# Familial partial lipodystrophy syndromes

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## ABSTRACT

Lipodystrophies are a heterogeneous group of rare conditions characterised by the loss of adipose tissue. The most common forms are familial partial lipodystrophy (FPLD) syndromes, which include a set of disorders, usually autosomal dominant, due to different pathogenetic mechanisms leading to improper fat distribution (loss of fat in the limbs and gluteal region and variable regional fat accumulation). Affected patients are prone to suffer serious morbidity via developing metabolic complications associated to insulin resistance and an inability to properly store lipids. Although no well-defined diagnostic criteria have been established for lipodystrophy, there are certain clues related to medical history, physical examination and body composition evaluation that may suggest FPLD prior to confirmatory genetic analysis. Its treatment must be fundamentally oriented towards the control of the metabolic abnormalities. In this sense, metreleptin therapy, the newer classes of hypoglycaemic agents and other investigational drugs are showing promising results. This review aims to summarise the current knowledge in FPLD syndromes while describing their clinical and molecular picture, diagnostic approaches and recent treatment modalities.

## INTRODUCTION

Lipodystrophy syndromes are a heterogeneous group of rare diseases characterised by the selective loss of adipose tissue, which can be diagnosed once other causes associated to wasting or weight loss have been ruled out [1,2].

It has been estimated that their global prevalence is 1.3-4.7 cases per million inhabitants worldwide (1.7-2.8 cases per million for partial lipodystrophy) [3]. Thus, to date, the most common forms, excluding HIV-related lipodystrophies, are familial partial lipodystrophy (FPLD) syndromes, which are usually autosomal dominant Mendelian disorders, due to variants in genes related to adipogenesis and lipogenesis.

FPLD syndromes include a set of disorders which share subcutaneous fat loss from the limbs and gluteal region, as well as variable regional accumulation of excess fat [4-6]. To date, six subtypes and another four unclassified variants of FPLD have been described. In addition, several progeroid and autoinflammatory syndromes associated with partial lipodystrophy have also been defined. However, they are out of the focus of this review. Patients with FPLD are characterised by a predisposition to develop metabolic complications related to insulin resistance [7] and an inability to properly store lipids, such as diabetes, hypertriglyceridemia, hepatic steatosis and cardiovascular complications [8-10]. Although there is currently no cure for these disorders and there is no treatment for regenerating adipose tissue, recent treatment approaches have shown promising results in mitigating the burden of the disease.

This review aims to gather the most relevant scientific evidence regarding FPLD syndromes, while describing their clinical and molecular picture, diagnosis and treatment strategies.

## CLASSIFICATION AND ETIOPATHOGENESIS

Lipodystrophy syndromes may be generalised if the loss of adipose tissue affects the whole body, or partial if only part of the body is affected. In addition, depending on their aetiology, they can also be genetic or acquired [1]. Thus, four main lipodystrophy subtypes can be established: congenital generalised lipodystrophy (CGL), FPLD, generalised acquired lipodystrophy (AGL) and partial acquired lipodystrophy (APL) [11]. However, this classification has become more complex over the years as new phenotypes have been discovered. In addition, FPLD syndromes also include several variants with different aetiologies and pathogenic mechanisms which translate into different clinical characteristics. Table 1 shows an updated classification and molecular basis for FPLD syndromes.

Most FPLDs are mendelian disorders, which act as informative models of inadequate adipose storage capacity. Identification of the causative genes has provided unique insights into the biological function and roles of the genes/proteins involved in the regulation of adipogenesis, insulin signalling, lipid storage and synthesis (Figure 1).

### Genes involved in adipogenesis and insulin signalling

The genes associated to FPLD whose variants are considered to cause defects in adipogenesis, adipocyte apoptosis and insulin signalling are *LMNA*, *PPARG*, *AKT2*, *PIK3R1* and *PCYT1A*.

*LMNA*, which is altered in FPLD type 2 and in other laminopathies related to premature ageing, codifies for lamin A/C, which is an intermediate filament protein present in the nuclear lamina that is an important determinant of nuclear and cellular architecture. Heterozygous variants in this gene are the most common cause of monogenic partial lipodystrophy [12-15] and their most fascinating traits are their complex genotype-

phenotype associations and clinical heterogeneity. However, the precise mechanisms linking nuclear envelope abnormalities to partial lipodystrophy remain unknown. The pathogenicity of variants in the *LMNA* gene has been explained through different theories over the years [13,16-26]: structural theory (those cells subjected to mechanical load, such as skeletal muscle or cardiomyocytes, would be especially affected); gene expression theory (due to alterations in transcription factors such as SREBP1C); the theory of the alteration in cell proliferation/differentiation (lamin organisation is important in the differentiation of mesenchymal stem cells, mediating sequestration of the retinoblastoma protein); the theory of prelamin A toxicity (the accumulation of farnesyl-prelamin A alters the nuclear envelope and chromatin organisation, generating a premature aging phenotype). Nevertheless, in recent years, new pathogenetic mechanisms leading to improper fat distribution in lamin A-linked lipodystrophies have been proposed. Thus, subcutaneous adipose tissue loss and fat accumulation in FPLD type 2 has been related to impaired white adipocyte turnover and failure of adipose tissue browning due to early activation of autophagy in laminopathic adipocyte precursors followed by autophagic flux impairment [27]. In addition, it has also been proposed a model of how lamin A may modulate adipogenic differentiation, with p.(R482W) variant presenting a dominant-negative effect on chromatin organisation and epigenetic states regulating expression of the anti-adipogenic microRNA miR-335 in adipocyte progenitors [28].

