accumulation and winged neck. His dizygotic female twin (patient 2) exhibited a more severe phenotype with triglycerides levels approached 700 mg/dL, insulin resistance, and polycystic ovarian morphology (PCOM). Their 68-year-old mother, also a carrier, showed only mild dyslipidemia and unstable angina. The comparison of dizygotic twins and their mother carrying the same *LMNA* variant provides a unique opportunity to illustrate how sex, age, and hormonal status modulate metabolic severity in FPLD2. These findings reinforce the clinical relevance of family-based evaluation and early metabolic surveillance, even in mildly affected or asymptomatic carriers.

Keywords: lipodystrophy, familial partial, LMNA protein, human, genetic variation, insulin resistance, dyslipidemias

Introduction

Familial partial lipodystrophy type 2 (FPLD2 OMIM: 151660), also known as Dunnigan syndrome, is a rare autosomal dominant disorder caused by pathogenic variants in the lamin A (*LMNA)* gene, particularly affecting the position 482.[1,2] It is characterized by selective loss of subcutaneous fat from the extremities and trunk, and abnormal fat accumulation in other areas such as the face and neck.[2] The phenotype is often associated with severe metabolic complications, including insulin resistance, hypertriglyceridemia, hepatic steatosis, and increased cardiovascular risk. In women, additional findings such as polycystic ovary syndrome (PCOS) and reproductive abnormalities are frequently observed.[3]

Although FPLD2 is a rare disease, with an estimated prevalence of <1 in 1.000.000 individuals, it is likely under-diagnosed due to its clinical overlap with common metabolic syndromes and its variable phenotypic expressivity.[4] Patients often present in adolescence or early adulthood with signs of insulin resistance, including hypertriglyceridemia, low levels of high density lipoprotein-cholesterol (HDL-C), hepatic steatosis, and type 2 diabetes mellitus, despite having a normal or even lean body mass index. The dyslipidemia observed in FPLD2 is typically mixed and severe, frequently

https://doi.org/10.2147/TACG.S570428
Received: 26 September 2025
Accepted: 30 January 2026
Published: 13 February 2026

involving fasting triglyceride levels exceeding 500 mg/dL, thereby increasing the risk of pancreatitis and premature cardiovascular disease.[4]

Sex-based differences in phenotypic expression are well documented; females often exhibit a more pronounced phenotype, including reproductive endocrine disorders such as polycystic ovary syndrome (PCOS), menstrual irregularities, and earlier onset of metabolic complications.[5,6] In contrast, males may show a subtler phenotype, making clinical diagnosis more challenging. This sexual dimorphism suggests hormonal and epigenetic factors may modulate the clinical presentation.[3]

Despite its monogenic origin, FPLD2 shows incomplete penetrance and variable expressivity, even within the same family.[7] These differences are thought to be influenced by environmental exposures, diet, physical activity, and intrinsic biological factors such as age, hormonal status, and epigenetic regulation, including alterations in chromatin structure and microRNA expression that affect adipocyte differentiation.[8–10] This report describes a family in which three individuals —two siblings and their mother— carry the same pathogenic variant *LMNA* c.1444C>T (p.R482W). By presenting two dizygotic twins and their mother carrying the same pathogenic *LMNA* variant, this report highlights clinically meaningful intrafamilial variability and illustrates how identical genotypes can translate into divergent metabolic trajectories. This comparative familial approach provides practical insights for clinicians regarding diagnosis, monitoring, and genetic counseling in FPLD2.

Case Report

Patient 1

Male patient, currently 29 years old, of non-consanguineous parents, product of a multiple pregnancy with a dizygotic twin sister, who presented intrauterine growth restriction during gestation. He attended the medical genetics service for the first time when he was 16 years old due to the presence of a winged neck caused by a lipoma, but he did not continue to attend due to problems with travel to the consultation site. He came again 7 years later, referred by the endocrinology service, this time with a history of hypertension, dyslipidemia, hepatic steatosis, and hydronephrosis; at the time of consultation, he was under controlled pharmacological treatment.

