The Physician’s Guide to
Lipodystrophy Disorders

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What are Lipodystrophy Disorders?

Lipodystrophies are disorders characterized by selective loss of adipose tissue (body fat) from various regions of the body. The extent of fat loss can range from very small areas on one part of the body to near total absence of adipose from the entire body. Some patients may have only cosmetic problems while others may also have severe metabolic complications. The magnitude of fat loss determines the severity of metabolic complications related to insulin resistance, such as diabetes mellitus, high levels of serum triglycerides and fatty liver. The two major types of lipodystrophies are inherited (familial or genetic lipodystrophies) or secondary to various types of illnesses or drugs (acquired lipodystrophies). Genetic lipodystrophies are monogenic disorders caused by mutations (alterations or blips) in a gene. Several genes responsible for inherited lipodystrophies have been identified. Some physicians also use the term “lipoatrophy” for these disorders.

Inherited Lipodystrophies

In the last 15 years, considerable progress has been made in understanding the molecular basis of many subtypes of inherited lipodystrophy. Congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPL) are the two main subtypes of inherited lipodystrophy; the other subtypes are extremely rare.

Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disorder characterized by near total absence of body fat from birth. Homozygous or compound heterozygous mutations in four genes, 1-acylglycerol-3-phosphate-O-acyltransferase 2 (AGPAT2), Berardinelli-Seip congenital lipodystrophy 2 (BSCL2), caveolin 1 (CAV1), and Polymerase I and transcript release factor (PTRF; also known as cavin) are associated with the four subtypes CGL1, CGL2, CGL3, and CGL4, respectively.
Familial partial lipodystrophy (FPL) is mostly inherited as an autosomal dominant condition caused by heterozygous mutations in genes, such as, lamin A/C (LMNA), peroxisome proliferator-activated receptor gamma (PPARG), v-AKT murine thymoma oncogene homolog 2 (AKT2) and perilipin 1 (PLIN1). Recently, a patient with autosomal recessive FPL has been identified with a homozygous mutation in cell death–inducing Dffa-like effector C (CIDEC).

Mandibuloacral dysplasia (MAD) associated lipodystrophy is an autosomal recessive condition with skeletal manifestations and partial or generalized lipodystrophy. Homozygous or compound heterozygous mutations in the LMNA and zinc metalloproteinase (ZMPSTE24) genes have been linked to MAD.

The genetic basis of SHORT syndrome, neonatal progeroid syndrome (NPS) and some other rare types of lipodystrophy remains to be elucidated.

**Congenital Generalized Lipodystrophy (CGL)**

CGL is a rare autosomal recessive disorder in which near total absence of the adipose tissue is usually evident from the birth. It was originally described by Berardinelli (1954) and Seip (1959), and since then, approximately 300 cases have been reported. The diagnosis of CGL is usually made at birth or soon after. Assuming that only 1 in 4 patients are reported in the published literature, the estimated worldwide prevalence is about 1 in 10 million.

**Clinical Features**

Patients with CGL have extreme muscularity at birth that is due to near total loss of body fat. They grow at an accelerated rate during early childhood, have markedly increased appetite, and may have slightly enlarged hands, feet and mandible, known as, acromegaloïd features. Nearly all patients have umbilical hernia or enlargement of the umbilicus. Patients also present with acanthosis nigricans (dark velvety pigmentation of the skin) in the axilla, neck, and groin and sometimes even over the trunk, hands, knees, elbows and ankles. Liver enlargement due to excess fat deposition is usually noticed during infancy. A few patients develop cirrhosis (liver damage) and its complications later on in life. Many patients also develop splenic enlargement. In females, it is common to see mild hirsutism (excess hair on the body especially on the upper lip and chin), enlargement of clitoris, irregular menstrual periods and even lack of menstruation and polycystic...
ovaries. Most affected women are unable to conceive, however, a few patients have had successful pregnancies. Affected men usually have normal reproductive ability.

Metabolic complications associated with insulin resistance such as impaired glucose tolerance, diabetes, and hypertriglyceridemia are evident at a young age and are often difficult to control. Extreme hypertriglyceridemia may result in recurrent episodes of acute pancreatitis. Of the four distinct subtypes of CGL, type 1 and type 2 are the most common. Table 1 shows various distinguishing features of each subtype of CGL.

