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# Lipodystrophy - A Rare Condition with Serious Metabolic Abnormalities

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## Abstract

Lipodystrophy is a rare lipid storage disorder that is characterized by a loss of adipose tissue. It can be inherited due to monogenic mutation or acquired by medication and autoimmune illness. Two primary forms of inherited lipodystrophy are congenital generalized lipodystrophy manifested as a near-complete loss of fat tissue since birth and familial partial lipodystrophy with progressive, partial loss of fat tissue during late childhood and puberty. Lipodystrophy results in severe metabolic conditions, including insulin resistance, type 2 diabetes, hepatosteatosi, polycystic ovary syndrome, acanthosis nigricans, and hypertension. This chapter summarizes the symptoms, causes, and treatments of inherited and acquired lipodystrophy.

**Keywords:** adipose tissue, adipogenesis, metabolic syndrome, lipid disorders, ectopic lipid

## 1. Introduction

In order to survive and adapt to challenging environment, living organisms have equipped themselves with different mechanisms of energy storage that can be accessed when there is a shortage of food supply. In mammals, fat is mainly stored in adipose tissues [1]. There are two types of adipose tissues: white adipose tissue that stores the majority of the body fat and also functions as an endocrine organ and brown adipose tissue that generates the body heat [2]. In adipocytes, fat is stored in lipid droplets (LDs) in the form of neutral lipids, e.g., triacylglycerol (TAG) and cholesteryl ester (CE). White adipocytes contain unilocular LDs that occupy up to 90% of the cytoplasmic space, while brown adipocytes contain multilocular LDs. Obesity is characterized by both increase in the size and number of white adipocytes [3]. Fat storage in white adipose tissue is essential for proper metabolic homeostasis [4]. In contrast, when fat storage in white adipose tissue is compromised or overwhelmed, the ectopic fat accumulation in non-adipose tissues will result in severe metabolic disorders [5].

Lipodystrophy is an extreme fat storage condition, in which white adipose tissue is selectively lost [6]. Partial or generalized loss of fat in this condition causes an array of complications including insulin resistance, type 2 diabetes and acanthosis nigricans, hypertriglyceridemia, hepatic steatosis, hypertension, polycystic ovarian syndrome, and proteinuric kidney disease [7, 8]. The severity of lipodystrophy depends on the level of adipocyte depletion in the body. Fat loss can occur in nearly

the entire body known as congenital generalized lipodystrophy (CGL) or partial loss in small and discrete areas known as familial partial lipodystrophy (FPLD). While CGL is manifested early in life at birth or soon after, partial fat loss in FPLD occurs during late childhood and puberty. CGL can be determined by measurements of skinfold thickness with calipers or by whole-body magnetic resonance imaging (MRI) scan [9]. Since lipodystrophy is a monogenetic disorder, it can also be diagnosed and confirmed by genotyping.

Lipodystrophy is a very rare genetic disease (1 in 10 million for CGL). Currently, there have been around 300–500 CGL cases and 1000 FPLD cases reported; however, the number of undiagnosed patients is suspected to be three times more [10]. Nearly 20 loci for different subtypes of lipodystrophy have been identified. These genes are implicated in the regulation of either the development of white adipose tissue or the expansion of LDs in white adipocytes. In this chapter, we will outline these lipodystrophy-causative gene loci as well as describe in brief the acquired condition of lipodystrophy.

## 2. Genetics of congenital generalized lipodystrophy

There are four different genetic subtypes of CGL that result from different mutations.

### 2.1 Type 1 CGL (CGL1) and AGPAT2

Mutations that are responsible for CGL1 (Online Mendelian Inheritance in Man [OMIM] #608594) occur in the region of 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*) on chromosome 9q34. Only 4% of compound heterozygotes with a null and a missense mutation still maintain some residual enzymatic activity [7]. Also, homozygous missense mutations have been reported to be 2% of CGL1 patients. Interestingly, there is no strong correlation between the type of mutation and lipodystrophy phenotype (the level of adipocyte malfunction) [7, 11]. On the contrary, a founder mutation variant might exist in a particular population [11]. In fact, almost all patients that have African origin have the founder mutation in intron 4, c589-2A>G of one or both alleles [7, 12]. In the past 5 years, several novel variants of *AGPAT2* have been identified in CGL patients: c.144C>A, c.667\_705delinsCTGCG, c.268delC, and c.316+1G>T; c.134C>A and c.216C>G [13]; c.514G>A [14]; c.685G>T, and c.514G>A [15]. In addition, a very rare case of dual mutations (c.493-1G>C and c.299G>A) in *AGPAT2* was identified in two Chilean sisters [16].

