

# Familial Partial Lipodystrophy (FPLD): Recent Insights

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**Abstract:** Lipodystrophies are a heterogeneous group of congenital or acquired disorders, characterized by partial or generalized loss of adipose tissue. Familial partial lipodystrophy (FPLD) presents with genetic and phenotypic variability with insulin resistance, hypertriglyceridemia and hepatic steatosis being the cardinal metabolic features. The severity of the metabolic derangements is in proportion with the degree of lipoatrophy. The underpinning pathogenetic mechanism is the limited capacity of adipose tissue to store lipids leading to lipotoxicity, low-grade inflammation, altered adipokine secretion and ectopic fat tissue accumulation. Advances in molecular genetics have led to the discovery of new genes and improved our knowledge of the regulation of adipose tissue biology. Diagnosis relies predominantly on clinical findings, such as abnormal fat tissue topography and signs of insulin resistance and is confirmed by genetic analysis. In addition to anthropometry and conventional imaging, new techniques such as color-coded imaging of fat depots allow more accurate assessment of the regional fat distribution and differentiation of lipodystrophic syndromes from common metabolic syndrome phenotype. The treatment of patients with lipodystrophy has proven to be challenging. The use of a human leptin analogue, metreleptin, has recently been approved in the management of FPLD with evidence suggesting improved metabolic profile, satiety, reproductive function and self-perception. Preliminary data on the use of glucagon-like peptide 1 receptor agonists (GLP1 Ras) and sodium-glucose co-transporter 2 (SGLT2) inhibitors in cases of FPLD have shown promising results with reduction in total insulin requirements and improvement in glycemic control. Finally, investigational trials for new therapeutic agents in the management of FPLD are underway.

**Keywords:** lipodystrophy, partial lipodystrophy, familial lipodystrophy, leptin

## Introduction

Lipodystrophies are a heterogeneous group of disorders characterized by selective partial or generalized loss of adipose tissue. They can be either congenital or acquired in origin, and according to the distribution of adipose tissue loss, lipodystrophies are categorized to localized, partial, or generalized. Lipodystrophy is an ultra-rare syndrome with an estimated prevalence of 1.3–4.7 cases per million,<sup>1</sup> although this might be an underestimate, as many cases remain unrecognized. Congenital lipodystrophies, based on the pattern of adipose tissue loss, can be categorized into either familial partial lipodystrophy or congenital generalized lipodystrophy (CGL). Familial partial lipodystrophy (FPLD) is a disease with considerable genetic and phenotypic variability that was first described in the 1970s<sup>2,3</sup> but attracted greater attention in the last 20 years due to the expanded knowledge on genetics, adipose tissue biology and discovery of the leptin gene. Depending on the extent of fat loss, described as lipoatrophy by many

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authors, affected individuals may present with primarily cosmetic problems whereas others may develop severe metabolic complications such as insulin resistance and diabetes, hypertriglyceridemia, non-alcoholic steatohepatitis (NASH) and premature atherosclerosis. Treating these patients has proven to be challenging, but new modalities such as recombinant human leptin therapy have shown some promising results. The purpose of this review is to summarize the latest insights and findings for FPLD, focusing on new knowledge on the pathogenesis, molecular genetics and therapeutic options.

## Pathophysiology of Metabolic Disorders Associated with FPLD

So far, six different types of FPLD (FPLD1 to FPLD6) and several other unclassified forms of partial lipodystrophy in the context of rare genetic syndromes with distinct phenotypic characteristics and genetic causes have been described (Table 1).<sup>4,5</sup>

FPLDs are generally dominantly inherited and are characterized by loss of subcutaneous adipose tissue (usually during late childhood or puberty) from the upper and lower extremities as well as from the truncal region.<sup>6</sup> Common clinical features of patients with lipodystrophies are shown in Table 2. Limited capacity of adipose tissue to store lipids and failure of buffering post-prandial lipid refluxes have a fundamental role in the pathogenesis of the metabolic disorders associated with lipodystrophies. It has been proposed that, when the genetically determined capacity of adipose tissue to expand is surpassed, lipotoxicity, macrophage infiltration, mitochondrial dysfunction and oxidative stress develop within dysfunctional lipodystrophic adipocytes leading to altered adipokine secretion.<sup>7-10</sup> As a result, ectopic fat tissue accumulates in the liver, muscle, pancreas and the vasculature, resulting in insulin resistance and abnormal lipid and glucose metabolism.<sup>7</sup> The metabolic derangement is generally in proportion with the degree of lipotrophy.

Low levels of leptin and adiponectin may in part explain some of the metabolic and reproductive changes observed in those patients with more extensive fat loss.<sup>11</sup> Indeed, low adiponectin levels promote insulin resistance and are closely related to the development of diabetes and cardiovascular disease whereas low leptin levels result in hyperphagia and reduced energy expenditure.<sup>12</sup> Lipodystrophy-associated metabolic derangements have recently been associated with increased levels of mitochondrial DNA damage and

**Table 1** Classification of Partial Lipodystrophies, Prevalence and OMIM (Online Mendelian Inheritance in Man) Phenotype Number

Familial Partial Lipodystrophy	Prevalence	OMIM Phenotype #
FPLD 1 or Köbberling type	Unknown	608,600
FPLD 2 or Dunnigan type (LMNA-related)	>500 Patients reported	151,660
FPLD 3 or PPARC-related	20 Families	604,367
FPLD 4 or PLIN1-related	4 Families	613,877
FPLD 5 or CIDEC-related	1 Patient	615,238
FPLD 6 or LIPE-related	2 Families	615,980
CAVI-related FPLD	3 Patients	606,721
ADRA2A-related FPLD	1 Family	-
AKT2-related FPLD	1 Family	-
Progeroid syndromes		OMIM Phenotype #
MAD type A	Extremely rare	248,370
Werner syndrome	Extremely rare	277,700
MDPL syndrome	Extremely rare	615,381
Complex genetic syndromes with partial lipodystrophy		OMIM Phenotype #
Bloom syndrome	Extremely rare	210,900
SHORT syndrome	Extremely rare	269,880
Autoinflammatory syndromes		OMIM Phenotype #
CANDLE syndrome	Extremely rare	177,046

