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Genetics of Lipodystrophy

Marissa Lightbourne, MD, MPH¹ and Rebecca J. Brown, MD, MHSc²

¹Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

²National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

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Background

The lipodystrophy syndromes are genetic or acquired disorders characterized by selective loss of adipose tissue, which may involve the entire body (generalized) or only certain adipose depots (partial). Over 1000 cases have been reported with prevalence <1:1,000,000 although underreporting is likely [1]. The characterization of the various phenotypes has been evolving and many molecular defects have been elucidated. The diagnosis is dependent on regional or generalized lack of adipose tissue on physical examination, potentially including body composition analysis, combined with supportive data from history, laboratory testing, imaging, and molecular genetic testing in some cases.

The major subtypes of lipodystrophy include congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL) (Figure 1). There are also other systemic disorders associated with lipodystrophy, such as the progeroid disorders (Figure 2) and autoinflammatory disorders. Localized forms of lipodystrophy and lipodystrophy in HIV infected patients are the more common acquired forms of lipodystrophy, but are beyond the scope of this discussion.

Metabolic complications of lipodystrophy are key factors in morbidity and mortality. The deficiency in adipose mass results in leptin deficiency, leading to hyperphagia and ectopic lipid storage, causing insulin resistance. Insulin resistance and associated complications

Author contact information: Marissa Lightbourne, 10-CRC/1-3330, MSC 1103, 10 Center Dr., Bethesda, MD 20892, Marissa.lightbourne@nih.gov. **Corresponding author:** Rebecca J. Brown, Building 10-CRC, Room 6-5942, 10 Center Drive, Bethesda, MD, 20892, brownrebecca@mail.nih.gov.

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include diabetes mellitus, hypertriglyceridemia, non-alcoholic fatty liver disease, polycystic ovaries, acanthosis nigricans, and premature atherosclerosis [2].

Although genetic testing is not necessary for the diagnosis, it is very helpful for identifying subtypes of the familial lipodystrophies. Genetic testing can help identify at risk family members, especially for lipodystrophy subtypes associated with subtle physical phenotypes or those with high risk of morbidity and mortality (e.g. cardiomyopathy and arrhythmias found in the LMNA mutations). A negative genetic test does not rule out a genetic condition, as there are forms of lipodystrophy for which the genetic mutations are unknown.

Congenital generalized lipodystrophy (CGL)

Congenital generalized lipodystrophy (Berardinelli-Seip syndrome) was first reported by Berardinelli [3] from Brazil and Seip [4] from Scandinavia in the 1950s. Patients have since been reported worldwide, including patients of African, European, Middle Eastern, Native American, and Latino descent [5]. CGL is a rare autosomal recessive disorder, and four distinct mutations have been reported. CGL1, the most common variant, is due to mutations in 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*) [6], CGL2 is caused by mutations in Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*) [7], CGL3 is caused by mutations in caveolin 1 (*CAVI*) [8], and CGL4 is caused by mutations in the polymerase I and transcript release factor (*PTRF*) gene [9].

Although each mutation has distinct features, they share many similar characteristics that can be used to phenotypically identify CGL. These common features include a near-total lack of body fat, prominent muscularity, and very low leptin levels [5]. CGL is recognizable at birth or soon after based on the paucity of subcutaneous adipose tissue. In infancy, hepatosplenomegaly and umbilical prominence or hernia [5, 10] are often present. During childhood, patients often have voracious appetites, accelerated growth, advanced bone age, and acanthosis nigricans [5, 11]. Metabolic complications become more prevalent as children age, and by adolescence many have diabetes mellitus with severe hyperinsulinemia and dyslipidemia (high triglycerides and low high density lipoprotein cholesterol) [5, 6, 12]. Hypertriglyceridemia may be severe enough to cause acute pancreatitis [5, 11]. Non-alcoholic fatty liver disease is common, and can lead to cirrhosis [13]. Females with CGL may develop hirsutism, menstrual irregularity, polycystic ovaries and infertility similar to PCOS, with occasional clitoromegaly [1]. Clinical features specific to each genetic subtype are discussed below.