*AGPAT2* is a member of lysophosphatidic acid acyltransferases (LPAATs) including *AGPAT* family (*AGPAT1*–*AGPAT11*) and others such as CGI-58 and endophilin [17]. In fact, *AGPAT2* was identified with *AGPAT1* by searching an EST database for human homologs of yeast LPAAT in 1997 [18]. There are 11 isoforms of *AGPATs* that are involved in the de novo synthesis of phospholipids (PLs) and triacylglycerol from glycerol-3-phosphate (G3P). *AGPAT2* is predominantly expressed in adipose tissue, and its mRNA level increases by 30-fold during the differentiation of adipocytes [19]. Patients with CGL1 normally suffer extreme loss of all metabolically active adipose tissue in most subcutaneous areas, intra-abdominal areas, intrathoracic regions, and bone marrow; however, it is postulated that the redundancy of other *AGPAT* isoforms or the enhanced expression of other *AGPAT* genes helps preserve mechanical fat depots located in the palms, soles, under the scalp, retro-orbital, periarticular regions, perineum, vulva, and pericalyceal regions of the kidneys [7, 20].

In adipose tissue, the synthesis of PLs and TAG begins with the acylation of G3P with FA-CoA by glycerol phosphate acyltransferase (GPAT) at the S<sub>N</sub>1 position to form 1-acylglycerol-3-phosphate or lysophosphatidic acid (LPA). Then AGPAT2 catalyzes the conversion of LPA into phosphatidic acid (PA) via an acylation reaction at the S<sub>N</sub>2 position. PA is a pivotal intracellular signaling lipid for it sits at the branching point of de novo PL and TAG synthesis pathway and acts as a precursor for the lipin-mediated production of diacylglycerol (DAG), followed by phosphatidylcholine (PC), phosphatidylethanolamine (PE), and TAG, and as the substrate for the cytidine diphosphate synthase (CDS)-mediated generation of cytidine diphosphate diacylglycerol (CDP-DAG), followed by phosphatidylinositol (PI), phosphatidylglycerol (PG), and cardiolipin [21]. PA is a cone-shaped lipid that has the capacity to alter the curvature of the membranes, and it has been shown to mediate membrane fusion in both soluble N-ethylmaleimide-sensitive factor attachment protein (NSF)-receptor (SNARE)-dependent and SNARE-independent fashions [22, 23]. It has been implicated in the fusion of multiple LDs to form a gigantic LD [24]. In addition, PA is believed to be an endogenous antagonist of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) that is the master transcription factor in adipocyte differentiation [25]. The malfunctioned AGPAT2 in CGL1 is assumed to cause dysregulated PL and TAG synthesis, leading to defective adipose tissue development [11, 19]. However, the exact mechanism of how AGPAT2 deficiency causes lipodystrophy remains unraveled. Intriguingly, the same effect cannot be achieved by knocking out other key enzymes in the TAG synthesis including glycerol-3-phosphate acyltransferase 1 (GPAT1), GPAT4, lipin, and diacylglycerol acyltransferase 1 (DGAT1) and DGAT2 [26–30].

Ablation of *Agpat2* induces severe lipodystrophy in mice with the loss of both WAT and BAT during the first week of postnatal period, due to inflammatory infiltration to adipose tissue and massive adipocyte cell death [31]. In addition, both male and female mice have extreme insulin resistance, type 2 diabetes, hepatic steatosis, as well as organomegaly including hepatosplenomegaly, nephromegaly, and elongated small intestines as seen in human CGL [32]. Since almost all adipose tissues have disappeared, *Agpat2*<sup>-/-</sup> mice are not an ideal model to study the development of lipodystrophy; however, this type of animals can be particularly useful for the investigation of lipodystrophy-induced metabolic disorders in non-adipose tissues such as severe hepatic insulin resistance and steatosis in CGL [20]. Up to 90% of the total AGPAT activity is compromised in the liver tissue of *Agpat2*<sup>-/-</sup> mice and that can be restored by adenoviral delivery of *Agpat1* or *Agpat2*. However, overexpression of *Agpat1* or *Agpat2* in *Agpat2*<sup>-/-</sup> liver failed to alleviate hepatic steatosis, indicating that the ectopic hepatic lipid accumulation was derived from insulin resistance and loss of body fat [33]. While reduced AGPAT activity is supposed to result in a reduction in PA synthesis, the PA level was seen to increase in the liver of male *Agpat2*<sup>-/-</sup> mice, which suggests an alternative pathway for PA synthesis with a compensatory activation of DAG kinase or phospholipase D [32, 34]. A high level of PA predisposes *Agpat2*<sup>-/-</sup> liver to elevated hepatic glucose production, which is attributed to insulin resistance [34]. PA accumulation was also found in differentiated *Agpat2*<sup>-/-</sup> murine embryonic fibroblast (MEF) adipocytes [31]. At day 6 of the differentiation, ultrastructural alterations in mitochondria, plasma membrane, and autophagosomes were found in *Agpat2*<sup>-/-</sup> MEF adipocytes, suggesting that in the absence of AGPAT2, cells can initiate adipogenesis, but a variety of cellular abnormalities eventually block the terminal phase of adipogenesis [31]. Enforcing adipocyte differentiation by overexpression of PPAR $\gamma$ , the master regulator of adipogenesis can also promote adipogenesis of *Agpat2*<sup>-/-</sup> MEFs; nevertheless, massive cell death occurred before they reached full differentiation [31]. In agreement with



this finding, preadipocytes from *Agpat2*<sup>-/-</sup> interscapular BAT underwent progressive cell death during the adipogenic induction with no activation of caspase 3 [35].