**Abbreviations:** FPLD, familial partial lipodystrophy; MAD, mandibuloacral dysplasia; MDPL, mandibular hypoplasia-deafness-progeroid features-lipodystrophy.

transcriptional activation of genes involved with antioxidant response and DNA repair.<sup>13</sup> Features of polycystic ovarian syndrome and subfertility are common in women with lipodystrophies. Although leptin receptors are present in the ovaries and the prostate gland, current evidence suggests that the primary leptin actions on human reproductive function are central and that its effects on peripheral reproductive tissues are most likely indirect.<sup>14,15</sup>

Interestingly, data suggest the existence of tissue-selective insulin resistance<sup>8</sup> with inhibition of insulin signaling in liver and muscle leading to increased gluconeogenesis, increased lipogenesis and reduced peripheral glucose uptake. On the other hand, insulin seems to preserve its mitogenic effect on the ovarian theca cells and its anabolic action

**Table 2** Clinical Features of Familial Partial Lipodystrophies

Metabolic abnormalities Insulin resistance, acanthosis nigricans Hyperglycemia, diabetes mellitus Hypertriglyceridemia, eruptive xanthomas, pancreatitis Ectopic fat deposition
Liver Hepatic steatosis, hepatomegaly Non alcoholic steatohepatitis Liver cirrhosis
Heart Cardiomyopathy Atherosclerotic coronary heart disease
Reproductive Hyperandrogenemia, hirsutism Oligomenorrhoea, subfertility Polycystic ovarian syndrome
Other Proteinuric renal disease Myopathy

causing hyperandrogenemia and acromegaloïd features, respectively.<sup>16</sup> This pathway selective insulin resistance leads to the development of the cardinal metabolic disorders found in lipodystrophic syndromes, namely diabetes mellitus, dyslipidemia, hepatic steatosis and reproductive dysfunction (reduced fertility, PCOS). Furthermore, recent evidence from genome-wide association studies (GWAS) in a general population suggests that genetic variants related to gluteofemoral versus abdominal fat storage are associated with increased risk of cardiovascular disease and type 2 diabetes.<sup>17</sup> These findings support the hypothesis that similar genetically determined mechanisms may play a role in the pathogenesis of the common metabolic syndrome and of the much rarer lipodystrophy syndromes.<sup>5</sup>

## Molecular Pathogenesis, Genetics and Association with Clinical Phenotype

In recent years, research has shed light on the molecular pathogenesis of familial lipodystrophies. Despite progress, in many cases no known mutations are found in patients presenting with clinical features of lipodystrophy, suggesting that there are still more genes to be identified. In general, the responsible genes can be categorized into those involved in: i) adipogenesis ii) lipid droplet formation and lipolysis iii) cell membrane integrity and iv) DNA

repair (Table 3; Figure 1). FPLD type 1 (Köbberling type lipodystrophy) is thought to have a polygenic etiology and will be described separately.<sup>18</sup>

## Adipogenesis – Adipocyte Differentiation-Related Genes

In this category belong the two most common genetic causes for FPLD, that is the pathogenic variants in the peroxisome proliferator-activated receptor  $\gamma$  (*PPAR* $\gamma$ ) and *LMNA* genes as well as some rarer gene mutations (Table 3).

*PPAR* $\gamma$  gene variants are associated with variable lipodystrophy phenotypes.<sup>19</sup> Dominant-negative mutations in the *PPAR* $\gamma$  are related to FPLD type 3.<sup>20</sup> Patients typically present in late childhood with loss of subcutaneous fat in the extremities and gluteofemoral region and “reactive” fat deposition in the viscera. Face and neck regions are usually spared. Metabolic complications secondary to insulin resistance present in adulthood and are more prominent in women. Early cardiovascular disease has also been reported.<sup>21</sup>

*PPAR* $\gamma$ , the master regulator of adipogenesis and adipose tissue maintenance,<sup>22</sup> is expressed in many tissues but predominantly found in white and brown adipose tissue.<sup>23</sup> It promotes lipogenesis without creating larger adipocytes; more and smaller are created instead.<sup>24</sup> Furthermore, its action is to promote subcutaneous to visceral fat differentiation.<sup>25</sup>

*LMNA* gene encodes intermediate filament proteins called lamins. Lamins A and C are the major proteins expressed by the gene and provide structural stability to the nuclear envelope and the cytoskeleton. Lamins are expressed in all cell types and mutated variants lead to premature apoptosis of the cells.<sup>26</sup> Autosomal dominant mutations of *LMNA* gene are associated with FPLD type 2 (Dunnigan type), the most common form of FPLD,<sup>27</sup> whereas autosomal recessive mutations are linked to mandibuloacral dysplasia (MAD) type A.<sup>28</sup> The onset of lipodystrophy in FPLD2 is gradual; lipodystrophic phenotypic characteristics may not be present until puberty, a period when fat depots expand due to sex hormone abundance.<sup>29</sup> However, recent data from Patni et al suggest that body fat distribution may change at earlier stages. Using objective measurements of adiposity (dual-energy X-ray absorptiometry, DXA) in a cohort of 46 patients with FPLD2, the authors showed that distal lipodystrophy is present earlier than thelarche.<sup>30</sup> Muscular “pseudo-hypertrophy” is commonly observed especially in females, and accumulation of fat on the face, neck and supraclavicular

**Table 3** Gene Mutations Involved in Familial Partial Lipodystrophy (FPLD) Pathogenesis, Mode of Inheritance and Corresponding Phenotypes