Morbidity and mortality are usually associated with metabolic derangements and include complications of diabetes mellitus, hyperlipidemia (e.g. acute pancreatitis), and cirrhosis. Depending on the mutation, patients may also have cardiomyopathy and rhythm disturbances.

Congenital Generalized Lipodystrophy Type 1 (CGL1)

Genetics: CGL1 is caused by recessive mutations in 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*) on chromosome 9q34 [6]. It was identified via genome-wide linkage analysis with positional cloning [6]. Although equal sex distribution is expected

based on the inheritance pattern, there is a female predominance of reported patients [5], and it has been postulated that less severe fat loss in patients with *AGPAT2* mutations can result in the diagnosis being missed in some males. It has been described in many diverse pedigrees (with origins in Europe, Africa, Pakistan, Argentina, Germany, Mexico, and the United Arab Emirates). Most patients with CGL of African origin have CGL1 [5].

Phenotype: Phenotypic characteristics that distinguish CGL1 from other forms of generalized lipodystrophy include absent bone marrow fat and preserved mechanical adipose tissue in the retroorbital and periarticular regions, palms, and soles. Patients can also develop enlargement of the hands, feet, and mandible, resulting in an acromegaloid appearance [14] and hyperhidrosis [5]. The onset of diabetes is at a median age of 12.5 years [5]. Focal lytic lesions in the appendicular bones have been almost exclusively linked to the *AGPAT2* mutation [5, 14].

Mechanism: *AGPAT*s are critical enzymes involved in the biosynthesis of triglycerides and phospholipids from glycerol-3-phosphate. There are 11 known *AGPAT* isoforms, each encoded by different genes, with distinct tissue expression and biochemical properties. *AGPAT2* catalyzes the acylation of lysophosphatidic acid to phosphatidic acid [15]. There is high expression of *AGPAT2* mRNA in adipose tissue and deficiency may cause lipodystrophy by limiting triglyceride biosynthesis and decreasing the bioavailability of phosphatidic acid and glycerophospholipids.

Congenital Generalized Lipodystrophy Type 2 (CGL2)

Genetics: CGL2 is caused by recessive mutations in Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*) on chromosome 11q13 [7]. It was identified via genome-wide linkage analysis with positional cloning. Patients have been identified with origins from Turkey, Brazil, India, Pakistan, China, Japan, Europe, Native American, United Kingdom, Portugal, Norway, and Lebanon. Most patients of Lebanese and Norwegian origin have CGL2 due to founder mutations [5].

Phenotype: CGL2 is considered to be the most severe variety of CGL. Infants are born without any body fat. In addition to lack of metabolically active adipose tissue in the subcutaneous, intra-abdominal, and intrathoracic depots, patients lack mechanical adipose tissue and bone marrow fat. Consistent with the severe deficiency of body fat, patients with *BSCL2* mutations have very low leptin levels [5]. Patients with CGL2 have earlier onset of lipotrophic diabetes mellitus compared to those with CGL1, with median age of onset 10 years (range 8-30 years) [5]. Half of patients with CGL2 have mild mental retardation, which is not a feature of other lipodystrophy subtypes [5, 11, 12]. Cardiomyopathy is three times more frequent in patients with CGL2 compared to CGL1 [16, 17].

Mechanism: *BSCL2* encodes the protein, seipin. The function of seipin is complex and incompletely understood, but it appears to be involved in lipid droplet assembly, particularly the fusion of nascent lipid droplets [18]. Seipin may also aid in trafficking of lipids or proteins between the lipid droplet and the endoplasmic reticulum, and may also play a role in phospholipid and triglyceride synthesis via interactions with *AGPAT2* [19].

Congenital Generalized Lipodystrophy Type 3 (CGL3)

Genetics: CGL3 has been reported only in a single patient, and is caused by autosomal recessive mutations in *CAVI* on chromosome 7q31, which encodes the protein caveolin-1 [8]. The gene was identified via a candidate gene approach and is a nonsense mutation where a nucleotide change c.112G3T leads to substitution of the glutamic acid residue at position 38, resulting a stop codon (p.Glu38X). Heterozygous mutations in *CAVI* have been linked to an atypical partial lipodystrophy [20] and neonatal progeroid syndrome [21, 22].