*PPARG* is considered to be the master regulator of adipogenesis. It is essential for adipocyte differentiation, leading to the formation of small adipocytes and the control of the expression of genes crucial for lipid storage capacity [29-32]. In addition, *PPARG* is also involved in insulin sensitivity independently of its effect on adipogenesis [33]. While heterozygous dominant-negative variants in this gene are associated with FPLD type 3

[34-38], other heterozygous missense variants are benign, which suggests that gene-environment interactions are important [39,40].

*AKT2* mediates hormonal regulation of energy homeostasis in insulin-responsive tissues, such as adipose tissue. The loss of this *AKT* isoform has been associated to FPLD [41].

Finally, *PCYT1A* participates in the regulation of phosphatidylcholine biosynthesis, which plays an essential role in the normal functioning of white adipose tissue and insulin action. Loss-of-function variants in this gene have also been associated to atypical FPLD [42].

**Genes involved in lipid storage and synthesis**

*PLIN1*, *CIDEC*, *LIPE* and *ADRA2A* are the main genes associated to FPLD whose alterations are responsible for lipid droplet dysfunction and perturbed lipolysis.

*PLIN1*, altered in FPLD type 4, encodes perilipin-1, a structural lipid droplet protein that regulates lipolysis. Thus, pathogenic variants in this gene disrupt the ability of perilipin-1 to inhibit triglyceride basal lipolysis [43,44]. In keeping with *LMNA* and *PPARG*-related lipodystrophies, only variants with specific molecular mechanisms are likely to cause pathogenicity [45,46].

*CIDEC*, which is altered in FPLD type 5, is required for the formation of unilocular lipid droplets, mediating their fusion and limiting lipolysis in mature adipocytes [47,48].

The *LIPE* gene, which was found to be altered in FPLD type 6, encodes hormone-sensitive lipase, capable of hydrolysing a variety of esters and mobilising triglyceride deposits from lipid droplets [49-51].

Activation of *ADRA2A* inhibits cAMP production and reduces lipolysis in adipocytes. Thus, the *ADRA2A* variant reported in the literature causes a rare atypical FPLD by inducing excessive lipolysis in some adipose tissue depots [52].

**Genes involved in other well-defined mechanisms associated to partial lipodystrophy**

Mitochondrial activity also plays an important role in adipocyte differentiation and function. *MFN2* encodes mitofusin 2, a bound mediator of mitochondrial membrane fusion and inter-organelle communication. Specific variants in this gene produce tissue-selective mitochondrial dysfunction and are associated with FPLD and upper body adipose overgrowth [53].

## CLINICAL MANIFESTATIONS AND COMORBIDITIES

The main differential clinical features and comorbidities of these disorders are summarised in Table 2.

*FPLD type 1 or Köbberling syndrome* is characterised by the loss of adipose tissue restricted to the limbs and buttocks and an abnormal accumulation of fat in the abdominal region (Figure 2A), which usually begins in childhood or puberty. Affected subjects frequently develop severe insulin resistance, diabetes and hypertriglyceridaemia [5,54,55]. Although Köbberling syndrome normally follows an autosomal dominant pattern of inheritance, no responsible gene has yet been found [54]. However, a polygenic pattern has been suggested [54,56,57]. Thus, the diagnosis of this syndrome is challenging, and this particularly android phenotype makes it difficult to identify affected males.

*FPLD type 2 or Dunnigan disease* is characterised by the loss of adipose tissue in the limbs, trunk and gluteal region and its accumulation in the face, neck, axillae, interscapular area, labia majora and abdominal viscera (Figure 2B). It occurs around puberty in women and later in men [2,4,7,11,58,59]. In fact, affected men are generally

diagnosed based on their female relatives. There is also a tendency towards the formation of subcutaneous lipomas (Figure 3A), which can guide the diagnosis in a subject with an FPLD phenotype. Phlebomegaly (Figure 3C) and muscular hypertrophy (Figure 3D) in the upper and lower limbs are, likewise, common features in these patients [1,60]. Affected subjects present early insulin resistance [7], with hyperinsulinemia, which can be associated to acanthosis nigricans (Figure 3B) and acrochordons, increasing the risk of developing diabetes mellitus in adulthood [8,9]. Hypertriglyceridemia with resultant pancreatitis, low HDL cholesterol levels and hepatic steatosis are common [8,9,58,61-65]. Polycystic ovary syndrome, androgenisation stigmata, fertility problems and a higher rate of miscarriages and stillbirths may also be present [58,61-64,66]. An anticipation phenomenon with the occurrence of metabolic complications, such as diabetes and hypertriglyceridemia, at an earlier age across generations, has been described [67,68]. Furthermore, the cardiovascular spectrum is broad, with complications such as premature atherosclerosis, rhythm disturbances, hypertrophic cardiomyopathy and valvular heart disease [8,69-72]. In addition, patients with non-R482 variants present more frequently with arrhythmias than R482 carriers [9].