Gene	Inheritance	Clinical Phenotype	Ref
Adipogenesis – Adipocyte Differentiation			
<i>PPAR-γ</i> (FPLD3)	Autosomal dominant	Distal lipoatrophy – gluteofemoral fat loss, visceral adiposity, cardiovascular disease	[19–21, 107,108]
<i>LMNA</i> (FPLD2)	Autosomal dominant	Distal and truncal lipoatrophy, “cushingoid” appearance due to neck and face sparing, muscular dystrophy, dilated cardiomyopathy	[27,31–37,109]
<i>LMNA</i> (MAD type A)	Autosomal recessive	Distal and truncal lipoatrophy, mandibular and clavicular hypoplasia, acroosteolysis, delayed dentition, progeroid features	[28,110–112]
<i>ZMPSTE24</i> (MAD type B)	Autosomal recessive	Distal and truncal lipoatrophy, mandibular and clavicular hypoplasia, acroosteolysis, delayed dentition, progeroid features, segmental glomerulosclerosis	[37,38,113]
<i>AKT2</i>	Autosomal dominant	Distal lipoatrophy, severe insulin resistance	[42]
<i>PIK3R1</i> (SHORT syndrome)	Autosomal dominant	Short stature, joint hyperextensibility, ocular depression, Rieger anomaly, teething delay, facial - truncal - upper limbs lipoatrophy with sparing of lower limbs	[43–45]
Lipid Droplet Assembly – Lipolysis			
<i>CIDEA</i> (FPLD5)	Autosomal recessive	Lower limbs lipoatrophy, visceral adiposity, ketosis prone insulin resistance, multilocular lipid droplets	[48,114]
<i>PLIN1</i> (FPLD4)	Autosomal dominant	Lower limbs lipoatrophy, facial acromegaloid features, muscular hypertrophy	[50,115,116]
<i>LIPE</i> (FPLD6)	Autosomal recessive	Distal lipoatrophy, visceral adiposity, progressive myopathy, vitiligo	[52,53,117]
<i>ADRA2A</i>	Autosomal dominant	Distal lipoatrophy, visceral and upper trunk adiposity, muscularity	[54]
<i>CAVI</i>	Polygenic	Facial and upper trunk lipoatrophy, cataracts, hypertriglyceridemia,	[58]
Cell Membrane Integrity			
<i>PCYT1A</i>	Autosomal recessive	Distal lipoatrophy, short stature, visual impairment, spondylometaphyseal dysplasia	[59,60]
<i>PSMB8</i> (CANDLE syndrome)	Autosomal recessive	Fever, dermatosis, facial oedema, distal lipoatrophy, joint contractures	[61,62,118,119]
DNA Repair			
<i>WRN</i> (Werner syndrome)	Autosomal recessive	Distal lipoatrophy, short stature, progeroid features, Achilles ulcerations	[64,120]
<i>POLD1</i> (MDPL syndrome)	Autosomal dominant	Mandibular hypoplasia, deafness, progeroid features, distal lipoatrophy with visceral adiposity, hypogonadism	[65]
<i>BLM</i> (Bloom syndrome)	Autosomal recessive	Growth restriction, photosensitivity, telangiectasia, recurrent infection, increased cancer risk	[66,67]
FPLD type I	Polygenic	Distal lipoatrophy, visceral adiposity, insulin resistance, NASH	[69]

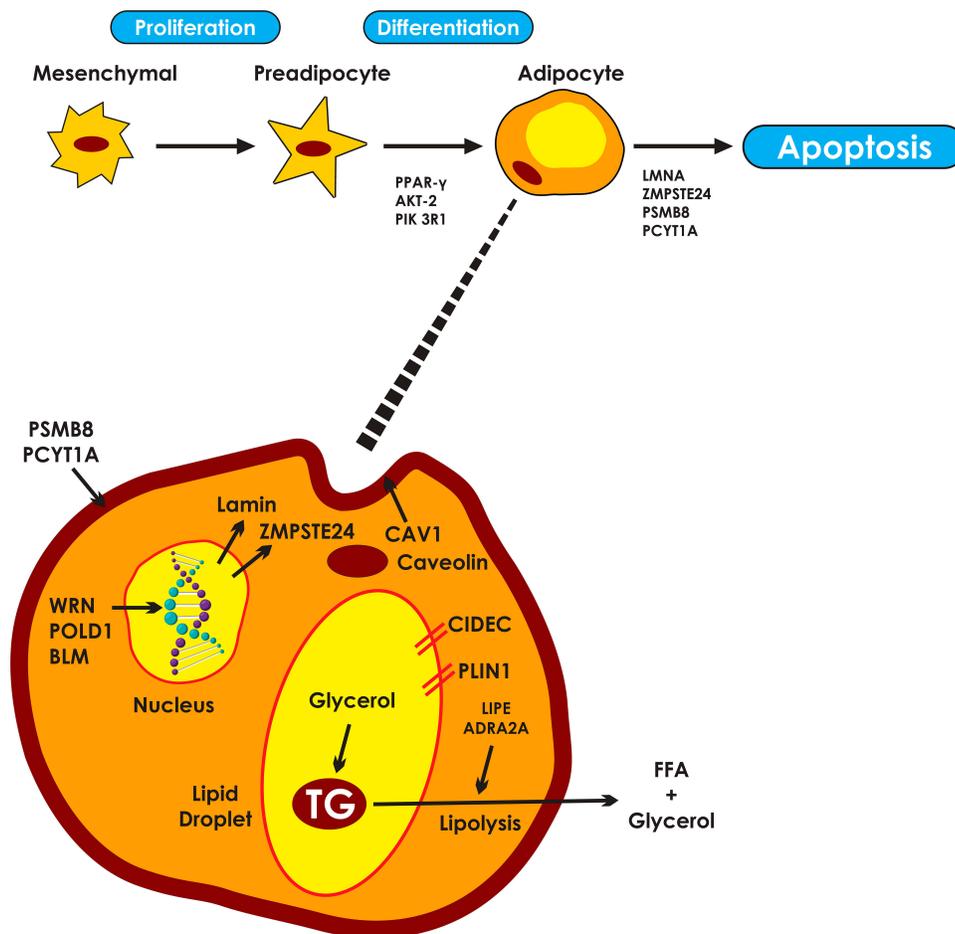
**Note:** Genes are grouped according to function.