Physical examination revealed a square face with facial asymmetry, a winged neck with abundant posterior cervical lipomatosis causing limited mobility, truncal adiposity (Figure 1), hepatomegaly 1 cm below the costal margin, bilateral flat feet, shortening of the left lower limb (post–flat-foot surgery), and overweight.

Imaging studies confirmed osteopenia by densitometry, non-infiltrative posterior cervical lipomatosis on magnetic resonance imaging (MRI), and hepatic steatosis grade II–III on abdominal ultrasound and computed tomography scan (CT).

Laboratory tests showed abnormal fat distribution consistent with familial partial lipodystrophy type 2. The lipid profile reported total cholesterol 122 mg/dL, HDL-C 37 mg/dL (low), low-density lipoprotein cholesterol (LDL-C) 36.8 mg/dL, very-low-density lipoprotein (VLDL-C) 48.2 mg/dL, and triglycerides 241 mg/dL (hypertriglyceridemia). Fasting plasma glucose was 80 mg/dL, with a fasting insulin level of 21.8 μU/mL, resulting in a HOMA-IR index of 4.3, consistent with significant insulin resistance. According to the American Diabetes Association (ADA) criteria, the patient was classified as having a prediabetic metabolic state, despite normal fasting glucose levels, in the context of insulin resistance and borderline HbA1c values; an oral glucose tolerance test (OGTT) was not performed. Hepatic enzymes revealed aspartate aminotransferase (AST) 28 U/L and alanine aminotransferase (ALT) 68 U/L (mild elevations). Bilirubin levels were: total 0.81 mg/dL, direct 0.35 mg/dL, and indirect 0.46 mg/dL. Testosterone was within the normal male range (617 ng/dL) (Table 1).

Cardiovascular assessment revealed stage I hypertension while on losartan and amlodipine therapy, as well as trivial tricuspid regurgitation on echocardiography.

Genomic analysis was performed using whole-exome sequencing (WES) on genomic DNA extracted from peripheral blood leukocytes. Exonic regions and flanking intronic boundaries were captured using the Illumina DNA Prep with Exome 2.5 Plus Enrichment kit (Illumina Inc., San Diego, CA, USA), which incorporates genomic content from Twist Bioscience (South San Francisco, CA, USA) covering clinically relevant coding regions. Libraries were sequenced on an

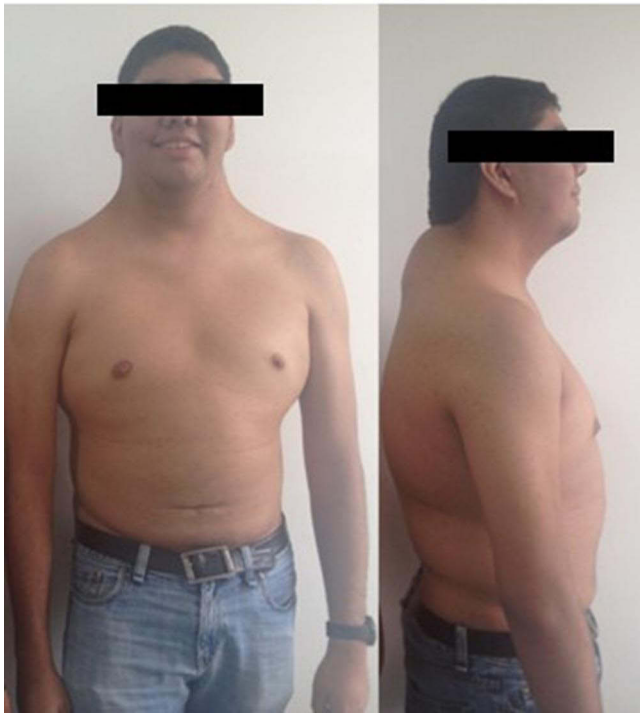

Figure 1 Patient 1: male twin. Frontal and lateral photographs of patient 1 showing characteristic physical features associated with FPLD2. Notable findings include a winged neck due to dorsocervical lipomatosis, truncal adiposity with relative loss of subcutaneous fat in the limbs, and mild facial asymmetry.