In addition, these BAT-derived preadipocytes exhibit an increased expression of autophagy-related proteins but a decreased autophagic flux [35]. In isolated muscle-derived multipotent cells (MDMCs) from CGL1 patients and 3T3-L1 preadipocyte cells with the knockdown of AGPAT2, cell death also proceeds during adipogenesis, which might be associated with defective Akt activation as a result of altered PI composition [36, 37]. The constitutively active Akt and PPAR $\gamma$  agonist pioglitazone partially rescued the adipogenic defect in the *Agpat2*<sup>-/-</sup> cells [37]. In addition, regarded as a therapy for CGL patients, leptin treatment normalizes the levels of plasma TAG, insulin, and glucose as well as improves hepatic steatosis in *Agpat2*<sup>-/-</sup> mice, which is independent of hepatic leptin receptor [38]. The role of AGPAT2 in LD biology has been rarely reported. In contrast to WT adipose tissue that manifests large unilocular LDs, *Agpat2*<sup>-/-</sup> adipocytes are featured by smaller multilocular LDs. Although LDs in *Agpat2*<sup>-/-</sup> MEFs are smaller than *Agpat2*<sup>+/+</sup> cells, they are still normally coated with perilipin 1 (Plin1) [31].

## 2.2 Type 2 CGL (CGL2) and SEIPIN

In CGL2 (OMIM #269700), mutations happen in the *BSCL2* gene located on chromosome 11q13. The *BSCL2* gene encodes Seipin. Null mutations found in CGL2 patients occupy approximately 75% of all mutations in the *BSCL2* gene, and the rest are missense mutations [39]. Phenotypically, there are no significant differences between patients with null and missense mutations. However, mutagenic truncated forms of Seipin fail to bind lipin-1, while missense mutants still preserve this type of interaction. Although CGL2 affects a diverse range of people from Europe, Mediterranean and Middle Eastern Arabs, and Japanese, patients that have Lebanese origin share a common homozygous *BSCL2* mutation of c.315\_319delGTATC (p. Tyr106Cysfs\*6) [20, 40].

Unlike patients with CGL1, patients with CGL2 suffer a near-total loss of both metabolically active and mechanical adipose tissues [41]. In addition, these patients have significantly low median serum levels of leptin (0.01 ng/ml) and adiponectin (3.3  $\mu$ g/ml) as compared to normal healthy individuals who had median serum levels of 4.6 ng/ml and 7.8  $\mu$ g/ml for leptin and adiponectin, respectively [42]. Also, they suffer cardiomyopathy and mild mental retardation in a more prevalent way [7, 8, 43]. One single patient with CGL2 has been reported to have teratozoospermia, a condition characterized by sperm defects including abnormalities in sperm morphology and bundled sperm with two or more sperms joined together by large ectopic LDs [44]. Additionally, three patients in a family from Pakistan with *BSCL2* mutations have been reported to suffer spastic gait, a movement-related complication due to upper motor neuron [45]. While null mutations in *BSCL2* can also result in early-onset, fatal neurodegenerative syndrome as reported in four patients, gain-of-function heterozygous *BSCL2* mutations located in the N-glycosylation motif causes distal hereditary motor neuropathy [46].

SEIPIN is a 398 amino acid transmembrane protein in the endoplasmic reticulum (ER), which regulates the transport of macromolecules including proteins and lipids between the ER and the LD [47]. Therefore, it plays a role as a docking protein to regulate LD biogenesis and adipogenesis [48, 49]. Seipin, an integral ER membrane, participates in lipid homeostasis via various complex mechanisms. One of them is to assist LD assembly and fusion as well as adipocyte differentiation [50]. In fact, SEIPIN deficiency in mammals or its yeast ortholog Fld1p/Sei1p can lead to changes in LD morphology, manifested as clustering of multiple small LDs or supersized LDs [5]. Recently, SEIPIN/Fld1p has been found to be stabilized to

ER-LD contacts to assist the protein and lipid trafficking into growing LDs. SEIPIN strengthens the contact site between ER and LD to regulate the growth of immature LDs [51]. The protein might also be involved in PL and TAG synthesis by its binding and interaction with phosphatidic acid phosphatase lipin-1 and AGPAT2 [52, 53].

*Bscl2*<sup>-/-</sup> mice manifest complete loss of WAT and have most metabolic complications including hyperinsulinemia, insulin resistance, and hepatic steatosis [54–56]. These animals have low plasma levels of glucose and TAG compared to their wild-type (WT) counterparts but have postprandial hypertriglyceridemia [54, 57]. Insulin signaling in the liver of *Bscl2*<sup>-/-</sup> mice was diminished after 4 h of fasting but improved after 16 h [57]. Knocking out *Bscl2* specifically in adipose tissue causes the mice to have an adipocyte hypertrophy with enlarged LDs, reduced lipolysis, adipose tissue inflammation, progressive loss of both WAT and BAT, insulin resistance, and hepatic steatosis [40].