Phenotype: Mechanical adipose tissue and bone marrow fat are preserved in CGL3. The patient had the typical metabolic complications of lipodystrophy (insulin resistance, hypertriglyceridemia, hyperandrogenism, and hepatic steatosis) in addition to some unique features including short stature and presumed vitamin D resistance [8].

Mechanism: Caveolin-1 is a highly conserved 22-kDa protein and an integral component of plasma membrane invaginations known as caveolae. Caveolae are abundant on adipocyte membranes, and act to bind fatty acids and translocate them to lipid droplets [20].

Congenital Generalized Lipodystrophy Type 4 (CGL4)

Genetics: CGL-4 is caused by autosomal recessive mutations in polymerase I and transcript release factor (PTRF) on chromosome 17q21.2, encoding the protein cavin-1 [9]. It was identified via a candidate gene approach, and has been reported in approximately 30 patients [19].

Phenotype: Patients may have some body fat present at birth, but progress to generalized lipodystrophy during infancy, with preservation of mechanical and bone marrow fat [19, 23]. In addition to metabolic complications of lipodystrophy, there can be associated cardiac, neuromuscular, gastrointestinal and skeletal diseases. Clinical features unique to CGL4 include congenital myopathy with percussion-induced muscle mounding and elevated creatine kinase levels, pyloric stenosis, atalantoaxial instability, cardiac rhythm disturbances including prolonged QT interval and exercise-induced ventricular tachycardia, and sudden death [11, 23].

Mechanism: PTRF is involved in biogenesis of caveolae and regulates expression of caveolins 1 and 3 [9]. Also important for lipid traffic, it assists in the proper formation of membrane caveolae.

Familial partial lipodystrophy (FPLD)

The majority of FPLD are autosomal dominant. Phenotypically, patients with FPLD lack extremity and gluteal subcutaneous fat. In most cases, body fat distribution is normal during infancy and early childhood with onset of fat redistribution occurring around puberty. Adipose tissue in the face, neck and intraabdominal areas is preserved, and may be increased, leading to a Cushingoid appearance. Patients may also have acanthosis nigricans and muscular hypertrophy [24]. Diabetes and metabolic complications occur in adulthood. Men are less likely to be recognized phenotypically because the fat distribution of partial lipodystrophy overlaps with normal male habitus. Men are also less likely to be recognized

because metabolic disease is less severe [25]. Women may have reduced fertility with irregular menses and hirsutism [26]. Metabolic complications are common and include coronary artery disease [27, 28].

Familial partial lipodystrophy type 1 (FPLD1)

Genetics: FPLD1 [29], otherwise known as the Kobberling type of familial partial lipodystrophy, is usually autosomal dominant but the genetic cause is unknown. It is possible that FPLD1 is actually a group of disorders with multiple genetic etiologies.

Phenotype: Patients exhibit loss of fat to the extremities, including the buttocks, increased fat in the face, neck, and abdomen resulting in a Cushingoid appearance, and increased waist to hip ratio with high BMI. The classic fat distribution typically develops during childhood, although there is a single report of fat redistribution occurring after menopause [29]. There is classically a prominent ledge of fat above the gluteal area, upper medial thigh and upper arm over the deltoid and upper triceps. Extremities can be muscular with phlebomegaly or thin without phlebomegaly (supporting the concept that there are multiple genetic causes). Patients have typical metabolic complications of lipodystrophy, which may include severe hypertriglyceridemia and acute pancreatitis, and early coronary artery disease [29]. FPLD1 has only been described in females to date, which may be due to mild or lethal forms in men [30].

Familial partial lipodystrophy type 2 (FPLD2)

Genetics: FPLD2, also known as the Dunnigan variety of FPLD, is caused by autosomal dominant mutations in the *LMNA* gene on chromosome 1q21-22 [31, 32]. *LMNA* encodes nuclear lamin A/C. The most common mutation is the R482Q mutation.