**Abbreviations:** *AKT2*, protein kinase B; *MAD*, mandibuloacral dysplasia; *MDPL*, mandibular hypoplasia-deafness-progeroid features-lipodystrophy; *PCYT1A*, phosphate cytidyltransferase 1A; *PIK3R1*, phosphatidylinositol 3 kinase regulatory subunit 1; *POLD1*, DNA polymerase delta 1; *PPAR γ*, peroxisome proliferator-activated receptor γ; *PSMB8*, proteasome subunit beta type 8; *ZMPSTE24*, zinc metalloproteinase STE24.

areas is also noted, giving patients a “Cushingoid appearance”.<sup>6</sup> Insulin resistance is present in >80% of the cases leading to hepatic steatosis, hypertriglyceridemia, acanthosis nigricans and early atherosclerotic disease. Patients with *LMNA*-related lipodystrophy may also manifest

muscular dystrophy,<sup>31</sup> dilated cardiomyopathy<sup>32</sup> and proteinuric nephropathy.<sup>33</sup>

Mandibuloacral dysplasia (MAD) is an extremely rare autosomal recessive disorder with progeroid features and lipodystrophy. These patients develop two distinct



**Figure 1** Pathways involved in the molecular pathogenesis of familial partial lipodystrophies. Responsible genes may affect adipocyte differentiation, cell membrane integrity, DNA repair, lipid droplet formation and lipolysis. *PPAR $\gamma$* , the “master regulator” of adipogenesis coordinates the transcription of proteins central to the adipocyte function. *AKT2* and *PIK3R1* are involved in insulin signaling pathways, mediating adipocyte differentiation. *LMNA* gene encodes lamins A/C which are essential components of the nuclear envelope. *ZMPSTE24* is responsible for the proteolysis of prelamin A to mature/active lamin A. *PSMB8* and *PCYT1A* are responsible for the composition and integrity of cell membranes. Mutations lead to intracellular oxidative stress, inflammation and apoptosis. *WRN*, *POLD1* and *BLM* participate in DNA repair and replication, ensuring genomic stability. Caveolin 1, the product of *CAV1*, participates in the formation of caveolae. Caveolin vesicles are created from endocytosis of caveolae which carry cholesterol and sphingolipids from the cell surface. Caveolin vesicles are merged with the lipid droplet, mediating the transcytosis of fatty acids. *CIDEA* is responsible for the formation of unilocular lipid droplets and *PLIN1* for the structure of the lipid droplets. Finally, *LIPE* and *ADRA2A* regulate triglyceride lipolysis to free fatty acids and glycerol.

patterns of lipoatrophy; in type A (MADA), which is due to *LMNA* gene mutations, there is loss of fat from the extremities but normal or excessive fat deposition in the neck and trunk whereas in type B (MADB), which is caused by mutations of the zinc metalloproteinase (*ZMPSTE24*) gene, loss of subcutaneous fat is more generalized.<sup>34</sup> *ZMPSTE24* gene encodes a Zinc metalloproteinase which is responsible for the proteolysis of prelamin A to mature lamin A. Deficiency in *ZMPSTE24* causes toxic prelamin accumulation<sup>35</sup> and is linked to a spectrum of phenotypes, varying from restrictive dermopathy (total loss of enzyme activity) to MADB and generalized lipodystrophy.<sup>36</sup> Both types of MAD share common characteristics such as mandibular and clavicular hypoplasia, acroosteolysis and delayed

dentition.<sup>37</sup> Progeroid features such as pointed nose, microstomy, high-pitched voice, skin atrophy, nail dysplasia and alopecia characterize both types but are more prominent in MADB.<sup>38</sup> Metabolic complications are mild in both types, whereas patients with MADB are at risk of myopathy,<sup>39</sup> calcified skin nodules<sup>40</sup> and focal segmental glomerulosclerosis.<sup>41</sup>

*AKT2* (protein kinase B) is involved in the insulin signaling pathway, mediating adipocyte differentiation. Missense mutation in *AKT2* gene has been reported in only one family (four subjects) who presented with severe insulin resistance and partial distal lipodystrophy.<sup>42</sup>

*PIK3R1* encodes the 85KD regulator subunit of phosphatidylinositol 3 kinase, an enzyme playing a key role in insulin signaling. Missense mutation of *PIK3R1* gene is

related to SHORT syndrome<sup>43,44</sup> which manifests with short stature, hyperextensibility of the joints, ocular depression, Rieger anomaly, and teething delay. Patients present with partial lipoatrophy involving the face, arms and upper trunk, with lower extremities being spared. Severe insulin resistance is present, and the majority of cases develop diabetes mellitus after adolescence.<sup>45</sup> Recently, a mutation in *PRKCE* gene encoding protein kinase c epsilon, a protein involved in apoptosis and insulin signaling, was identified in a patient with clinical characteristics of SHORT syndrome but negative *PIK3R1* mutation.<sup>46</sup>

## Genes Involved in Lipid Droplet Formation and Lipolysis

This category of FPLD genetic causes includes the pathogenic variants in *CIDEA*, *PLIN1*, *LIPE*, *ADRA2A* and *CAVI*.