*Bscl2*<sup>-/-</sup> MEFs and stromal vascular cells failed to differentiate due to uncontrolled lipolysis activated by cyclic AMP (cAMP)-dependent protein kinase A (PKA) [55, 58]. It causes loss of LDs and subsequently impaired adipogenesis by silencing the expression of adipose-specific transcription factors. This loss of function can be rescued by inhibitors of lipolysis but not by a PPAR $\gamma$  agonist. Thiazolidinediones, antidiabetic drugs, are able to restore adipogenesis but unable to intervene the unbridled lipolysis happening in *Bscl2*<sup>-/-</sup> MEFs [56]. Interestingly, LDs in lymphoblastoid cell lines have been reported to have an increase in numbers but shrinkage in size from 12 patients with CGL2 with null *BSCL2* mutations [59]. In addition, it has been observed that there is a shift in the proportion of monounsaturated fatty acids to saturated fatty acids in hepatic triglycerides and phosphatidylethanolamine, implicating a defect in acyl-CoA desaturase activity in these cell lines [59].

### 2.3 Type 3 CGL (CGL3) and CAV1

CGL3 (OMIM #612526) is induced by mutations in the *CAV1* gene located on chromosome 7q31. The *CAV1* gene encodes caveolin-1. Kim et al. first described a CGL3 patient from Brazil who has a homozygous “loss of function” mutation at p.E38X in the *CAV1* gene [60]. This patient possesses generalized lipodystrophy with near-total loss of metabolically active adipose tissue but preserves mechanical adipose tissue and fat in the bone marrow. She also manifests acanthosis nigricans, severe hypertriglyceridemia, hepatic steatosis and splenomegaly, short stature, functional megaesophagus, hypocalcaemia, primary amenorrhea, and chronic diarrhea. She also developed diabetes mellitus at age 13 [60]. Almost at the same time, Cao et al. reported a case of a typical partial lipodystrophy caused by heterozygous frame-shift mutation in *CAV1*, designated I134 fsdelA-X137 and –88deltaC [61]. This female patient has subcutaneous fat loss in the upper part of her body and face but spared her legs, gluteal region, and visceral fat stores [61]. Since 2015, two novel variants of *CAV1* have been identified: de novo heterozygous null mutations, c.424C>T (p.Q142X) and c.479\_480delTT (p.F160X) in a 7-year-old male and a 3-year-old female of European origin, respectively [62]. Both of the patients have generalized fat loss, thin mottled skin, and progeroid features at birth [62]. The male patient has cataracts requiring extraction at 30 months of age, and the female patient has pulmonary arterial hypertension [62–64].

Caveolin-1 is the scaffolding protein primarily constituting specialized vesicular invaginations of 50–100 nm called caveolae [1, 36]. It was discovered by Anderson Lab in 1992 [65, 66]. Its potential function in vesicle transport was reported by Glenney using cDNA encoding caveolin-1 from lungs [67]. There are three caveolin isoforms: CAV1, CAV2, and CAV3. While CAV3 is muscle specific, CAV1 and CAV2

are predominantly expressed in adipose tissue, endothelial cells, and fibroblasts [68, 69]. As the main component of caveolae, caveolin-1 plays an essential role in the caveolae assembly alongside with other caveolar proteins, such as cavin1–cavin4, Pacsin2, and EH domain-containing 2 (EHD2) [70]. In addition to its essential role in caveolae formation, caveolin-1 is also a key determinant of normal lipid homeostasis, vesicular trafficking, and signaling transduction [71]. Caveolae plays a regulatory role in maintaining the integrity and function of the LDs as well as binding and transporting fatty acids and cholesterol by budding off the plasma membrane [70]. Moreover, they serve as a platform for augmenting insulin and PKA signaling [72]. In adipocyte cells, the expression of caveolin-1 is increased 10-fold during adipogenesis [73, 74]. The abundance level of caveolin-1 determines the PL and surface protein composition in LDs and the LD growth. In fact, the expression of *Cav1* in adipose cell lines and mice leads to an increase in the density of caveolae and enhances adipocytes' capacity to have larger LDs and promote cell growth through increased glucose utilization [75].

Similar to caveolin-1 deficiency, lacking another caveolar protein cavin-1 in humans also causes another type of congenital generalized lipodystrophy (type 4 CGL) [76–78]. Interestingly, subcutaneous injection of caveolin-1 overexpressed preadipocytes could form fat pads and larger adipocytes [75]. Both caveolin-1 and cavin-1 are the strong indicators of adipogenic differentiation in human tumors and liposarcoma [79]. Taken together, these data indicate the critical role of adipocyte caveolae in adipose tissue development.

*Cav1*<sup>−/−</sup> mice show complete loss of morphologically identifiable caveolae in endothelial and adipose tissue [74]. Likewise, primary cells derived from *Cav1*<sup>−/−</sup> MEFs fall short of functional caveolae [74]. *Cav1*<sup>−/−</sup> mice have dramatically smaller fat pads, reduced adipocyte size, and poorly differentiated white adipose parenchyma than their WT littermates [80]. While the animals are hyperphagic, they are resistant to diet-induced obesity [20, 81]. Their BAT undergoes hypertrophy [80, 82].