Phenotype: Onset of fat loss typically occurs at puberty with loss of fat in the buttocks and limbs, and gain of fat to the face, neck, abdominal viscera, and labia. Patients have acanthosis nigricans, muscle hypertrophy, phlebomegaly, eruptive xanthomata, lipomas, and hirsutism. Cardiovascular complications include coronary artery disease and hypertension, while metabolic complications include insulin resistance, diabetes mellitus, hypertriglyceridemia with resultant pancreatitis, and hepatic steatosis, which tend to increase with age [33, 34]. Women can also have PCOS, breast hypoplasia, preeclampsia, and miscarriages. Men with FPLD2 have a less obvious physical phenotype and milder metabolic abnormalities [25].

Mechanism: The mechanism by which *LMNA* mutations result in partial lipodystrophy is discussed under Laminopathies, below.

Familial partial lipodystrophy type 3 (FPLD3)

Genetics: FPLD3 is caused by autosomal dominant mutations in the peroxisome proliferator-activated receptor gene (*PPAR γ*) on chromosome 3p25 [35-38].

Phenotype: The onset of fat loss is usually in the second decade, with loss of fat to the trunk, buttocks and limbs. There is no increase in head and neck fat (in contrast to FPLD2).

There may be gain of fat to the abdomen [39]. FPLD3 is associated with typical metabolic complications of lipodystrophy, and may also have an increased risk of hypertension [38].

Mechanism: PPAR γ is highly expressed in adipocytes and is considered a master regulator of adipocyte differentiation [40]. It is not clear how germline mutations in PPAR γ lead to region-specific loss of adipose tissue.

Familial partial lipodystrophy types 4, 5, and 6 (FPLD4, FPLD5, FPLD6), and AKT2-linked lipodystrophy

Genetics & Mechanism: FPLD4 is caused by autosomal dominant mutations in *PLIN1*, encoding perilipin-1 [41]. FPLD5 has been reported in only a single case, caused by an autosomal recessive mutation in *CIDEA* [42]. Perilipin-1 and CIDEA are involved in the structure and function of adipocyte lipid droplets. FPLD6 is caused by autosomal recessive mutations in *LIPE*, encoding hormone sensitive lipase, which is involved in regulation of lipolysis [43, 44]. Akt2-linked lipodystrophy was described in a single family, and is caused by autosomal dominant mutations in *AKT2*, which is a key mediator of insulin signaling downstream of the insulin receptor [45].

Phenotype: FPLD4, FPLD 5, FPLD 6 and Akt2-linked lipodystrophy share common phenotypes. The typical onset is at puberty with loss of fat to the buttocks and limbs and a gain of fat to the face, neck and abdomen. Skin changes include acanthosis nigricans, phlebomegaly, eruptive xanthomata and hirsutism. Patients can also have calf hypertrophy. Metabolic complications include insulin resistance, diabetes mellitus and hypertriglyceridemia. Cardiovascular complications include hypertension and coronary artery disease.

Acquired lipodystrophies—Acquired lipodystrophies are only briefly discussed, as they are thought to be autoimmune in origin rather than genetic.

Patients with acquired generalized lipodystrophy (AGL), or Lawrence syndrome, are born with normal body fat, and experience a progressive loss of fat that eventually affects almost all fat depots, including mechanical fat [46]. In some cases, fat in the face, neck, and axillae may be preserved. Onset is most commonly in childhood, but can occur at any age. There is a 3 to 1 female to male ratio. Patients experience typical metabolic complications of lipodystrophy, including insulin resistance, diabetes, hypertriglyceridemia, and non-alcoholic steatohepatitis. In addition, patients frequently have other associated autoimmune diseases (juvenile dermatomyositis, type 1 diabetes, autoimmune hepatitis, and others) and complement abnormalities.

Acquired partial lipodystrophy (APL), or Barraquer Simons syndrome, is a unique form of lipodystrophy in which loss of fat occurs in a cranio-caudal direction, beginning in the face, and variably progressing to include the neck, shoulders, arms, and trunk [47]. Excess fat accumulation may occur in the lower body, including the hips, buttocks, and legs. Onset of fat loss typically occurs in childhood or adolescence, and there is a 4 to 1 female preponderance. APL is associated with other autoimmune conditions including membranoproliferative glomerulonephritis in 20% of cases, low serum C3, and the presence

of C3 nephritic factor [47, 48]. Unlike other forms of lipodystrophy, metabolic complications are infrequent, perhaps due to the preservation of fat in the lower body. A single study has linked APL to mutations in *LMNB* (see Laminopathies, below) [49].