*CIDEA* encoded protein promotes the formation of unilocular lipid droplets by transferring lipids from the smaller to larger droplets.<sup>47</sup> Up to date, one case of partial lipodystrophy has been recognized as secondary to nonsense *CIDEA* mutation. The patient presented with lack of subcutaneous fat from the lower limbs and the femorogluteal region but preserved visceral and neck fat. Metabolically, insulin-resistant diabetes, hepatic steatosis, hypertriglyceridemia and hypertension were present. Fat biopsy revealed white adipocytes with multilocular lipid droplets.<sup>48</sup>

*PLIN1* is a structural protein of adipocyte lipid droplets, which also regulates lipolysis by controlling intracellular lipases.<sup>49</sup> Autosomal dominant frameshift mutations have been associated with FPLD type 4, a syndrome manifesting with lower limb lipoatrophy, facial acromegaloid features and muscular hypertrophy. All affected cases (eight families) share common metabolic characteristics, such as insulin resistance, hyperandrogenaemia, hypertension, hypertriglyceridemia and hepatic steatosis.<sup>50</sup> Recent work though by Laver et al<sup>51</sup> suggested that null variants of *PLIN1* are not related to overt lipodystrophy and should not be considered pathogenic. This observation suggests that only *PLIN1* variants with specific genetic mechanisms are associated with lipodystrophic syndromes.

*LIPE* encodes hormone-sensitive lipase, an enzyme highly expressed in adipose tissue responsible for hydrolyzing esters to free fatty acids. Mutations lead to dysmorphic and dysfunctional white adipocytes in FPLD type 6. Phenotypic manifestations include distal lipoatrophy with increased visceral fat depots and progressive

myopathy. Insulin resistance with dyslipidemia and hepatic steatosis is present, and vitiligo has also been described.<sup>52,53</sup>

*ADRA2A* is a non-adrenergic receptor regulating lipolysis in the adipocytes. Heterozygous mutations of the relevant gene have been described in one African-American pedigree. Affected individuals present with distal lipoatrophy and increased deposition of fat in the face and intraabdominal region. Increased muscularity is also present.<sup>54</sup>

*CAVI* gene encodes caveolin-1, a protein that serves in the formation of caveolae in plasma membranes. By binding fatty acids on the plasma membrane of the adipocyte and translocating them into lipid droplets, caveolin-1 appears to play a role in lipid droplet formation and adipocyte differentiation.<sup>55</sup> Homozygous and heterozygous *CAVI* variants cause CGL type3<sup>56</sup> and neonatal onset GL, respectively.<sup>57</sup> However, Cao et al also described three cases of different heterozygous *CAVI* mutations causing atypical partial lipodystrophy.<sup>58</sup> Patients had subcutaneous fat loss affecting the face and upper part of the body, hypertriglyceridemia and congenital cataracts with or without neurological findings.

## Cell Membrane Integrity-Related Genes

*PCYT1A* is involved in the phosphatidylcholine synthesis, a major component of all cell membranes. Phenotypic heterogeneity, depending on the affected protein domain, exists and patients can present with distal lipoatrophy, short stature, visual impairment due to cone-rod dystrophy and skeletal anomalies due to spondylometaphyseal dysplasia.<sup>59,60</sup>

Proteasome subunit beta type 8 (*PSMB8*) encodes a protein responsible for cell homeostasis and its deficiency leads to hypersecretion of interferons, cellular stress, inflammation and is linked to the Chronic Atypical Neutrophilic Dermatitis (CANDLE) syndrome (also known as JMP or Nakajo–Nishimura syndrome).<sup>61</sup> Up to date, more than 60 cases of this autosomal recessive syndrome have been described. Episodes of recurrent fever, with formation of cutaneous, erythematous, annular plaques present during the first months of life. Patients have typical facial characteristics with violaceous periorbital and periorcular oedema. Lipodystrophy begins in early childhood and follows a progressive pattern, primarily affecting the face, upper trunk and upper limbs. Other clinical features include arthralgia without arthritis, finger clubbing, joint contractures and cardiomyopathy. Lipodystrophy follows the development of autoimmune panniculitis and is attributed to the toxic effect of interferons on adipose tissue.<sup>62</sup>

## Genes Involved in DNA Repair

*WRN* encodes a helicase that plays an important role in repairing and maintaining the DNA structure.<sup>63</sup> Null mutations of *WRN* gene, inherited in an autosomal recessive way, are responsible for Werner syndrome. Patients typically develop normally until puberty when growth ceases resulting in short stature. Progeroid characteristics and distal lipoatrophy with truncal obesity develop in the late 20s. Patients develop premature cataracts, hypogonadism, osteoporosis, atherosclerosis and are at higher risk of malignancies. “Bird – like” facial appearance and Achilles tendon ulcerations are pathognomonic of the syndrome.<sup>64</sup>

*POLD1* encodes the catalytic subunit of the DNA polymerase delta, an enzyme responsible for DNA repair and stability. Mutations are related to MDPL syndrome, manifesting with mandibular hypoplasia, sensorineural deafness, progeroid features and acral lipoatrophy. Visceral fat depots are markedly increased. Other common characteristics include reduced muscle bulk in the limbs, hypogonadism, undescended testicles in males and poor breast development in females.<sup>65</sup>

*BLM* gene is responsible for the RecQ helicase production, a protein participating in the unwinding of the DNA helix. Autosomal recessive mutations in the *BLM* gene are related to the Bloom syndrome.<sup>66</sup> Patients present with pre and postpartum growth restriction, short stature, microcephaly and distal lipoatrophy. Photosensitivity and telangiectasia are also described. The syndrome is characterized by high mortality due to immune system deficiency leading to recurrent infections and increased cancer prevalence. Male sterility and female infertility due to early menopause are other features of the syndrome.<sup>67</sup>

## FPLD Type I (Köbberling-Type Lipodystrophy)

The syndrome described by *Köbberling* typically presents with distal lipoatrophy and increased facial, neck and visceral adiposity.<sup>68</sup> The hallmark diagnostic feature is the formation of a ledge between affected (lipodystrophic) and non-affected areas. Metabolic complications present in early adulthood and include insulin resistance, hypertriglyceridemia and NASH.<sup>69</sup> FPLD1 is commonly diagnosed on a clinical basis, mostly in female patients with limb lipoatrophy, central obesity and severe insulin resistance after exclusion of FPLD3 (*PPARG* mutations) which manifests a similar phenotype. It has recently been suggested that this phenotype has a strong polygenic contribution,

illustrating the contribution of common alleles to severe forms of insulin resistance.<sup>18</sup>