Illumina NextSeq 2000 platform (Illumina Inc., San Diego, CA, USA), following the manufacturer's protocols. Sequencing reads were aligned to the GRCh38/hg38 human reference genome, and germline variant calling was performed using DRAGEN Enrichment v4.2.7 (Illumina Inc., San Diego, CA, USA). Variants were filtered according to standard quality metrics, including call quality >20, minimum coverage >10×, and allele fraction >15%. Annotation and variant prioritization were carried out using Emedgene (Illumina Inc., San Diego, CA, USA) and Franklin (Genoox Ltd., Tel Aviv, Israel), incorporating data from ClinVar, HGMD, gnomAD, and OMIM.

In addition to LMNA, variant interpretation included a systematic, phenotype-driven review of genes known to be associated with lipodystrophy and severe dyslipidemia. This evaluation was performed using curated gene lists and clinical databases integrated within the annotation platforms, focusing on genes previously implicated in monogenic

Table 1 Clinical, Anthropometric and Metabolic Characteristics of the Three Patients with Familial Partial Lipodystrophy Type 2 (FPLD2)

Feature		Patient 1	Patient 2	Patient 3
Anthropometrics	**Age**	29	29	68
	Sex	Male	Female	Female
	Weight (kg)	96.5	59.5	43.5
	Height (cm)	182	162	160
	Body mass index (BMI, kg/m^2)	29.1	22.7	17
	Waist circumference (cm)	102.5	79.5	79.5
	Hip circumference (cm)	107	91	85

(*Continued*)

https://doi.org/10.2147/TACG.S570428

Table 1 (Continued).

Feature		Patient 1	Patient 2		Patient 3
	Waist-hip ratio	0.96 (increased risk)	0.87 (increased risk)		0.94 (high risk)
Morphological		Square face with facial asymmetry; winged neck with abundant posterior cervical lipomatosis causing limited mobility; hepatomegaly (1 cm below costal margin); bilateral flat feet; shortening of the left lower limb (post–flat-foot surgery). Overweight.	Triangular elongated face, broad thorax with high shoulders, umbilical hernia, bilateral hip gap, broad umbilical base. Preserved muscle volume, intact skin, no retractions or deformities.		Normal head, preserved ocular movements, mobile neck without masses, no abdominal masses or organomegalies.
Musculoskeletal		Osteopenia by densitometry. No reported fasciculations.	No atrophy, no fasciculations, preserved calf musculature, broad arms.		Osteoporosis (no fractures).
Adipose Tissue / Lipodystrophy		Abnormal fat distribution with posterior cervical lipomas/lipomatosis. Clinical phenotype consistent FPLD2	Preserved adipose distribution in calves. Phenotype consistent with FPLD2		Abnormal fat distribution and hepatic steatosis consistent with FPLD2
Metabolic	**Total Cholesterol**	122 mg/dL	229 mg/dL	115 mg/dL*	188 mg/dL
	HDL	37 mg/dL	30.5 mg/dL	46 mg/dL*	68 mg/dL
	LDL	36.8 mg/dL	59.5 mg/dL	24.2 mg/dL*	94.8 mg/dL
	VLDL	48.2 mg/dL	140 mg/dL	45 mg/dL*	25.2 mg/dL
	Triglycerides	241 mg/dL	698 mg/dL	121 mg/dL*	126 mg/dL
	HbA1C	5.70%	5.20%		5.30%
	Fasting insulin	21.8 μU/mL	18 μU/mL		10.8 μU/mL
	Fasting glucose	80 mg/dL	84 mg/dL		86 mg/dL
	HOMA-IR	4.3 (insulin resistance)	3.7 (insulin resistance)		2.3 (normal)
	Glycemic status (ADA criteria)	Prediabetes	Non-diabetic		Non-diabetic
Hepatic	**AST (TGO)**	28 U/L	66 U/L	106.3 U/L**	15 U/L (normal)
	ALT (TGP)	68 U/L	26 U/L	96.4 U/L **	13 U/L (normal)
	GGT	-	68.2 U/L		
	Total Bilirubin	0.81 mg/dL	0.62 mg/dL		0.61 mg/dL
	Direct Bilirubin	0.35 mg/dL	0.17 mg/dL		0.24 mg/dL
	Indirect Bilirubin	0.46 mg/dL	0.45 mg/dL		0.37 mg/dL
	Imaging	Hepatic steatosis grade II–III	Hepatic steatosis grade II–III		MRI showed simple hepatic cysts. Hepatic steatosis grade II
Reproductive		Testosterone within normal male range (617 ng/dL).	Polycystic ovarian morphology		History of C-section, postmenopausal, and osteoporosis

(*Continued*)

Table 1 (Continued).