## 2.4 Type 4 CGL (CGL4) and PTRF

CGL4 (OMIM #613327) is an autosomal recessive condition caused by mutations in the *PTRF* gene that is located on chromosome 17q21. *PTRF* gene encodes cavin-1 protein. The coincidence of generalized lipodystrophy and muscular dystrophy was found in some Omani patients as early as 2002 [83, 84]; however, the genetic basis underlies this new subtype of generalized lipodystrophy was not identified until 2009 [85]. CGL4 patients normally do not have severe lipodystrophy at birth but gradually develop progressive fat loss from infancy or early childhood [85]. Similar to CGL3, CGL4 subjects lose metabolically active adipose tissue but preserve mechanical adipose tissue and fat in bone marrow [83]. In contrast to the “classic” lipodystrophies, CGL4 is comprising congenital myopathy with high circulating creatine kinase, smooth and skeletal muscle hypertrophy, cardiac arrhythmias, osteopenia, distal metaphyseal deformation with joint stiffness, pyloric stenosis, atlantoaxial instability, as well as percussion-induced muscle mounding and local protracted muscle contractions [78, 83, 86, 87]. Since 2013, a few homozygous *PTRF* mutations identified in CGL4 patients have been reported: c.259C>T (p.Gln87\*) and c.481–c.482insGTGA (p.Lys161Serfs\*41) in two female Turkish teenagers [43, 88]; c.176A>T (p.Asp59Val) and c.471G>C (p.Gln157Hisfs\*52) in patients from Switzerland and Egypt, respectively [89]; c.550G>T (p.Glu184\*) in a Saudi family [90]; c.947delA in child of Moroccan origin [76]; and c.696\_697insC in a Japanese boy [91].

As mentioned before, cavin-1 interacts with caveolin proteins to form caveolae and to mediate cellular trafficking and lipid turnover [70, 85]. Cavin-1 can stabilize



caveolae and caveolin proteins probably via its interactions with cytoskeleton [20]. In agreement with this finding, *Ptrf*<sup>-/-</sup> mice do not possess morphologically detectable caveolae and exhibit dramatically impaired expression of all three caveolin isoforms [92]. Specifically, cavin-1 colocalizes with caveolin-1 in adipocytes [93]. Paradoxically, it is believed that PTRF deficiency, as seen with loss of *CAV1*, causes generalized lipodystrophy due to the defects in caveolar formation [1, 20]. Recently, Liu and Pilch have demonstrated that the insulin-induced phosphorylation of cavin-1 results in its translocation to the nucleus where it regulates ribosomal transcription [94]. Primary and cultured cavin-1-deficient adipocytes have much lower levels of ribosomal RNA and proteins, resulting in ribosomal stress, which in turn leads to fat loss over time. This caveolae-independent cavin-1 function provides a novel explanation to CGL4 phenotype [95]. *PTRF* also serves as a terminator transcription factor via its interactions with both the thyroid transcription factor 1 (TTF-1) and RNA polymerase 1. cDNA cloning and functional characterization were initially reported by Jansa et al. in 1998 [94].

*Ptrf*<sup>-/-</sup> mice are viable with no overt change in body weight; nonetheless, they exhibit considerably reduced adipose tissue mass, high circulating triglyceride levels, glucose intolerance, and hyperinsulinemia, phenocopying lipodystrophy as seen in humans [92]. Notably, there is no morphologically detectable caveolae in *Ptrf*<sup>-/-</sup> mice, due to the absence of cavin-1 protein [85, 92]. Epididymal white adipocytes from *Ptrf*<sup>-/-</sup> mice were smaller as the result of reduced triglyceride accumulation due to decreased fatty acid uptake and incorporation [92]. In addition, they are insensitive to insulin; as a result, lacked insulin-stimulated glucose transport [96]. Both *Cav1*<sup>-/-</sup> and *Ptrf*<sup>-/-</sup> white adipocytes are resistant to lipolytic stimulation due to impaired perilipin phosphorylation [72, 96]. Much as *Ptrf*<sup>-/-</sup> mice are resistant to diet-induced obesity as seen in *cav1*<sup>-/-</sup> mice, BAT and liver exhibited abnormal lipid metabolism [96].

### 3. Familial partial dystrophy

#### 3.1 Type 1 FPLD (FPLD1)

Type 1 FPLD (OMIM #608600), also known as Köbberling-type lipodystrophy, was first reported by Köbberling et al. in 1971 [97]. The syndrome manifests loss of subcutaneous fat in the extremities and gluteus, with normal or increased fat deposition in the face, neck, and trunk [97]. The ratio of skin thickness from the abdomen to the thigh is significantly higher in these subjects, which can be used as a diagnostic method [98]. Diabetes and other metabolic complications including hypertension, insulin resistance, and severe hypertriglyceridemia develop during adulthood, with higher severity in women than men [98, 99]. Similar to other types of lipodystrophy, FPLD1 is an extremely rare genetic condition whose chance of occurrence is 1 in 15 million [6, 36]. Unfortunately, the causative loci for FPLD1 have not been identified to unravel the underlying genetic mechanism of the syndrome.