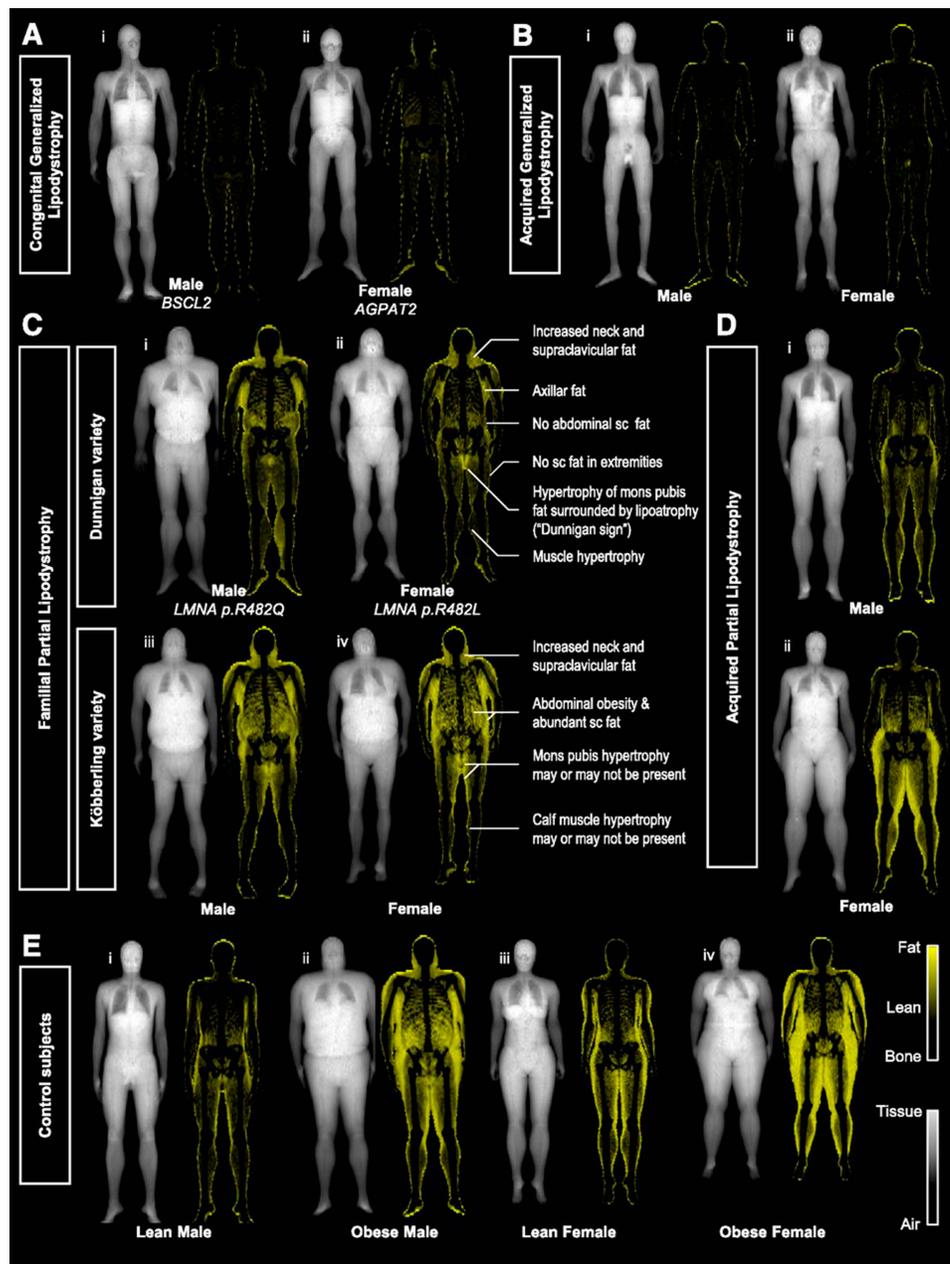
In conclusion, lipodystrophies despite being classified as monogenic disorders, exhibit great genetic, allelic and phenotypic variability ([Supplementary Table 1](#)).<sup>70</sup> Accumulating evidence suggests that patients’ phenotype is dictated not only by a given gene mutation but is also susceptible to genetic and environmental modifiers. Gender, race, coding and non-coding single nucleotide variants (SNVs) across the genome can alter expression of genes, leading to variable clinical features. Epigenetic (DNA methylation, histone modification) and environmental factors, such as nutrition, pregnancy and ageing, may also modulate gene expression.<sup>19</sup>

## Diagnosis

Clinical features of lipoatrophy with insulin resistance, dyslipidemia and hepatic steatosis should always pose lipodystrophy as part of the differential diagnosis. Information regarding the onset and severity of symptoms and family penetration is crucial in establishing the lipodystrophy subtype.<sup>4,71</sup> Thorough clinical examination may reveal abnormal topography of adipose tissue deposition, increased or prominent musculature, phlebomegaly and signs of insulin resistance such as acanthosis nigricans.

Anthropometry such as skinfold thickness and waist to hip ratio are also used to support the diagnosis. Objective measurements of adiposity (DXA and whole-body magnetic resonance imaging-MRI) provide information on the regional distribution of fat. Recently, Meral et al<sup>72</sup> described a simple method to diagnose lipodystrophic syndromes called “Fat Shadows”. Images derived from DXA scans are reconstructed in order to present adipose tissue as “shadow” ([Figure 2](#)). Radiological signs, such as the “Dunnigan sign” (hypertrophy of mons pubis fat surrounded by lipoatrophy), can be easily identified by this method allowing for early diagnosis of lipodystrophy subtypes.