Feature		Patient 1	Patient 2	Patient 3
Cardiovascular	**Hypertension**	Hypertension stage 1	No	Hypertension stage 1
	Imaging	Trivial tricuspid regurgitation on echocardiogram.	Trivial tricuspid regurgitation, otherwise normal echocardiogram.	History of coronary syndrome/ angina.
Treatment / Follow-up		On atorvastatin, losartan, amlodipine. Lifestyle measures recommended (exercise). Genetics and endocrinology follow-up every 12 months. Plastic surgery referral for cervical lipoma (non-cosmetic). No metreleptin indicated.	Follow-up every 6 months with endocrinology and genetics. Currently managed with lipid-lowering therapy.	Values correspond to ongoing treatment with Hiperlipen 100 mg daily, bisoprolol 1.25 mg daily, ASA 100 mg daily, calcium citrate, and vitamin D. Denosumab was prescribed but not initiated. Genetics follow-up annually. Endocrinology follow-up recommended.

Notes: Values marked with a single asterisk (*) correspond to post–lipid-lowering therapy, while values marked with a double asterisk (**) correspond to the 4-year follow-up.

lipodystrophy syndromes and inherited metabolic disorders affecting lipid metabolism. Mean coverage across target regions was sufficient for clinical interpretation. Molecular analysis identified the pathogenic LMNA c.1444C>T (p. Arg482Trp) variant in the proband, classified according to American College of Medical Genetics and Genomics (ACMG) criteria (PS3, PS4, PM1, PM2, PP1, PP2, PP3), confirming the diagnosis of Dunnigan-type familial partial lipodystrophy with autosomal dominant inheritance.

The patient is currently managed with atorvastatin, losartan, and amlodipine, in addition to lifestyle measures (exercise). He is under follow-up with endocrinology and genetics every 12 months. A referral was made to plastic surgery for evaluation of a posterior cervical lipoma (non-cosmetic).

Patient 2

A 29-year-old female patient, product of a twin pregnancy with a dizygotic twin, who was diagnosed with a pathogenic variant *LMNA* c.1444C>T (p.R482W). Among her clinical history of importance is a familial dyslipidemia, and hepatic steatosis grade 2.

On physical examination, the patient exhibited a triangular and elongated facial shape, a broad thorax with elevated shoulders, an umbilical hernia with a wide base, and a bilateral hip gap. Muscle mass was preserved in the extremities, especially in the calves, with marked muscular definition due to loss of subcutaneous fat (Figure 2). The skin appeared intact, without visible alterations, and posture was functional with complete plantar support, without tendon retractions or joint deformities.

Laboratory studies highlighted significant metabolic alterations. Early profiles without treatment showed severe hypertriglyceridemia (TG 698 mg/dL), elevated total cholesterol (229 mg/dL), and reduced HDL-C (30.5 mg/dL). LDL-C 59.5 mg/dL, and VLDL-C 140 mg/dL. Fasting plasma glucose was 84 mg/dL, with a fasting insulin level of 18 µU/mL, yielding a HOMA-IR index of 3.7, consistent with insulin resistance. According to ADA criteria, both fasting glucose and HbA1c values were within the normal range, and the patient was classified as non-diabetic; OGTT was not performed. Subsequent follow-up demonstrated biochemical improvement with lipid-lowering therapy, though HDL-C levels remained persistently low (Table 1).

Pelvic ultrasound revealed bilateral polycystic ovarian morphology. Menarche occurred at 10 years of age, and the patient reported regular menstrual cycles, with no history of oligo- or amenorrhea. No clinical signs of hyperandrogenism were observed, and no biochemical evidence of hyperandrogenism was documented at the time of evaluation. The patient has never been pregnant and reported no history of infertility or fertility treatments.