<table>
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<tr>
<th>Clinical features</th>
<th>CGL1 (AGPAT2)</th>
<th>CGL2 (BSCL2)</th>
<th>CGL3 (CAV1)</th>
<th>CGL4 (PTRF)</th>
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<td>Congenital myopathy</td>
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*–* absent; *++* present.

**Molecular Basis**

**CGL1 locus: AGPAT2**

Located on the long arm of chromosome 9 (9q34) is the gene that encodes for the enzyme AGPAT2 which is responsible for the synthesis of
triglycerides (fat) and phospholipids. Mutations (alterations) in this gene may result in lipodystrophy either due to lack of triglyceride synthesis or due to abnormal adipocyte (fat cell) function.

**CGL2 locus: BSCL2**

Located on the long arm of chromosome 11 (11q13) is the gene BSCL2 that encodes a protein, Seipin. Studies in yeast have suggested that Seipin may play a role in fusion of lipid droplets. Recent data also suggest that it plays a role in adipocyte differentiation.

**CGL3 locus: CAV1**

The CAV1 gene is located on chromosome 7q31. Caveolin-1 is expressed in abundance in caveolae, invagination on cell membranes of adipocytes. Caveolae play a role in lipid droplets formation by bringing lipids and phospholipids from outside to inside of the cell.

**CGL4 locus: PTRF**

PTRF gene located on chromosome 17 encodes polymerase I and transcript release factor (PTRF; also known as cavin). The gene is located on chromosome 17. PTRF is a highly abundant caveolae component and plays a critical role in the biogenesis of caveolae. PTRF regulates the expression of caveolins 1 and 3 and may also contribute to lipid droplet formation.

**Other loci: unknown**

Some patients with CGL (less than 20 percent) have mutations in none of the four known genes, suggesting that additional loci and other distinct pathways are involved.

**Familial Partial Lipodystrophy (FPL)**

FPL is a rare autosomal dominant disorder which is characterized by variable loss of body fat from the extremities as well as from the truncal region. Individuals, both males and females, of several generations can be affected. The chance of transmission from an affected parent to offspring is 50%. Most of the reported patients have been of European origin; however, patients of African-American and Indian origin have been noted.

**Clinical Features**

Patients with familial partial lipodystrophy (FPL) have reduced subcutaneous (sc) fat in the limbs as well as in the truncal regions but may have excess sc fat deposition in non lipodystrophic regions (e.g. neck, face, and intra-
abdominal regions). The phenotype can be easily recognized in affected women; however, affected men are often more difficult to diagnose clinically, as many normal men are also quite muscular. The diagnosis should be suspected in patients who show signs of insulin resistance early in life manifested by acanthosis nigricans or polycystic ovarian syndrome (menstrual irregularity, hirsutism) and early onset of diabetes and severe hypertriglyceridemia. Several distinct subtypes of FPL have been reported and the molecular genetic basis of five distinct subtypes is known. The most common subtype is FPL, Dunnigan variety (FPLD or FPL, type 2) which is due to missense lamin A/C (LMNA) mutations. It is also the most well characterized disorder. These patients have normal body fat distribution during early childhood, but around the time of puberty, sc fat from the extremities and trunk is progressively lost. Some patients at the same time gain excess fat on the face, chin (‘double chin’), and neck (‘Cushingoid appearance with buffalo hump’). Acanthosis nigricans, and hepatomegaly due to steatosis are common and 20-25% of affected females have hirsutism (increased body hair), menstrual abnormalities, and polycystic ovaries (enlarged ovaries) are observed. Women are more severely affected with metabolic complications such as diabetes, hypertriglyceridemia and low levels of high density lipoprotein cholesterol. Affected women with FPLD are more pre-disposed to coronary artery disease and other types of atherosclerotic vascular disease.

**Molecular Basis**

**FPL Type 1: Kobberling variety: unknown**

Kobberling and co-workers from Germany reported a phenotype of FPL which was distinct from that reported by Dunnigan. The Kobberling variety is less common and has been reported in only two small pedigrees and four sporadic cases. The age of onset of lipodystrophy and the mode of inheritance are not clear. On the basis of clinical findings, the loss of adipose tissue in the Kobberling variety is said to be restricted to extremities only. Patients have normal amounts of fat in the face area and may have normal, or even excess, sc fat in the truncal area. The genetic basis for this particular variety is unknown.