#### 3.2 Type 2 FPLD (FPLD2) and LMNA

FPLD2 (OMIM #151660) is an autosomal dominant condition that is caused by heterozygous mutations in the *LMNA* gene located on chromosome 1q21–1q22. In contrast to FPLD1 patients who preserve trunk fat, FPLD2 subjects suffer variable and progressive fat loss from the anterior abdomen and chest that occurs after the gradual loss of subcutaneous fat in extremities [6]. Accompanying the loss of



subcutaneous fat is the accumulation of intramuscular (in limbs) and intra-abdominal fat [100]. Despite the similar pattern of fat loss in men and women, women are more prone to develop diabetes, dyslipidemia, and cardiovascular diseases [99].

Most cases of FPLD2 are caused by mutations in the lamin A/lamin C (*LMNA*) gene at the codon position 482 in exon 8 with a variety of mutations, such as p.R482W, p.R482Q, and p.R482L [101, 102]. Subsequently, many more missense mutations in *LMNA* have been reported including p.D230N, p.R399C, p.R439C, p.G465D, p.R471G, p.P485R, p.K486 N, and p.H506D [6, 103, 104]. In the past 3 years, several novel variants of *LMNA* have been identified such as c.1634G>A (p.R545H) [105], c.1001\_1003delGCC (p.S334del) [106], c.175C>CG (p.L59 V) [107], c.683A>T (p.E228V) [108], c.139G>A (p. D47N) [109], and c.1543A>G (p.K515E) [110]. Notably, mandibuloacral dysplasia type A (MADA), an autosomal recessive disorder, is also caused by homozygous mutations of the *LMNA* gene. Although MADA is a form of lipodystrophy, it is distinctive from FPLD2 [101].

The *LMNA* gene encodes proteins lamin A and lamin C in the nuclear lamina [102]. The lamin proteins have been shown to be able to interact with and affect other regulatory proteins such as chromatin and transcription factors [101]. Therefore, any defects in this structural protein might disrupt the formation and integrity of the nuclear envelope, leading to premature cell death in many tissues, including adipocytes [6, 12]. Recently, lamin A and lamin C have been shown to interact with sterol response element-binding protein 1 (SREBP1), a transcription factor for genes involved in lipid metabolism and adipocyte differentiation [111]. Interestingly, the overexpression of the R482W mutation in primary human preadipocytes and endogenous expression of A-type lamins R482W in fibroblasts of FPLD2 patient fibroblasts impaired the interaction with SREBP1 and thus upregulate many SREBP1target genes [112]. This implies overexpression of SREBP1might lead to the inhibition of adipogenic in FPLD2, which opens a window of SREBP1-targeting therapies against FPLD2 [112].

*Lmna*<sup>-/-</sup> mice have been employed to study dilated cardiomyopathy and muscular dystrophy [113]. In both WAT and BAT of *Lmna*<sup>-/-</sup> mice, rapamycin inhibits mTORC1 but not mTORC2, leading to the suppression of lipolysis and the restoration of thermogenic uncoupling protein 1 (UCP1) levels, respectively. It indicates that altered mTOR signaling in *Lmna*<sup>-/-</sup> mice contributes to lipodystrophic phenotype that can be rescued with rapamycin [113].

Lamin A is matured from pre-lamin A via multiple-step posttranslational modifications [114]. This process involves a cleavage reaction carried out by an endoplasmic reticulum membrane protease full name ZMPSTE24 located on chromosome 1p34 [115]. Mutations in ZMPSTE24 have been shown to cause mandibuloacral dysplasia type B and autosomal-dominant FPLD2, due to the lack of functional lamin A [116]. Nonetheless, the question as to whether there is an accumulation of pre-lamin A remains controversial. On the one hand, using lamin A/lamin C antibodies and pre-lamin A-specific monoclonal antibodies, one recent study has shown that fibroblasts carrying lipodystrophy-related *LMNA* mutations (R482W, I299V, C591F, T528 M) do not exhibit an accumulation of pre-lamin A as compared with their WT counterpart [117]. On the other hand, one prior study has demonstrated that the pre-lamin A level is upregulated in *zmpste24*<sup>-/-</sup> mice [117].