Figure 2 Patient 2: female twin. Lower limbs of the patient illustrating evident loss of subcutaneous fat with accentuated muscular definition. The absence of peripheral adipose tissue is consistent with the clinical phenotype of partial lipodystrophy.

Other findings were hepatic steatosis reaching grade III by imaging, and trivial tricuspid regurgitation on echocardiography.

Patient 3

A 68-year-old woman with a history of dyslipidemia, hepatic steatosis, and unstable angina —treated with cardiac catheterization at age 65—also had a prior cholecystectomy and bilateral carpal tunnel release. She was referred to the genetics clinic after her son was diagnosed with partial lipodystrophy.

Physical examination revealed a narrow thorax, pronounced thinning of the upper limbs, and generalized bony prominence. In the lower extremities, distal muscle wasting with visible superficial veins, marked thinning of the tibial and peroneal regions, and loss of subcutaneous tissue were observed, consistent with the FPLD2 phenotype (Figure 3).

Metabolic studies while on treatment showed total cholesterol of 188 mg/dL, HDL-C 68 mg/dL, LDL-C 94.8 mg/dL, and triglycerides 126 mg/dL. Fasting plasma glucose was 86 mg/dL and fasting insulin was 10.8 µU/mL, resulting in a HOMA-IR index of 2.3, which does not support the presence of insulin resistance. According to ADA criteria, the patient was classified as non-diabetic with normal glucose tolerance; OGTT was not performed. Renal tests noted a borderline elevation of blood urea nitrogen (BUN 21 mg/dL) with normal creatinine. Liver function remained preserved, with AST at 15 U/L, ALT at 13 U/L, and total bilirubin at 0.61 mg/dL (Table 1).

Imaging demonstrated grade II hepatic steatosis on ultrasound at age 62 and simple hepatic cysts on MRI three years later. Gynecological evaluation identified uterine myomatosis, consistent with her postmenopausal status. She also had a history of osteoporosis, for which denosumab was prescribed but never initiated.

Cardiovascular assessment documented stage I hypertension and a history of coronary syndrome with angina, requiring hospitalization at age 65.

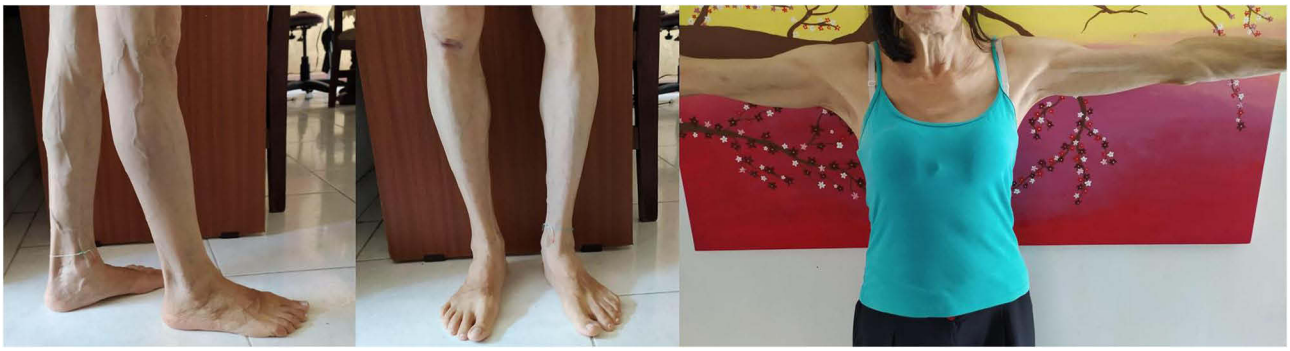

Figure 3 Patient 3: mother. Clinical images of the patient showing generalized loss of subcutaneous adipose tissue in the lower and upper limbs, with prominent muscular definition and visible superficial veins. These findings are consistent with the phenotype of partial lipodystrophy.