Autoinflammatory disorders—Three distinct but overlapping recessive autoinflammatory disorders associated with lipodystrophy are caused by mutations in the proteasome subunit beta type 8 (*PSMB8*) on chromosome 6. These syndromes include the joint contractures, muscle atrophy, microcytic anemia (JMP) panniculitis-induced lipodystrophy syndrome [50], the Nakajo-Nishimura syndrome [51], and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome [52]. *PSMB8* encodes the immunoproteasome subunit $\beta 5i$. Abnormal incorporation of $\beta 5i$ mutants into the immunoproteasome results in decreased proteasome activity, leading to cellular accumulation of ubiquitinated and oxidized proteins and increased sensitivity to apoptosis. The mechanism by which dysfunction of the immunoproteasome leads to lipodystrophy and other features of the autoinflammatory syndromes remains to be elucidated. However, the autoinflammatory response may result in infiltration of adipose tissue with lymphocytes and other immune cells, leading to loss of nearby adipocytes.

JMP was initially described in three patients belonging to 2 pedigrees from Portugal and Mexico [53]. Features of the disease include lipodystrophy beginning in childhood, muscle atrophy, joint contractures, skin lesions, microcytic anemia, hepatosplenomegaly, and hypergammaglobulinemia,.

Nakajo-Nishimura syndrome has been reported in over 20 Japanese patients, and presents in infancy with rash, periodic fevers, nodular erythematous skin eruptions, and myositis [51]. Atrophy of the subcutaneous fat and muscles is progressive, with joint contractures. Additional features include hepatosplenomegaly, hypergammaglobulinemia, and basal ganglia calcifications.

CANDLE syndrome typically presents in the first year of life with recurrent fevers, annular violaceous plaques, arthralgias, anemia, lipodystrophy, and elevated acute phase reactants [52]. Lipodystrophy is variable, but usually begins in infancy with loss of subcutaneous fat from the face, with loss of fat from upper (and occasionally lower) limbs later in childhood [52].

Progeroid disorders—Many progeroid disorders include lipodystrophy as a manifestation, and a detailed discussion of each of these is beyond the scope of this manuscript. A list of progeroid disorders, including their causative gene and its function, inheritance, and lipodystrophic regions, is in Table 1. Further discussion of progeroid disorders with lipodystrophy related to genetic defects in nuclear lamins is below (Laminopathies).

Other syndromes associated with lipodystrophy—Mutations in *PCYT1a*, which cause either generalized or partial lipodystrophy, and the short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly, and teething delay (SHORT) syndrome, caused by mutations in *PIK3R1*, are briefly discussed in Table 2.

Laminopathies—Several lipodystrophy syndromes fall in the class of disorders known as “laminopathies.” The laminopathies are heterogeneous disorders caused by mutations in genes encoding nuclear lamina proteins (*LMNA*, *LMNB1*, *LMNB2*), post-translational processing of these proteins (*ZMPSTE24*), or that interact with lamins (e.g. *EMD*, encoding the protein emerin) [54]. There are four categories of diseases associated with lamin dysfunction, including lipodystrophies, progeroid disorders (many of which are associated with lipodystrophy), muscle diseases, and neuropathies. The Dunnigan variety of familial partial lipodystrophy, described above, is caused by mutations in *LMNA*. Acquired partial lipodystrophy (Barraquer Simons syndrome) has been linked to *LMNB* mutations in a single study, but it is not inherited as a Mendelian trait, and expression is likely linked to other genes and/or environmental factors [49]. Progeroid laminopathies include Hutchinson-Gilford progeria syndrome, atypical Werner syndrome, restrictive dermopathy, mandibuloacral dysplasia type A, and atypical progeroid syndrome. The most common laminopathies are muscle-related diseases, including Emery-Dreifuss muscular dystrophy (autosomal dominant, autosomal recessive, and X-linked), limb-girdle muscular dystrophy type 1B, dilated cardiomyopathy 1A with conduction defect, and heart-hand syndrome (Slovenian type) [54]. Neuropathies include Charcot-Marie-Tooth disease type 2B1, and adult-onset autosomal dominant leukodystrophy [54].