Most patients with the classic phenotype are those who harbour heterozygous missense variants affecting the arginine residue at 482 position in exon 8 of the *LMNA* gene [15,73,74]. However, other *LMNA* pathogenic variants in other exons have also been described [70,75-77], and are considered to produce "atypical" FPLD [64,78]. In addition, some phenotypic and metabolic differences even in subjects with different variants within the same exon, confirm the heterogeneity and variable expressivity of this disorder [79]. Other laminopathies, including Emery Dreifuss muscular dystrophy, Limb-Girdle muscular dystrophy and familial dilated cardiomyopathy, can also be associated with FPLD type 2 or may even be present in other members of the family [80,81].

*FPLD type 3* is characterised by less severe loss of adipose tissue in the limbs and buttocks during adolescence or in early adulthood. Ectopic fat accumulation in the face and neck may or may not be present. Other differentiating phenotypic characteristics include the presence of some subcutaneous fat in the upper arms, without phlebomegaly and less prominent musculature in the forearms and calves (Figure 2C). However, clinical manifestations and comorbidities are more severe than in Dunnigan disease, with marked resistance to insulin, earlier appearance of diabetes and severe and poorly-controlled hypertension. There may also be pre-eclampsia or eclampsia during pregnancy [34-38].

*FPLD type 4* is a rare entity with only ten families harbouring pathogenic variants in the *PLIN1* gene reported worldwide [43,44,46,82]. Lipoatrophy appears in childhood or in adulthood and mainly affects the limbs and femorogluteal region, although a reduction in subcutaneous adipose tissue in the trunk has also been observed. In some cases, facial fat accumulation may be present, with cushingoid appearance. These patients also show muscular hypertrophy, ovarian dysfunction, with chronic oligomenorrhea and hirsutism. Metabolic complications, such as hyperinsulinemia or insulin-resistant diabetes, accompanied by acanthosis nigricans, hypertriglyceridaemia and liver steatosis, are also present [43,46].

Regarding *FPLD type 5*, only one case has been reported in the literature (in 2009). The patient developed the lipodystrophic phenotype in early childhood, with loss of fat in the femorogluteal region and lower limbs and preservation of visceral, neck and axillae fat. Hypermuscular lower limbs were also observed. She presented hypertriglyceridaemia with resultant pancreatitis, diabetes mellitus prone to ketosis, microalbuminuria, hypertension, hepatomegaly and hepatic steatosis [47].

*FPLD type 6* appears in adulthood. It is associated with lipoatrophy in the buttocks, hips and lower limbs and with multiple lipomatoses as well as the abnormal accumulation of

fat in the neck, supraclavicular area, axillae, the area below the triceps, back, abdomen and labia majora. The presence of muscular dystrophy and elevated creatine kinase levels has also been described. Hypertriglyceridaemia, diabetes mellitus, hypertension and hepatic steatosis are not uncommon [50,83,84]. Ophthalmological investigations have revealed numerous auto-fluorescent drusen-like retinal deposits in these subjects [85].

*AKT2-related FPLD* was observed in four cases from the same family in 2004, who presented severe insulin resistance, diabetes and hypertension, along with partial lipodystrophy [86].

*PCYT1A-related FPLD* has only been reported in two unrelated patients, both in 2014. Lipoatrophy appeared in childhood and affected the upper and lower limbs and buttocks, with preservation of adipose tissue in the trunk, dorsocervical and submandibular regions, mons pubis and labia majora. Unlike other subtypes of FPLD, this subtype presents with short stature and muscular atrophy. Diabetes secondary to insulin resistance appears in the second decade of life. These patients also present hypertriglyceridaemia, low HDL cholesterol levels, severe insulin resistance and severe hepatic steatosis [42].

Regarding *ADRA2A-related FPLD,* three cases belonging to the same pedigree were reported in the literature in 2016. The phenotypic characteristics appear during adolescence, with loss of fat in the limbs and trunk and its accumulation in the neck, posterior cervicothoracic and intra-abdominal regions, as well as a unique loss of fat from the scalp and orbits. The patients also presented increased muscularity of the limbs. Metabolic complications, including diabetes, hypertension and dyslipidaemia, appeared later in adulthood [52].