As part of the genetic evaluation, segregation analysis by Sanger sequencing confirmed the heterozygous *LMNA* c.1444C>T (p.R482W) pathogenic variant, the same as identified in her son, thereby establishing the diagnosis of Dunnigan-type familial partial lipodystrophy with autosomal dominant inheritance.

She is currently managed with fenofibrate 100 mg daily, bisoprolol 1.25 mg daily, acetyl salicylic acid (ASA) 100 mg daily, calcium citrate, and vitamin D. She continues under annual follow-up in genetics and endocrinology.

Metabolic and anthropometric parameters of the three individuals are summarized in Table 1.

With the information collected, it was possible to construct a familiogram showing the inheritance pattern of this family (Figure 4).

This study and the publication of the case details were approved by the Ethics Committee of Hospital Universitario Fundación Valle del Lili. Written informed consent for publication (clinical data and photographs) was obtained from all participants.

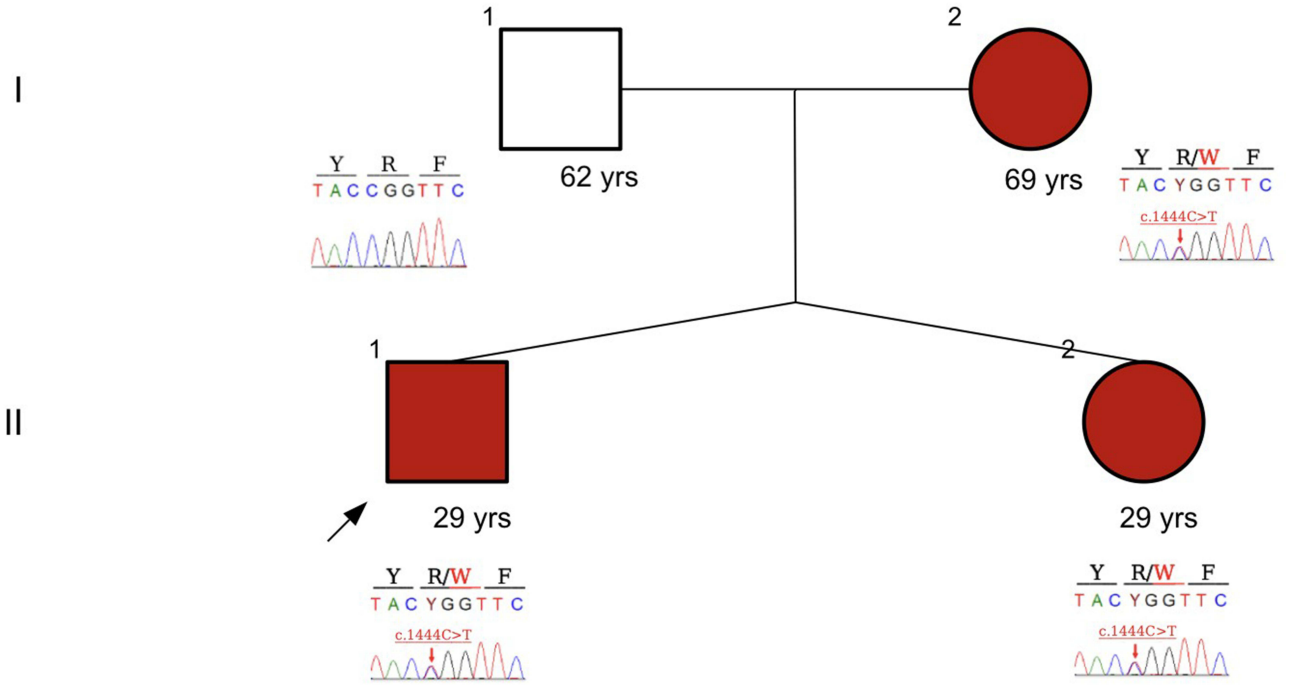

Figure 4 Pedigree showing segregation of the *LMNA* c.1444C>T variant; individuals carrying the variant are shown in red. The proband (arrow) (II.1) and his sister carry the heterozygous change (II.2). At the same time, the mother is also a carrier (I.2) and the father is wild type (II.1). Electropherograms confirm the presence of the variant in affected individuals.