The laminopathies are of particular interest from a genetic perspective due to both the diversity of phenotypes, and the relatively poor genotype-phenotype correlation. Most laminopathy syndromes can be caused by multiple mutations, and the same mutation can result in different clinical syndromes, possibly due to other genetic variants. Even different missense mutations of same amino acid residue can cause different syndromes (e.g. *LMNA* mutations R527H and R527C cause mandibulo-acral dysplasia [a progeroid lipodystrophy], but R527P causes Emery Dreifuss muscular dystrophy). Moreover, overlap syndromes exist, such as Dunnigan familial partial lipodystrophy combined with muscular dystrophy and/or cardiomyopathy or cardiac conduction defects [55].

Conclusion

There continues to be progress to uncover the genetic causes of lipodystrophy syndromes, but more genetic mutations remain to be discovered. For example, FPLD1 is usually autosomal dominant with no known genetic cause, and the phenotypic heterogeneity suggests that there may be multiple genetic etiologies. Although APL has been linked to mutations in *LMNB*, the acquired lipodystrophies are not inherited in a Mendelian manner, and are presumed to be caused by autoimmune destruction of adipocytes.

Progress in the field of the genetics of lipodystrophy has also led to increased understanding of the physiology of these disorders, and has the potential to lead to advancements in treatment. Leptin replacement has become a critical factor resulting in decreased morbidity [56]. Early identification of the genetic cause of lipodystrophy may lead to early treatment and better outcomes – for example, in patients identified to have the *BSCL2* mutation who may develop cirrhosis in the first decade of life, early diagnosis and treatment may halt or delay the advancement of liver disease [13]. Genetic screening and counselling may also

allow patients to make informed decisions regarding family planning and early management of disease in their children.

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Key Points

- Lipodystrophy syndromes are inherited or acquired disorders of missing body fat, with metabolic complications including insulin resistance, diabetes, and dyslipidemia.
- There are many genetic causes of lipodystrophy. Most genes encode proteins involved in adipocyte differentiation/survival, or lipid droplet formation; however, there remain unknown genetic causes.
- Congenital generalized lipodystrophy is caused by recessive mutations in *AGPAT2*, *BSCL2*, *CAV1* and *PTRF*.
- Most familial partial lipodystrophy is caused by autosomal dominant mutations in *LMNA*, *PPAR γ* , *PLIN1* and *AKT2*; recessive mutations can occur in *CIDEA* and *LIPE*.
- Acquired lipodystrophies are related to presumed autoimmune destruction of adipocytes; acquired partial lipodystrophy has been linked to mutations in *LMNB*.

Synopsis

Lipodystrophy disorders are characterized by selective loss of fat tissue with metabolic complications including insulin resistance, hypertriglyceridemia and non-alcoholic liver disease. These complications can be life threatening, affect quality of life, and result in increased healthcare cost. Major subtypes of lipodystrophy include congenital generalized lipodystrophy, familial partial lipodystrophy, acquired generalized lipodystrophy, and acquired partial lipodystrophy. There are also other systemic disorders associated with lipodystrophy, such as the progeroid and autoinflammatory disorders. In recent years, there have been many advances in the molecular genetics underlying these disorders. Genetic discoveries have been particularly helpful in understanding the pathophysiology of these diseases, and have shown that mutations affect pathways involved in adipocyte differentiation and survival, lipid droplet formation, and lipid synthesis. In addition, genetic testing can identify patients whose phenotypes are not clearly apparent, but who may still be affected by severe metabolic complications.