**FPL Type 2: Dunnigan variety (FPLD): LMNA mutations**

Using a genome wide linkage analysis approach in five large informative pedigrees, it has been reported that the FPLD locus is on chromosome 1q21-22. Subsequently, many missense mutations (alterations) have been
identified in the lamin A/C (LMNA) gene in patients with FPLD. LMNA has 12 exons and by alternative splicing in exon 10 two proteins prelamin A (full form) or C (short form), are encoded. Lamins A and C are components of the nuclear lamina which is located between chromatin and the inner nuclear membrane. Thus, it is likely that missense mutations may affect nuclear function and result in premature cell death of adipocytes (fat cells), thus causing lipodystrophy. Three-fourths of the FPLD patients have mutations at the codon position 482 where arginine is replaced by glutamine, leucine or tryptophan. Some patients with mutations in exon 11 have been observed to have less severe form of lipodystrophy than those with exon 8 mutations. Rare patients with FPLD reveal mutations in exon 1 and these patients develop cardiomyopathy (disease of heart muscles) which manifests as premature congestive heart failure and cardiac arrhythmias (rhythm disturbances), such as heart blocks and atrial fibrillation necessitating the use of cardiac pacemakers. Some of these patients require cardiac transplantation.

**FPL Type 3: PPARG mutations**

Employing a candidate gene approach, we were the first to report a heterozygous missense mutation, p.Arg397Cys, in the PPARG in a 64-year old woman who presented with FPL, diabetes, hypertriglyceridemia, hypertension and hirsutism. She had lipodystrophy of the face and extremities that was noticed much later in life. Since then, approximately 30 patients with FPL due to PPARG mutations have been reported. PPARG is located on the chromosome 3p25 which encodes peroxisome proliferator activator receptor gamma (PPARγ) a key transcription factor involved in adipocyte differentiation. It is highly expressed in the adipose tissue. Missense mutations in PPARγ cause FPL due to defective differentiation of adipocytes. Patients with PPARG mutations develop less severe lipodystrophy than those with FPLD and sc fat loss is more prominent from the distal extremities (calf and forearm) than from the thighs and arms.

**FPL Type 4: PLIN1 mutations**

Perilipin (PLIN1) is the most abundant protein coating lipid droplets in adipocytes. The gene is located on chromosome 15q26. It is considered to be essential for formation and maturation of lipid droplets and storage of triglycerides as well as release of fatty acids from these lipid droplets. Overexpression of mutant PLIN1 in 3T3-L1 pre-adipocytes have resulted in smaller lipid droplets as compared to the wild type PLIN1. Histopathology
report of sc adipose tissue from four patients with PLIN1 mutations have also shown reduced size of adipocytes and increased macrophage infiltration and adipose tissue fibrosis. A total of five FPL patients have been reported to have mutations in PLIN1 and all of them had fatty liver, hypertriglyceridemia and hyperinsulinemia. Lipodystrophy was most striking in the lower limbs and gluteo-femoral (buttocks) depots. Recent information suggests that mutant forms of PLIN1 fail to bind to AB-hydrolase containing 5, which results in constitutive co-activation of adipose triglyceride lipase and increase basal lipolysis.

**FPL Type 5: AKT2 mutation**

AKT2 is a phosphoinositide-dependent serine/threonine kinase and also known as protein kinase B. AKT2 is predominantly expressed in insulin sensitive tissues and is involved in post-receptor insulin signaling. AKT2 is located on the chromosome 19q13.2. A heterozygous missense mutation, p.Arg274His, in AKT2 was discovered in four subjects from a family who presented with insulin resistance and diabetes mellitus. The loss of adipose tissue in patients with heterozygous mutations in AKT2 may either be due to reduced adipocyte differentiation or dysfunctional post insulin receptor signaling.

**FPL AUTOSOMAL RECESSIVE: CIDEC MUTATION**

Recently, a patient with autosomal recessive FPL has been identified with homozygous mutation in CIDEC. Cidec/Fsp27 is a lipid droplet protein most highly expressed in adipocytes where its expression is induced during adipocyte differentiation. Adipose tissue biopsy of the affected patient showed multilocular lipid droplets in comparison to normal one large lipid droplet in adipocytes.

**Other Types of FPL**

It appears that five loci for FPL, LMNA, PPAR, AKT2, CIDEC and PLIN1 may not be able to explain the genetic basis of all the patients with FPL and there is likelihood of additional loci. In depth characterization of the clinical phenotype related to the pattern of loss of fat in FPL patients with mutations in different genes may be helpful in identification of different phenotypes without resorting to molecular diagnosis.