https://doi.org/10.2147/TACG.S570428

Discussion

FPLD2 or Dunnigan disease is a rare condition due to variants in the *LMNA* gene, usually affecting exons 8 to 11. This disorder is characterized by the lack of subcutaneous fat in the lower and upper limbs, buttocks, and abdomen, and the presence of insulin resistance with metabolic syndrome.[9] Although all three individuals carried the same pathogenic *LMNA* c.1444C>T (p.R482W) variant, the clinical and biochemical expression was variable. Common findings included hepatic steatosis and dyslipidemia, with predominantly hypertriglyceridemia and low HDL, consistent with the characteristic phenotype of FPLD2. Patient 1, showed a moderate metabolic phenotype, with elevated triglycerides, low HDL-C and compatible physical signs (winged neck, flat feet, facial asymmetry). Patient 2, despite being the same age, presented a more severe biochemical picture, with triglycerides above 700 mg/dL, elevated transaminases, and signs of insulin resistance, in addition to an ultrasound diagnosis of PCOM. Finally, patient 3 showed a milder phenotype, with a history of dyslipidemia, mild hepatic steatosis, and unstable angina, without marked metabolic alterations in the last available paraclinical tests.

The phenotypic variability observed among individuals carrying the same *LMNA* mutation can be explained by multiple modifying factors, including sex, age, lifestyle, hormonal status, epigenetic factors, and possible modifier genes. This variable expressivity and incomplete penetrance represent a diagnostic challenge and reinforce the need for a personalized genetic and clinical approach, even within the same family.[10,11]

From a clinical perspective, these cases underscore the need for individualized metabolic surveillance in FPLD2, even among carriers of the same pathogenic variant. The marked differences observed between the twins and their mother support early screening for dyslipidemia, insulin resistance, hepatic steatosis, and cardiovascular risk, particularly in female patients and during reproductive age. Management should be according to metabolic severity and may include lifestyle interventions, lipid-lowering therapy, antihypertensive treatment, and close endocrinological follow-up.

Further research is needed to elucidate the mechanisms underlying intrafamilial variability in FPLD2. Longitudinal studies integrating clinical, hormonal, metabolic, and molecular data, as well as larger family-based cohorts, may help identify genetic modifiers and epigenetic factors that influence disease severity. Such approaches could ultimately refine risk stratification and guide personalized therapeutic strategies.

In terms of gender, the reported clinical evidence has shown that women tend to have a more severe clinical and biochemical manifestation than men with more marked dyslipidemia, mixed and with higher cardiovascular risk,[3,10,12] in addition, cohort studies have shown that the diagnosis of FPLD2 increases the risk of reproductive and endocrine disorders such as the development of PCOS in women of childbearing age, accompanied by an increased risk of developing insulin resistance and an increased risk of type 2 diabetes in this population group.[2,13] In men, the clinical manifestation tends to be milder, with a more subtle dyslipidemia, which makes genetic diagnosis more challenging. In most cases, this occurs in family segregation studies, where a greater possibility of control through diet and lifestyle reduces cardiovascular risk.[6,7] However, in this particular case, the diagnosis was received first by the man since his first genetic test.

In terms of age, FPLD2 has been reported to have a progressive course of disease, with symptoms being milder especially dyslipidemia in early life and becoming severe in puberty and adolescence where most diagnoses are made, but decreasing with age,[1] this is consistent with that presented in patient 1, where the first genetic consultation is presented at the age of 16 years. As for patient 3, where the diagnosis was made later in life, this can be explained by the apparent progressive course of the disease, where, in more advanced stages of the family, especially in women over 50 years of age, the symptoms of hepatic steatosis and dyslipidemia may be milder and therefore the diagnostic difficulty may be greater.[14]

The hormonal status also seems to be a variable that directly influences the phenotypic and biochemical severity of this syndrome.[5] Recent research has shown that estrogens seem to directly influence the distribution of fat, being more evident in the phenotypic characteristics in women in puberty than in men, which increases the chances of diagnosis in this group.[15] The presence of estrogen and hormonal alterations also appears to be linked to the risk of developing reproductive and endocrine alterations, including PCOS and other fertility-altering syndromes in women, such as increased androgen concentrations.[3]