Figure 1. Common genetic forms of lipodystrophy

A) Adolescent with congenital generalized lipodystrophy due to recessive mutation in *AGPAT2*, demonstrating generalized lack of subcutaneous fat with prominent musculature, acromegaloid hands and feet, and insulin pump use. B) Adolescent with congenital generalized lipodystrophy due to recessive mutation in *BSCL2*, demonstrating generalized lack of fat including the face, hands, and feet, prominent umbilicus, and severe acanthosis nigricans. C) Adolescent with familial partial lipodystrophy due to *LMNA* mutation, demonstrating lack of fat in the buttocks and extremities, preserved truncal fat, and increased fat in the head, neck, and dorsocervical area.

Figure 2. Progeroid lipodystrophy syndromes

A) Two year old child with atypical progeria due to de novo mutation in *LMNA*, demonstrating generalized lack of fat and mandibular hypoplasia. B) 12 year old boy with mandibulo-acral dysplasia type B due to recessive mutation in *ZMPSTE24*, demonstrating generalized lack of fat with prominent veins, mandibular hypoplasia, and joint contractures. Subcutaneous calcifications were also present. C) 12 year old boy with atypical progeria due to de novo mutation in *LMNA*, demonstrating generalized lack of fat, mandibular hypoplasia, and mottled skin pigmentation on the neck.

Table 1

Progeroid disorders

Disorder	Gene (protein)	Gene function	Inheritance	Lipodystrophic areas	Reference
Hutchinson-Gilford progeria syndrome	<i>LMNA</i> (lamin A/C)	Structure and functions of nuclear lamina	<i>de novo</i>	Almost all fat lost (intra-abdominal fat spared)	[57] [58]
Mandibulo-acral dysplasia type A (with partial lipodystrophy)	<i>LMNA</i> (lamin A/C)	Structure and functions of nuclear lamina	AR	Upper and Lower limbs	[59]
Mandibulo-acral dysplasia type B (with generalized lipodystrophy)	<i>ZMPSTE24</i> (zinc metalloproteinase)	Prelamin A processing	AR	Almost all fat lost	[60]
Atypical progeria	<i>LMNA</i> (lamin A/C)	Structure and functions of nuclear lamina	AD, <i>de novo</i>	Partial or generalized fat loss Normal mechanical fat	[61]
Néstor-Guillermo progeria syndrome	<i>BANF1</i> (Barrier to autointegration factor)	Assembly of emerin and A-type lamins at the reforming nuclear envelope	AR	Almost all fat lost	[62]
Werner syndrome	<i>RECQL2</i> (WRN)	DNA helicase, DNA repair	AR	Limbs	[63]
Bloom Syndrome	BLM	DNA repair	AR	Limbs	[64]
Mandibular hypoplasia, deafness and progeroid features (MDP) syndrome	<i>POLD1</i> (subunit of DNA polymerase δ)	DNA polymerization and repair	<i>de novo</i>	Almost all fat lost	[65]
Neonatal Marfan progeroid syndrome	<i>FBN1</i> (fibrillin 1)	Connective tissue	<i>de novo</i>	Almost all fat lost	[66]
Neonatal progeroid syndrome	<i>CAV1</i> (Caveolin-1)	Caveolin-1, formation of membrane caveolae, lipid traffic	<i>de novo</i>	Face Distal extremities	[67]
Keppen-Lubinsky syndrome (KCNJ6)	<i>KCNJ6</i> (G protein-activated inward rectifier potassium channel 2)	Inwardly rectifying potassium channel	<i>de novo</i>	Almost all fat lost	[68]
Cockayne syndrome	<i>ERCC6</i> , <i>ERCC8</i>	DNA repair and transcription	AR	Almost all fat lost	[69]
Ruijs-Aalfs syndrome (SPRTN)	<i>SPRTN</i> (SprT-like N-terminal domain protein)	DNA repair	AR	Almost all fat lost	[70]

Table 2

Other lipodystrophic disorders

PCYT1-linked lipodystrophy	PCYT1A (phosphate cytidylyltransferase 1 alpha)	Synthesis of phosphatidylcholine	AR	Either generalized or partial loss of fat	[71]
Short stature, hyperextensibility, ocular depression, Rieger anomaly, and teething delay (SHORT) syndrome	<i>PIK3R1</i> (regulatory subunits of the phosphatidyl inositol-3 kinase)	Insulin signaling	AD, de novo	Almost all fat lost (most cases)	[72]