Diagnosis of FPLD cannot be confirmed or excluded based on serum leptin levels, as these are widely variable. Furthermore, due to lack of specific reference data, quantification of adipocytokines (such as leptin or adiponectin levels in serum) is not currently recommended as a diagnostic tool. Genetic analysis including single or a panel of candidate gene sequencing or whole-exome/whole-genome sequencing is required to establish the diagnosis and to guide further screening and counseling although a negative result cannot exclude lipodystrophic syndromes.<sup>71</sup>



**Figure 2** “Fat shadows”: reconstructed DXA scan images using color-coded representation to highlight adipose tissue. Patients with **(A)** congenital type 2 (i) and type 1 (ii) and **(B)** acquired generalized lipodystrophy have minimal residual fat depots. Patients with **(C)** FPLD of the Dunnigan (i and ii), and Köbberling variety (iii and iv), present with lipoatrophy of subcutaneous fat and hypertrophy of adipose tissue in the neck and upper trunk. Identification of the “Dunnigan sign” is diagnostic of FPLD2. Patients with acquired partial lipodystrophy **(D)** have loss of fat from the upper extremities and truncal region with lower half depots being either normal (i) or hypertrophied (ii). **(E)** Lean (i and iii) and obese (ii and iv) control subjects present gender-specific fat distribution. American Diabetes Association. “Fat Shadows” From DXA for the Qualitative Assessment of Lipodystrophy: When a Picture Is Worth a Thousand Numbers, *Diabetes Care*, 2018. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.<sup>72</sup>

## Treatment

The management of patients with FPLD is challenging, and requires a multidisciplinary approach focusing on both prevention and therapy of metabolic complications as well as cosmetic interventions.<sup>71</sup> Lifestyle changes with diet modification and exercise are recommended. Patients should be advised to

follow a balanced diet containing approximately 50–60% of carbohydrates, 20–30% fat, and 20% protein.<sup>4</sup> Individualized dietary advice should be provided in patients with diabetes or severe hypertriglyceridemia. Overfeeding to achieve “catch up” growth or improved cosmetic appearances is strongly contraindicated as it may increase the risk of metabolic

complications. On the other hand, food restriction, which might be needed to manage hyperphagia and obesity, is quite challenging during puberty and adolescence and caloric intake should match the developmental needs. Patients with FPLD should also be encouraged to engage in physical activity; however, those predisposed or already suffering from structural heart disease should avoid strenuous exercise.

In terms of hyperglycemia management, insulin sensitizers are a useful treatment option in patients with FPLD. Metformin is the first-line therapy although some patients may require additional agents including insulin. Paradoxically, metformin was recently shown to increase insulin resistance in a patient with SHORT syndrome, but further studies are required to confirm these findings.<sup>73</sup>

Thiazolidinediones (TZDs), which are direct agonists of *PPAR* $\gamma$  receptors leading to improved insulin sensitivity and conversion of visceral to subcutaneous fat, have been used in FPLD with mixed results. Some studies have shown an improvement in metabolic markers,<sup>74</sup> such as hyperglycemia, dyslipidemia and hyperandrogenism, whilst others have demonstrated increased overall adiposity due to fat accumulation in non-lipoatrophic areas.<sup>75</sup> Different mutations in the ligand-binding domain of *PPAR* $\gamma$  may affect the binding capacity to synthetic ligands, thus affecting the responsiveness of different subtypes of lipodystrophy to TZD.<sup>76</sup> Cardiomyopathy, when present, restricts the use of these medications.

Insulin treatment might also be needed and in cases of severe insulin resistance, concentrated forms of insulin (U500) can be used. High doses and multiply daily injections, of even the concentrated forms, are required with not always satisfactory results on glycemic control.

The newer classes of hypoglycemic agents have also been used in patients with FPLD. The use of a combined intravenous glucose tolerance-euglycemic clamp in cases of FPLD revealed not only increased insulin resistance but also impaired first-phase insulin secretion.<sup>77</sup> In addition, Valerio et al<sup>78</sup> showed that the increased visceral adiposity characterizing FPLD is directly related to low dipeptidyl peptidase 4 (DPP4) levels. The above observations led researchers to investigate the role of glucagon-like peptide 1 receptor agonists (GLP1 Ras) in the management of overt diabetes in FPLD cases with promising results such as improvement of glycemic control and reduced insulin requirements.<sup>77,79</sup>

The sodium-glucose co-transporter 2 (*SGLT2*) inhibitors have an insulin-independent effect on glucose control and have been proven to be beneficial in cardiovascular and renal disease

in type 2 diabetes mellitus. Evidence from cases of congenital generalized lipodystrophy has showed that use of *SGLT2* inhibitors is associated with improvement in all metabolic markers and reduced incidence of cardiomyopathy.<sup>80</sup> Preliminary data in FPLD reveal an improvement in the metabolic profile and a reduction in total insulin requirements.<sup>81,82</sup> Further studies are however needed to confirm the clinical benefits of the newer diabetes treatments (GLP1 Ras, *SGLT2* inhibitors) in the management of FPLD.

Management of hypertriglyceridemia can be challenging and requires the combination of diet and pharmacologic treatment with fibrates and long-chain omega-3 fatty acids. Caution is advised when combinations of fibrates with statins are used in patients with coexisting myopathy. Volanesorsen, an inhibitor of hepatic Apolipoprotein C-III, has been found to significantly reduce triglycerides in cases of familial chylomicronaemia<sup>83</sup> and is currently under study in patients with FPLD and resistant hypertriglyceridemia in a randomized control trial (BROADEN study, Ionis Pharmaceuticals Inc., ClinicalTrials.gov Identifier: NCT02527343). Plasmapheresis might be needed in refractory cases to avoid pancreatitis.