*MFN2-related FPLD* is characterised by the appearance of both upper body lipomatous masses and lipoatrophy in the gluteofemoral region, lower limbs and forearms. There is a great heterogeneity in the chronology of the onset of manifestations of the disease and

clinical signs may occur during childhood, adolescence or adulthood. It is also frequently associated to peripheral axonal neuropathy, Charcot-Marie-Tooth-like, with pes cavus. Regarding metabolic comorbidities, affected subjects may present hypertriglyceridaemia, low HDL cholesterol, insulin resistance and/or diabetes [57,87,88]. Strikingly, plasma leptin levels are undetectable [88].

## DIAGNOSIS

No well-defined diagnostic criteria have been established for lipodystrophy. Thus, its diagnosis is based on medical history, physical examination, body composition and the evaluation of metabolic complications [1].

FPLD should be suspected in subjects with regional loss of adipose tissue, mainly in the limbs, associated with the accumulation of fat in other areas [10]. However, this presentation may sometimes be subtle, which makes the diagnosis of the disease particularly challenging, especially in men. It should also be taken into account that FPLD may be confused with Cushing syndrome due to the accumulation of fat in the face and neck [6,11]. In that case, biochemical examinations must be carried out to discard this syndrome. In the case of FPLD type 3, there is a less severe fat loss and affected patients may not have accumulation of adipose tissue in the face and neck. However, they usually present marked insulin resistance with early-onset diabetes and severe hypertension [34,36-38]. On the other hand, the presence of subcutaneous lipomas suggests FPLD type 2 (Figure 3A), type 6, or *MFN2*-related FPLD [76,84,87,88]. Subjects with Dunnigan disease may also manifest cardiomyopathy, valvular heart disease, arrhythmias and muscular dystrophy [8, 69, 70-72]. In addition, myopathy can be seen in FPLD types 2 and 6 [83, 84], and ketosis in FPLD type 5 [47]. The age of onset of the symptoms also helps to identify the subtype of FPLD (onset in adulthood in the case of FPLD types 3

and 6). However, the loss of adipose tissue may be gradual, which can delay the diagnosis. Pedigree analysis will suggest the presence of familial lipodystrophy. In this sense, FPLD types 2, 3, 4, *AKT2* and *ADRA2A*-related FPLD, are autosomal dominant. The remaining subtypes follow an autosomal recessive inheritance (Table 1).

Anthropometry data, such as skinfold thickness, are also used to support the diagnosis. In fact, specific cut-off points have been proposed for the thickness and distribution of subcutaneous fat. Thus, regarding mid-thigh skinfolds, a cut-off of 11 mm in adult men and less than 22 mm in adult women is considered to be useful for supporting the diagnosis [1]. KöB index (subscapular/calf skinfold ratio, with a cut-off value of 3.477) has also proven to be helpful when distinguishing FPLD type 1 from androgenic obesity in women [54]. Dual Energy X-Ray Absorptiometry (DXA) and magnetic resonance imaging are likewise useful in the assessment of body composition and in the diagnosis of patients with lipodystrophy, providing not only quantitative but also qualitative information ("fat shadows") [89]. Identification of the "Dunnigan sign" (hypertrophy of mons pubis fat surrounded by subcutaneous lipoatrophy) is helpful in recognising subjects with FLPD type 2. It has also recently been determined that lower-limb fat below the 1st percentile according to DXA might direct the diagnosis of Dunnigan disease in women, especially if there are concomitant metabolic complications, and, therefore, genetic testing should be carried out in these cases [90].

Regarding biochemical assessment, there are no standardised cut-offs defined for leptin levels to confirm or exclude the diagnosis of FPLD. In addition, although leptin concentrations tend to be low in these patients (in fact, their levels are characteristically very decreased in patients with *MFN2* pathogenic variants [88]), they may overlap with the general population. Thus, they are not currently recommended as a diagnostic tool. On the other hand, the presence of elevated creatine kinase levels can be seen in FPLD

type 6 [84]. Furthermore, all patients should have a complete metabolic panel to detect diabetes, dyslipidaemia, non-alcoholic fatty liver disease, as well as cardiovascular and reproductive dysfunction [1].

Confirmatory genetic analysis, including a limited number of candidate genes, a panel of genes or the whole sequencing of the exome/genome, is required to determine the diagnosis of FPLD and to carry out genetic counselling and screening of family members. In fact, molecular screening is particularly important in families with specific *LMNA* variants related to cardiomyopathy and rhythm disturbances. However, it has to be taken into account that negative results cannot exclude a genetic lipodystrophy [1].

Recently, a mobile application (LipoDDx®) has been developed by our group, which can enable the identification of different subtypes of lipodystrophies and assist in their diagnosis, with 80% effectiveness [91].

## TREATMENT

There is currently no cure for lipodystrophy. However, the morbidity and mortality of these conditions improve with early intervention and, therefore, their treatment must be fundamentally oriented towards the control of the metabolic comorbidities.