### 3.3 Type 3 FPLD (FPLD3) and PPRAG

FPLD3 (OMIM #151660) is caused by mutations in the *PPRAG* gene on chromosome 3p25. The *PPRAG* gene encodes PPAR $\gamma$ , a nuclear hormone receptor involved in glucose metabolism, adipocyte differentiation, inflammation, and carcinogenesis [118–126]. Importantly, PPAR $\gamma$  is the master transcription factor that governs 60% of genes involved in adipogenesis [127]. Differential RNA splicing along with alternative

PPAR $\gamma$  gives rise to different isoforms of PPAR $\gamma$ . While PPAR $\gamma$  1 and PPAR $\gamma$  3 are ubiquitously expressed in most differentiated cells, PPAR $\gamma$  2 and PPAR $\gamma$  4 are strictly found in adipose tissue [126]. PPAR $\gamma$  has three functional domains: a ligand-binding domain (LBD), a DNA-binding domain (DBD), and an A/B domain [126]. Mutations in the PPAR $\gamma$  gene that lead to FPLD have been reported since 1999, mainly in the LBD and DBD [121, 126]. These mutations cause either haploinsufficiency or dysfunction in the normal receptor protein. It has been found that four out of seven mutations in the LBD result in reduced PPAR $\gamma$  activity [118]. For the mutations in the DBD, three out of six cause dysfunction in the wild-type protein [122]. In some cases, loss of function mutations in one of the alleles is also able to induce FPLD3 [126]. A D424N mutation found in two FPLD3 patients in the LBD leads to the downregulation of PPAR $\gamma$ -related transcriptional activity [124]. This loss-of-function effect can be rescued and corrected by the PPAR $\gamma$  agonist rosiglitazone [122]. In fact, treatment with 1  $\mu$ mol/l or 10  $\mu$ mol/l of rosiglitazone is able to normalize transcriptional activity of D424N PPAR $\gamma$  [126].

FPLD3 patients with PPAR $\gamma$ -induced FPLD suffer metabolic disorders including hypertriglyceridemia, insulin resistance with raised serum triglyceride and cholesterol levels and raised aminotransferase, and  $\gamma$ -glutamyltranspeptidase activities as well as manifest the symptoms of FPLD including subcutaneous fat loss from the arms, muscular hypertrophy in the legs, and arterial hypertension while having the subcutaneous fat buildup in the face, chin, trunk, and abdomen [128].

### 3.4 Type 4 FPLD (FPLD4) and PLIN1

It has been reported that null mutations in the *PLIN1* gene causes FPLD4 (OMIM #613877). *PLIN1* encodes perilipin 1 which is found in adipocytes as a LD surface protein [129]. Dysfunction of this protein is likely to cause FPLD4 via in the regulation of LDs and reduced fat mass [130]. However, a latest study using targeted next-generation sequencing of the *PLIN1* gene from 2208 individuals has revealed that haploinsufficiency in *PLIN1* does not result in FPLD [107].

### 3.5 Type 5 FPLD (FPLD5) and CIDEC

The rare FPLD5 (OMIM #615238) is caused by a homozygous nonsense mutation in the LD protein cell death-inducing Dffa-like effector C (*CIDEC*). The FPLD5 condition is manifested in a 19-year-old Ecuadorian girl with muscular lower limbs and prominent acanthosis nigricans [131]. The mutation induces a premature truncation of the CIDEC protein, and thus it restricts the LD expansion [132]. In fact, *Cidec*<sup>-/-</sup> mice have a reduced fat mass and impaired white adipocyte differentiation with multilocular LDs [133]. They are resistant to diet-induced obesity and insulin resistance as seen in the patient [133]. It is deduced from the observations in this study that CIDEC plays an indispensable role in the LD fusion, particularly for the development of unilocular LDs [108].

### 3.6 Type 6 FPLD (FPLD6) and LIPE

Exome sequencing has revealed another novel case of FPLD6 (OMIM #615980) that is caused by a homozygous nonsense mutation in the *LIPE* gene on chromosome 19. *LIPE* gene encodes hormone-sensitive lipase (HSL). HSL plays a vital role in lipolysis in which TAG and DAG are hydrolyzed to fatty acids in time of energy need [109]. Patients with FPLD6 have reduced lipolysis, small adipocytes, insulin resistance, and inflammation [134]. In addition, these patients exhibit downregulation of the PPAR $\gamma$ -induced genes in their adipose tissue, which suggests an inhibitory effect on the regulation of adipogenesis. Two FPLD6 patients from Italy have

been reported to have mild muscular dystrophy with an increased serum creatine kinase level as well as other metabolic features such as dyslipidemia and diabetes [135]. In rodents, HSL also plays an important role in reproduction, specifically in male testes where it participates in steroid hormone synthesis from cholesterol [136]. In fact, *Lipe*<sup>-/-</sup> mice manifest impaired spermatogenesis, azoospermia, and male infertility [136].

### 3.7 Type 7 FPLD (FPLD7) and CAV1

FPLD7 (OMIM #606721) is also caused by the mutation in the *CAV1* gene on chromosome 7q31. Different from the CGL3 that is caused by homozygous mutation in *CAV1*, FPLD7 results from a heterozygous mutation in the gene. *CAV1* gene encodes caveolin-1 [60]. Very few cases of FPLD7 have been reported in humans. These FPLD7 patients share common symptoms and complications of FPLD including deficiency in subcutaneous fat, poor weight gain, development of congenital cataracts, insulin resistance, hyperlipidemia, and muscle weakness [62].