The management of lipodystrophy, particularly partial forms associated with *LMNA* variants, requires a multidisciplinary approach centered on metabolic control. Given the heterogeneity of FPLD2, treatment should be individualized and include lifestyle interventions such as diet and exercise. In patients with severe metabolic complications—triglycerides >500 mg/dL, HbA1c >8%, and leptin <4 ng/mL—metreleptin may be considered.[14] This recombinant leptin analogue is approved in the United States and Europe for generalized lipodystrophy, and clinical studies have shown sustained improvements in triglycerides and hepatic steatosis, with more variable effects on glycemic control in FPLD2 cohorts.[16,17] In the patients described in this case, the potential use of metreleptin was discussed during a multidisciplinary medical board; however, its use was not considered appropriate in any of the three patients. None of the individuals met established criteria for metreleptin therapy, such as severe or uncontrolled metabolic complications.

This study has several limitations. Body composition data such as DXA-derived fat distribution were not systematically available, limiting detailed assessment of fat redistribution. In addition, no epigenetic analyses were performed in these patients, and mechanistic interpretations are therefore based on previously published experimental studies. Finally, the small number of individuals reflects the rarity of FPLD2 but limits the generalizability of the findings.

Recent studies have shown that other epigenetic regulatory mechanisms may influence the phenotypic expression of the syndrome.[3] In cellular models, a reduction in H3K27 methylation and an increase in acetylation in this region have been shown to generate an overexpression of MIR335, an inhibitor of adipocyte differentiation, contributing directly to the lipodystrophic phenotype characteristic of FPLD2.[8] In addition, a loss of heterochromatin and a disruption in the anchoring of LADs (lamina-associated domains) have been described, which compromises gene expression in multiple tissues.[18] Other mechanisms include the early remodeling of the extracellular matrix in adipose tissue and the accumulation of prelamin A, which affects nuclear structure and adipocyte maturation.[19] These findings support the idea that clinical variability, even within the same family, may be due not only to genetic, hormonal, and environmental factors but also to epigenetic modifications induced by the mutation itself.

Conclusion

This case report highlights the phenotypic variability associated with the pathogenic *LMNA* c.1444C>T (p.R482W) variant, even within members of the same family. Despite sharing the same genetic mutation, the three individuals presented different clinical severities and biochemical profiles, ranging from mild dyslipidemia to severe hypertriglyceridemia and features of insulin resistance and PCOM. Despite sharing the same *LMNA* variant, the family members show marked intra-familial phenotypic variability (particularly in relation to sex and age), which may be compatible with additional mechanisms such as epigenetic regulation. The findings emphasize the importance of a personalized and family-based diagnostic approach in hereditary metabolic disorders, particularly in cases with variable expressivity and incomplete penetrance, and support proactive genetic screening of first-degree relatives and early metabolic evaluation to prevent or mitigate long-term complications.

In addition to highlighting phenotypic variability, this case series provides practical clinical lessons. Clinicians should consider genetic testing and systematic metabolic evaluation in relatives of affected individuals, regardless of apparent disease severity. For researchers, these findings emphasize the importance of family-based studies and integrative approaches to better understand modifiers of disease expression in monogenic metabolic disorders such as FPLD2.

Data Sharing Statement

Information is available upon request from the corresponding author.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee #2022.1919 of the Hospital Universitario Fundación Valle del Lili. This approval also covered the publication of the case details. All participants provided written informed consent to participate in the clinical evaluation.

Consent for Publication

Written informed consent was obtained from all participants for the publication of this case report, including the use of clinical data and clinical photographs.

Acknowledgments

We thank the Genomic Medicine Laboratory of Universidad Icesi for their support.

Author Contributions

All authors made substantial contributions to the design and conception of the study, and acquisition, analysis and interpretation of data, and took part in either drafting or revising the manuscript. All authors gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

There is no funding to report.

Disclosure

Dr Harry Pachajoa reports support for attendance at academic activities and scientific conferences from CHIESI, outside the submitted work. The authors report no other conflicts of interest in this work.

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