### Diet and physical exercise

In this regard, diet, along with physical exercise, is an integral part of the treatment plan. Thus, most subjects should follow a diet with a balanced distribution of macronutrients (50% carbohydrates, 30% fats, 20% proteins), taking into account that this may vary depending on the metabolic complications of the patient. Low-calorie diets can achieve a reduction in the peripheral accumulation of fat and may help to improve metabolic anomalies [92]. Physical exercise, when there are no contraindications, can also help to

ameliorate metabolic parameters. Individuals with FPLD who are prone to developing cardiac arrythmias or to presenting cardiomyopathy (particularly those with specific pathogenic variants in the *LMNA* gene) must be subjected to a cardiological assessment before beginning any physical activity and should also avoid vigorous exercise [1,93].

**Treatment of comorbidities**

Regarding the hypoglycaemic agents available for the treatment of diabetes, metformin continues to be the therapy of choice. Thiazolidinediones, which selectively activate *PPARG*, improve insulin sensitivity primarily by increasing subcutaneous fat mass [94]. Thus, in patients with FPLD, thiazolidinediones have been shown to improve glycated haemoglobin (HbA1c), dyslipidaemia, transaminases and hyperandrogenism [95,96]. However, cardiomyopathy precludes prolonged use of this drug [97] and attention should be paid to the increase of regional fat [1,97]. Glucagon-like peptide-1 receptor agonists may also be a useful component of glucose-lowering therapy in individuals with FPLD and diabetes mellitus [98], taking into account the increase in dipeptidyl peptidase-4 levels exhibited in these patients [99]. Nevertheless, their use in patients at increased risk of pancreatitis should be taken with precaution. Sodium–glucose cotransporter 2 inhibitors may offer an additional option as they have been proved to decrease insulin resistance and have led to regression of fatty liver in several cases with FPLD syndrome [100,101]. Insulin might also be needed and, in patients with high requirements, concentrated preparations should be considered [102].

As far as dyslipidaemia is concerned, it is recommended to be managed in accordance with current guidelines for the general population, with statins being the therapy of choice. In the case of severe hypertriglyceridaemia (> 500 mg/dL), fibrates and long-chain omega-3 fatty acids should be added (1-Brown2016). In patients with FPLD syndrome accompanied with myopathy or muscular dystrophy, these drugs must be used

with caution [103]. In addition, the efficacy and safety of volanesorsen, an antisense inhibitor of apolipoprotein C-III, has been evaluated in the BROADEN study, a 52-week phase 2/3 study which randomised 1:1 to weekly administration of volanesorsen (300 mg) or placebo, showing an 88% reduction in serum triglycerides as well as a significant reduction in hepatic fat fraction in 40 subjects with FPLD [104]. Other agents working on hepatic lipid metabolism in FPLD are evinacumab, an inhibitor of ANGPTL3, and gemcabene, a monocalcium salt of a dialkyl ether dicarboxylic acid. The results of the clinical studies focused on these novel molecules will be seen in the coming years [105].

**Metreleptin therapy**

Metreleptin, a human recombinant leptin, has been approved by the European Medicines Agency (EMA), not only for generalised forms of lipodystrophy but also for FPLD patients > 12 years of age who have not responded to standard treatments (https://www.ema.europa.eu/en/medicines/human/EPAR/myalepta). It has also been approved for the treatment of diabetes and/or hypertriglyceridaemia in FPLD patients in Japan (http://www.shionogi.co.jp/en/company/news/2013/pmrltj0000000ufd-att/e_130325.pdf). Although its response in partial lipodystrophy is considered to be less robust than in generalised types, it has been shown to improve hypertriglyceridaemia, HbA1c, insulin sensitivity and liver volume in FPLD patients [106-112]. In addition, similar metabolic improvements were found when comparing subjects with *LMNA* and *PPARG* pathogenic variants [113]. On the other hand, in a recent study, significant reductions in albuminuria and proteinuria were observed in patients with CGL, but not in those with FPLD. However, it has to be taken into account that subjects with CGL also showed greater proteinuria at baseline than those with FPLD [114]. The development of neutralising antibodies has been reported [115], which, unlike in generalised forms, is of particular concern in subjects with partial lipodystrophy who produce significant amounts

of endogenous leptin, taking into account that antibodies may block both endogenous leptin and exogenous metreleptin. The use of setmelanotide, a selective melanocortin-4 receptor agonist targeting specific neurons downstream from the leptin receptor activation, was not effective in restoring metabolic control in a patient with atypical partial lipodystrophy and neutralising antibodies to metreleptin [116].

### Surgical treatment

Weight loss may be challenging in some cases taking into account the relative leptin deficiency and resulting hyperphagia. In this regard, bariatric surgery (Roux-en-Y bypass) has proved to be effective in subjects with FPLD types 1 and 2 while improving metabolic parameters [117-120]. In addition, patients sometimes relate physical discomfort or psychological distress due to their appearance, which is why cosmetic surgery may be considered. Thus, excess adipose tissue from the face, neck, and vulvar region can be removed by liposuction [6]. In addition, the local injection of deoxycholic acid is considered a novel technique which could be used for the treatment of submental fat in some subtypes of FPLD [121,122].