Roux-en-Y surgery has been considered in cases of FPLD and refractory metabolic disease. The procedure has been successfully tried in cases of FPLD 1 and 2, associated with central adiposity, with promising results such as sustained weight loss, improvement of metabolic parameters and even withdrawal of insulin treatment.<sup>84,85</sup> The dramatic improvement in glycemic control has been attributed to reduced lipotoxicity as well as increased postprandial levels of GLP-1.<sup>86</sup>

Efficacy of cosmetic treatment has been predominantly studied in cases of acquired partial lipodystrophy. Procedures such as liposuction, gluteoplasty, breast implants, facial reconstruction and autologous fat transplantation have been tried with variable results in an effort to improve appearances and self-esteem in affected patients.<sup>87,88</sup>

Metreleptin, a recombinant analogue of human leptin, is the only specific therapy available for the management of human lipodystrophies.<sup>89,90</sup> The drug was approved in the US, in 2014 for patients with congenital or acquired generalized lipodystrophy and is also approved in Japan for the treatment of diabetes and/or hypertriglyceridemia in patients with congenital or acquired lipodystrophy (generalized or partial). In 2018, metreleptin was approved in the European Union, for adults and children aged  $\geq 2$  years with generalized lipodystrophy as well as for adults and children aged  $\geq 12$  years with partial lipodystrophy (familial or acquired) for whom standard treatments have not

achieved adequate metabolic control (<https://www.ema.europa.eu/en/medicines/human/EPAR/myalepta>).

Leptin's main role is to reflect energy reserves and regulate appetite by signaling the hypothalamus. In this regard, it was assumed that the beneficial effects of leptin replacement in patients with lipodystrophy arise from reduced caloric intake. However, Brown et al suggested that independent of food intake, metreleptin has an additional favorable metabolic effect due to an improvement of insulin sensitivity.<sup>91</sup> Recently though, Püschel et al<sup>92</sup> after studying four cases of FPLD treated with metreleptin for over 3 years, demonstrated improved satiety, reduced hunger and meal frequency in agreement with the results of an older study with a shorter duration of leptin treatment.<sup>93</sup> Metreleptin has been shown to improve atherogenic profile, HbA1c, serum triglycerides and hepatic steatosis in patients with acquired and congenital lipodystrophy (generalized or partial).<sup>89,94,95</sup> Long-term effectiveness and safety of metreleptin has been demonstrated in patients with FPLD due to both *PPARG* and *LMNA* pathogenic variants.<sup>96,97</sup> Interestingly, results suggest that those patients with more severe baseline metabolic characteristics benefit most from metreleptin treatment.<sup>98,99</sup>

The pleiotropic effects of leptin replacement therapy on the gonadal axis have been described in many studies. Patients with lipodystrophy demonstrate increased gonadotropic (luteinizing hormone; LH) secretion following metreleptin treatment.<sup>100</sup> Female patients present with increased fertility and menstrual cycle normalization<sup>100,101</sup> whereas testosterone levels increase in males.<sup>102</sup> Furthermore, metreleptin use improves urinary protein excretion in CGL but has no significant effect on proteinuria in patients with FPLD.<sup>103</sup> It should however be noted that experience is limited as proteinuria occurs less frequently in partial lipodystrophy and that the degree of proteinuria was less severe in patients with FPLD compared to CGL in the study by Lee et al.<sup>33,103</sup> Patients with FPLD suffer social stigma with devastating effects on their psychology and self-esteem. In one of the largest cohorts studied up to date, patients treated with metreleptin for over a year experienced improvement in their appearance which had a positive impact on their self-perception.<sup>104</sup> Metreleptin is given subcutaneously, by once-daily injections and when body weight is >40kg, the initial dose in females is 5mg and in males 2.5 mg. The dose is adjusted according to the clinical response.

Treatment with metreleptin is generally well tolerated but poor adherence therapy is noted in up to 30% of the cases.<sup>104</sup> Injection site reactions due to lipoatrophy and the daily

reconstitution from the powder form have been described as the main contributing factors. Hypoglycemia secondary to reduced insulin requirements, after treatment initiation, has also been described. Paradoxical worsening of hyperphagia and adverse metabolism in metreleptin treated patients have been attributed to the development of neutralizing antibodies. At the same time, whereas the majority of metreleptin treated patients develop antibodies, only a small number will develop neutralizing activity.<sup>105</sup> Lymphoma development has been described in very few patients with acquired lipodystrophy who received metreleptin therapy, although this may be attributed to pre-existing immunodeficiency rather than to metreleptin use.<sup>71,89,106</sup>

Currently, investigational trials for new therapeutic agents are underway.<sup>89</sup> Results regarding the efficacy of lipid-lowering agents such as gemcabene (dialkyl ether dicarboxylic acid) and evinacumab (monoclonal antibody to ANGPTL3) as well as anorexigenic hormones modulators (setmelanotide – melanocortin receptor agonist) in the management of FPLD are highly anticipated.

## Conclusion

FPLD is a group of genetic disorders affecting predominantly adipogenesis, lipid droplet structure and function leading to altered adipose tissue topography. The altered storing capacity and endocrine function of affected adipocytes result into insulin resistance and ectopic fat accumulation with severe metabolic complications. Raised awareness amongst clinicians will lead to early diagnosis of the syndrome and management of comorbidities. In this regard, recently acquired knowledge on the genetics and the effectiveness of new treatment modalities will dictate new diagnostic and therapeutic strategies for these rare metabolic diseases.

## Abbreviations

CGL, congenital generalized lipodystrophy; DPP4, dipeptidyl peptidase 4; DXA, dual-energy absorptiometry; FPLD, familial partial lipodystrophy; GLP-1, glucagon-like peptide 1 receptor agonists; GWAS, genome-wide association studies; HbA1c, hemoglobin A1c; LH, luteinizing hormone; MAD, mandibuloacral dysplasia; MRI, magnetic resonance imaging; NASH, non-alcoholic steatohepatitis; PCOS, polycystic ovarian syndrome; PCYT1A, phosphate cytidyltransferase 1A; PIK3R1, phosphatidylinositol 3 kinase regulatory subunit; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$ ; PSMB8, proteasome subunit beta type 8; SGLT2, sodium-glucose co-transporter 2; SNVs, single nucleotide variants;

TZDs, thiazolidinediones; ZMPSTE24, zinc metalloproteinase STE24.

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