## 4. Acquired partial lipodystrophy (APL)

### 4.1 Barraquer-Simons syndrome

Barraquer-Simons syndrome (OMIM #608709) is named after Barraquer and Simons who first described the disease in the 1900s. Unlike other lipodystrophies, Barraquer-Simons syndrome occurs not due to inherited genetic mutations but normally derives from an acute viral transfection, such as measles [60]. Barraquer-Simons syndrome is extremely rare, with approximately 250 cases that have been reported in the literature with a male-to-female ratio of 1:4 [137]. The syndrome results in loss of subcutaneous fat mainly in the upper part of the body (face, neck, arms, and thorax) and upper abdomen; however, some adipose tissues are preserved in the gluteal regions and lower extremities [138]. Fortunately, Barraquer-Simons syndrome does not normally induce other metabolic complications such as insulin resistance, diabetes, and hypertriglyceridemia [137].

### 4.2 Highly active antiretroviral therapy (HAART)-induced lipodystrophy (LD-HIV)

LD-HIV can develop in some HIV-infected individuals who are undergoing antiretroviral therapy of more than 2 years [139]. Several cases have been reported since 1998 [140]. The toxicity of the treatment might result from HIV-1 protease inhibitors and nucleoside reverse-transcriptase inhibitors [141]. The latter ones have been shown to disrupt lipid metabolism and mitochondrial functions [141]. In patients with LD-HIV, subcutaneous fat loss occurs in the arms, legs, and face throughout the treatment course and does not cease after the therapy is discontinued [139]. Fortunately, this type of APL does not result in diabetes and insulin resistance, but some individuals might experience some conditions such as hypertriglyceridemia and coronary heart disease [139].

## 5. Management

Patients with lipodystrophy normally seek medical treatments toward the specific symptoms that they encounter. Since the disease affects its patients in multiple



aspects, care and management require a multidisciplinary team involving pediatricians, surgeons, cardiologists, endocrinologists, nutritionists, and psychiatrists [20]. Mental health supports should also be made to patients who suffer depressions from the diagnosis and anxieties about their appearance [142]. In addition, special education might be necessary for those who have an intellectual disability [142]. Furthermore, such cosmetic surgery as reconstructive facial surgery and bilateral gluteus maximus muscle flap advance might benefit the patients in improving their appearance and quality of life [20].

Dietary restriction is of paramount importance in the disease management. Particularly, those with CGL should follow a high-carb and low-fat diet, since it can raise very-low-density lipoprotein (VLDL) TAG levels while alleviating chylomicronemia [143]. Sufficient energy supply along with regular exercise is highly important in children with CGL to ensure their normal growth [20]. However, strenuous exercise is not recommended for CGL4 patients who can be treated with  $\beta$ -adrenergic blockers along with other antiarrhythmic medications to prevent catecholaminergic polymorphic ventricular tachycardia [144]. Also, in this case, an implantable pacemaker or defibrillator can be quite beneficial [144]. It remains unclear whether patients with CGL2 and cardiomyopathy should restrict exercise [145].

The first-line therapy for diabetes mellitus, such as metformin and sulphonylureas, can be prescribed to patients with CGL [146]. The lack of subcutaneous fat in the abdomen and thighs might pose a potential barrier for insulin injection, and the patients might necessitate higher doses of insulin [147]. Furthermore, kidney damage such as diabetic nephropathy and end-stage renal disease might occur in patients with long-standing diabetes as the result high blood glucose exposure. Treatments for such condition might involve hemodialysis and kidney transplantation [20].

Metreleptin can be a promising therapeutic drug in the near future as recent studies have shown its potency in improving metabolic complications involving diabetes mellitus, hypertriglyceridemia, and hepatic steatosis in CGL [146, 148–151]. In fact, 63% reduction in circulating levels of TAG along with 30% increase in insulin sensitivity, and 20% reduction in liver volume are observed in seven patients treated with metreleptin over the period of 4 months [20]. Three patients with CGL2 and two patients with CGL treated with recombinant leptin therapy in Japan during the treatment course of 36 months have shown ameliorated fasting glucose and TAG levels as well as increased insulin sensitivity [152]. Metreleptin therapy can also reduce symptoms of other conditions such as macroalbuminuria, microalbuminuria, and hyperfiltration as well as improve the balance in sex hormone profile [151, 152]. Patients treated with metreleptin might suffer such adverse effects as hypoglycemia, headache, nausea, decreased weight, and abdominal pain [153, 154]. In addition, there is a rare possibility that antileptin antibodies might develop severe infections [154]. Metreleptin therapy can reduce appetite signaled from the hypothalamus, as *Agpat2*<sup>-/-</sup> mice with selective deletion of leptin receptor do not respond to the treatment [153]. The use of metreleptin in combination with dietary management has been approved by the Food and Drug Administration in the treatment for patients with CGL and APL in 2014, and Japan has approved it to be an anti-lipodystrophic drug in 2013 [20].

## 6. Conclusions

Lipodystrophy is a rare genetic disease characterized by near-total loss or partial loss of body fat. The syndrome can result in an array of metabolic complications such as insulin resistance, type 2 diabetes, hypertriglyceridemia, and hepatic steatosis. The disease is managed with dietary restriction and exercise programs in line with the leptin therapy.



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