## CONCLUSION

FPLD syndromes are a group of rare diseases characterised by the loss of adipose tissue mainly from the limbs and gluteal region, as well as variable regional fat accumulation, which may confer a cushingoid appearance. Affected patients present a predisposition to develop metabolic complications related to insulin resistance and an inability to properly store lipids. Although there is currently no cure for lipodystrophy, it is known that the morbidity and mortality of these syndromes improve with early intervention and, therefore, their treatment must be fundamentally oriented towards the control of the

metabolic comorbidities. In this sense, recent treatment modalities have shown promising results in FPLD patients. Greater awareness of the disease among clinicians is necessary in order to establish an early diagnosis and management.


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## DISCLOSURE OF INTEREST

D.A.V. received lecture fees and advisory board honoraria from Amryt Pharma and Aegerion Pharmaceuticals. The rest of the authors declare no conflict of interest.

## INFORMED CONSENT STATEMENT

All subjects provided written informed consent for participation in the study and for the publication of their clinical, biochemical and molecular information.

## AUTHOR CONTRIBUTIONS

Conceptualization, A.F.-P. and D.A.-V.; investigation, D.A.-V., A.F.-P., and S.S.-I; writing-original draft preparation, A.F.-P..; writing-review and editing, A.F.-P., S.S.-I., D.A.-V., H.A.-M., S.C.-G.; supervision, D.A.-V.; project administration, D.A.-V.;

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**Table 1.** Classification and molecular basis for familial partial lipodystrophy syndromes.

| Syndrome | Inheritance | Gene | Function | OMIM |
|---|---|---|---|---|
| FPLD1 (Köbberling syndrome) | Polygenic | Unknown | Unknown | #608600 |
| FPLD2 (Dunnigan disease) | AD | *LMNA* | Nuclear lamina alteration | #151660 |
| FPLD3 | AD | *PPARG* | Adipogenesis dysregulation | #604367 |
| FPLD4 | AD | *PLIN1* | Lipid droplet impairment | #613877 |
| FPLD5 | AR | *CIDEC* | Lipid droplet impairment | #615238 |
| FPLD6 | AR | *LIPE* | Lipolysis dysregulation | #615980 |
| *AKT2*-related FPLD | AD | *AKT2* | Insulin signal transduction alteration | - |
| *PCYT1A*-related FPLD | AR | *PCYT1A* | Dysregulation of phosphatidylcholine biosynthesis | - |
| *ADRA2A*-related FPLD | AD | *ADRA2A* | Lipolysis dysregulation | - |
| *MFN2*-related FPLD | AR | *MFN2* | Mitochondrial dysfunction | - |

FPLD: familial partial lipodystrophy; AD: autosomal dominant; AR: autosomal recessive.

**Table 2.** Summary of the main characteristics of the different subtypes of FPLD for their differential diagnosis.

| Subtype | Onset of fat loss | Abnormal fat distribution | Clinical features | Main comorbidities | Ref. |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| FPLD1 | Childhood. Puberty or adulthood | Loss of fat in the lower limbs and buttocks. Accumulation of abdominal fat. | KöB index > 3.477 | Insulin resistance and metabolic syndrome, PCOS. | 54-56 |
| FPLD2 | Puberty in women, later in men | Loss of fat in the limbs, trunk and gluteal region. Accumulation of fat in the face, neck, axillae, interscapular area, labia majora and abdominal viscera. | Subcutaneous lipomas. Muscular hypertrophy, phlebomegaly. "Dunnigan sign". | Diabetes, hypertriglyceridaemia, hepatic steatosis, fertility problems, PCOS, cardiovascular disease, arrhythmias. May associate cardiomyopathy, muscular dystrophy. | 4, 7-9, 12, 15, 58-81 |
| FPLD3 | Adolescence or early adulthood | Less severe loss of fat in the limbs and buttocks. The accumulation of fat in the face and neck may not be present. | Less prominent musculature, no phlebomegaly. | Earlier and more severe metabolic complications. Diabetes, hypertension. | 34-38 |
| FPLD4 | Childhood or adulthood | Loss of fat in the limbs and femorogluteal region. Facial fat accumulation may be present. | Muscular hypertrophy. | Diabetes, hypertriglyceridaemia, hepatic steatosis, ovarian dysfunction, | 43-46, 82 |
| FPLD5 | Childhood | Loss of fat in the limbs and femorogluteal region. | Muscular hypertrophy. | Diabetes, ketosis, hypertriglyceridaemia, hypertension, hepatic steatosis. | 47 |
| FPLD6 | Adulthood | Loss of fat in the buttocks, hips and lower limbs. Accumulation of fat in the neck, supraclavicular area, axillae, back, abdomen and labia majora. | Multiple lipomatoses. Muscular dystrophy. | Diabetes, hypertriglyceridaemia, hypertension, hepatic steatosis. Auto-fluorescent drusen-like retinal deposits. Elevated creatine kinase levels. | 50, 83-85 |
| *AKT2*-related FPLD | Adulthood | NA | NA | Diabetes, hypertension. | 41, 86 |

| | | | | | |
|---|---|---|---|---|---|
| *PCYT1A*-related FPLD | Childhood | Loss of fat in the limbs and buttocks. | Short stature, muscular atrophy. | Diabetes, hypertriglyceridaemia, hepatic steatosis. | 42 |
| *ADRA2A*-related FPLD | Adolescence | Loss of fat in the limbs and trunk. Accumulation of fat in the neck and intra-abdominal region. | Hypermuscular limbs. | Diabetes, hypertension, dyslipidaemia. | 52 |
| *MFN2*-related FPLD | Childhood, adolescence or adulthood | Loss of fat in the limbs, forearms and femorogluteal region. | Lipomatous masses. | Peripheral axonal neuropathy. Diabetes, hypertriglyceridaemia. | 53, 87, 88 |

FPLD: familial partial lipodystrophy; PCOS: polycystic ovary syndrome; NA: not available.

## FIGURE LEGENDS

**Figure 1.** Visual scheme of the molecular pathogenesis of familial partial lipodystrophies. Genes marked in green represent those related to adipogenesis, adipocyte differentiation and insulin signaling (*LMNA* codifies for lamin A/C, which influences transcriptional regulation; *PPARG* coordinates the transcription of proteins central to adipogenesis; *AKT2* is a part of the insulin signal transduction pathway; *PCYT1A* is involved in phosphatidylcholine synthesis). Genes marked in yellow represent those related to lipid droplet formation and lipolysis (*PLIN1*, *LIPE* and *ADRA2A* regulate lipolysis from lipid droplets; *CIDEC* promotes lipid droplet formation).

**Figure 2.** Adipose tissue distribution in the most common subtypes of familial partial lipodystrophy.

Fig. 2A: patient with Köbberling syndrome, manifesting an abnormal accumulation of fat in the abdominal region along with loss of fat in the limbs and buttocks; Fig. 2B: patient with Dunnigan disease, presenting loss of fat in the limbs, trunk and gluteal region and its accumulation in the face, neck, axillae and interscapular area; Fig 2C: patient with FPLD type 3, characterised by less severe loss of fat in the limbs and buttocks. Ectopic fat accumulation in the face and neck is not present in this case.

**Figure 3.** Common clinical features in Dunnigan disease.

Fig 3A: subcutaneous lipomas; Fig 3B: acanthosis nigricans due to early insulin resistance; Fig 3C: phlebomegaly; Fig 3D: muscular hypertrophy.

Figure 1

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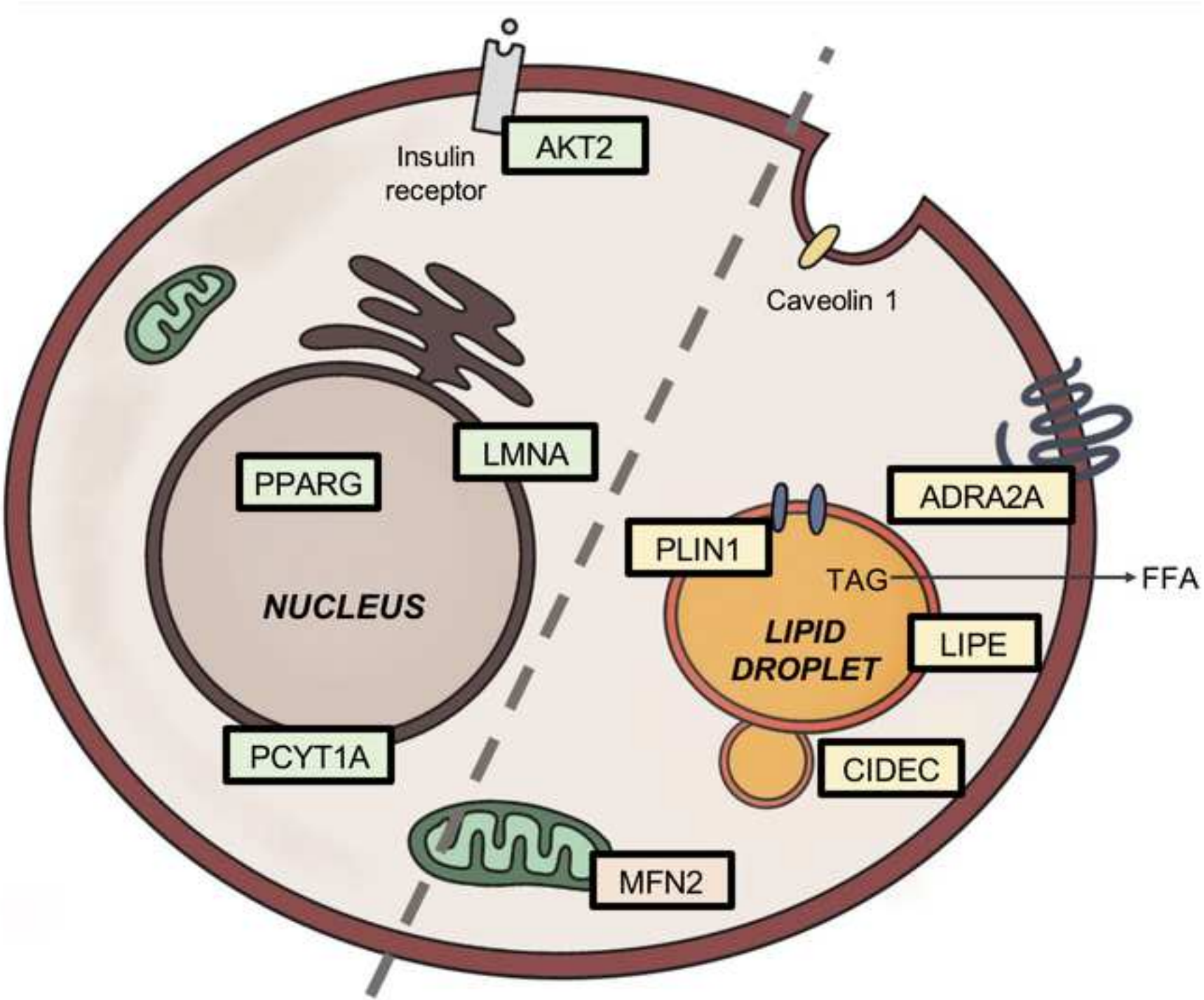

Figure 2



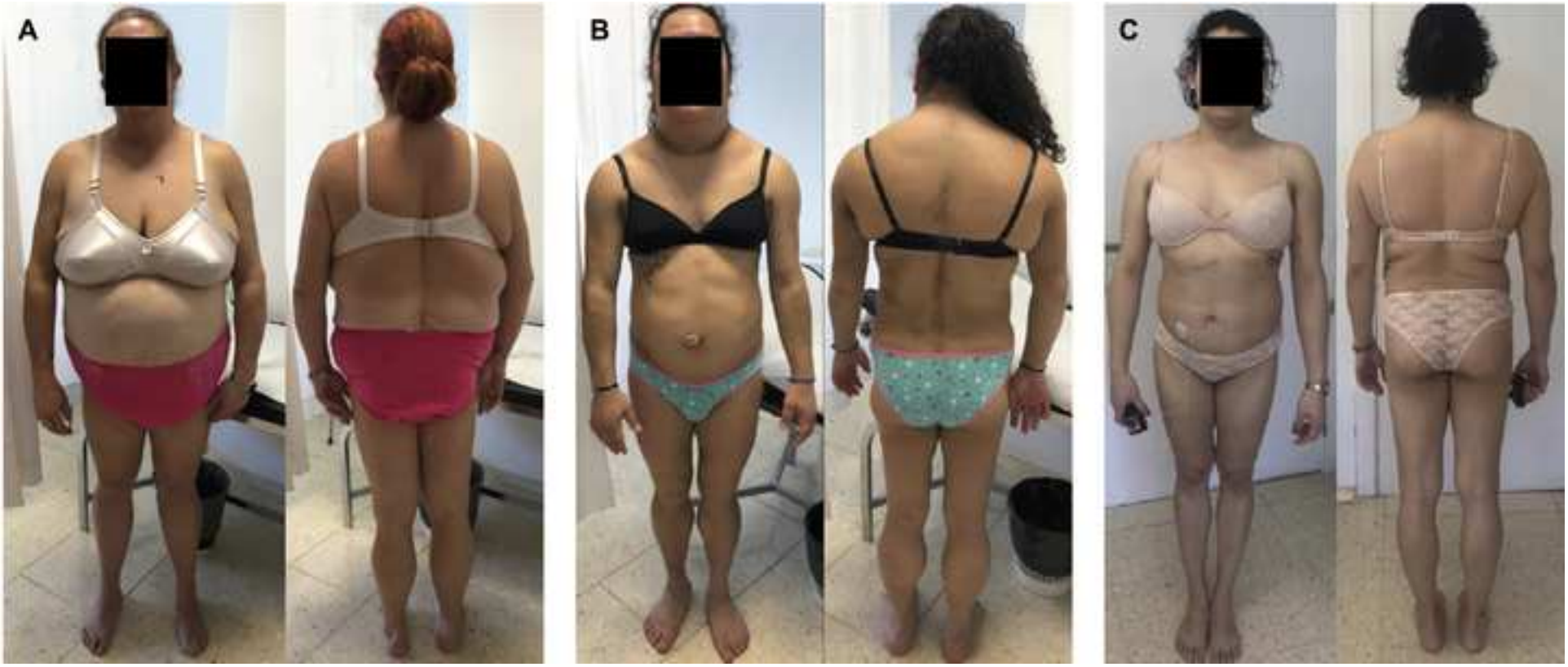

Figure 3

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