**Mandibuloacral Dysplasia (MAD) associated Lipodystrophy**

Mandibuloacral dysplasia (MAD) is a rare autosomal recessive syndrome
characterized by mandibular hypoplasia, delayed cranial suture closure, dysplastic clavicles, club-shaped terminal phalanges, acro-osteolysis, and atrophy of the skin of the hands and feet, and typical facial changes. Patients also show “progeroid features” such as bird-like facies, high-pitched voice, skin atrophy, pigmentation, alopecia, and nail dysplasia. The disorder has been reported in about 40 patients so far. Patients with MAD either have partial loss of sc fat from the extremities (type A) or more generalized loss of sc fat involving the face, trunk and extremities (type B). The syndrome is also associated with lipodystrophy and clinical features of metabolic syndrome such as insulin resistance, impaired glucose tolerance, diabetes mellitus and hyperlipidemia.

**Molecular Basis**

**MAD Type A: LMNA mutations**

Patients with MAD frequently have partial lipodystrophy and insulin resistance, and the disease is caused by mutations in the LMNA gene. Many patients with MAD and type A (partial) lipodystrophy have homozygous p.Arg527His mutation in LMNA. So far, a total of 30 patients with MAD due to various LMNA mutations have been reported. Some patients may develop severe progeroid manifestations, similar to those seen in progeria patients such as alopecia, loss of eyebrows, delayed sexual maturation and premature loss of teeth. Most of the LMNA mutations causing MAD are located in the C-terminal region affecting exons 8-10. How these specific LMNA mutations cause resorption of bones such as mandible, clavicles and terminal phalanges remains unclear.

**MAD Type B: Zinc metalloproteinase (ZMPSTE24) mutations**

Compound heterozygous mutations in ZMPSTE24 in a Belgian woman with MAD have been reported. She also had progeroid features and generalized lipodystrophy. She died at age 24 years as a result of complications of chronic renal failure due to focal segmental glomerulosclerosis. Three other MAD patients with mutations in the same gene have been reported. It is suggested that accumulation of prelamin A and/or lack of mature lamin A in the cells may be the underlying mechanism. A total of eight patients with this subtype have been reported and most of them have been young children. There are no reports of diabetes among them. Patients with ZMPSTE24 mutations are premature at birth, have early onset of skeletal defects including acro-osteolysis, have more progeroid appearance and develop subcutaneous calcified nodules on the phalanges.
Other Types of MAD

Some patients with mandibuloacral dysplasia have no apparent alterations in either the LMNA or ZMPSTE24 gene, suggesting the existence of other as yet unmapped loci for this disorder.

Mandibular hypoplasia, Deafness, Progeroid features (MDP) associated lipodystrophy syndrome

This syndrome was recently reported in seven patients and is characterized by mandibular hypoplasia, deafness; progeroid features (MDP) -associated lipodystrophy. None of them had any mutations in LMNA or ZMPSTE24. As compared to MAD patients, they showed distinct characteristics such as sensorineural hearing loss, and absence of clavicular hypoplasia and acro-osteolysis. All males with MDP had undescended testes and hypogonadism. One adult female showed lack of breast development. Two of the seven patients had diabetes mellitus. The molecular basis of MDP syndrome remains to be elucidated.

Autoinflammatory Lipodystrophy Syndrome

This autosomal recessive autoinflammatory disorder is characterized by childhood onset of recurrent fever, joint stiffness and severe contractures of the hands and feet, erythematous skin lesions with subsequent development of lipodystrophy. Recently, joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (JMP) were reported in two pedigrees where affected patients developed progressive lipodystrophy during childhood. Similar patients had been previously reported from Japan. Additional clinical features include muscle weakness and atrophy and hepatosplenomegaly. Two groups recently have also reported five patients with Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) syndrome who have recurrent fever, annular violaceous plaques during infancy which result in loss of sc fat from the face and upper limbs.

Molecular Basis

A homozygous, missense, loss of function, mutation in proteasome subunit, beta-type, 8 (PSMB8) gene has been reported in affected patients with JMP syndrome. Subsequently, missense PSMB8 mutations were reported in Japanese patients with auto inflammatory lipodystrophy and also in those with CANDLE syndrome. The PSMB8 gene is located on chromosome 6p21.3 and encodes the β5i subunit of the immunoproteasome.
Immunoproteasomes are responsible for proteolysis of antigens presented by major histocompatibility complex (MHC) class I molecules and result in generation of immunogenic epitopes. Mutations in PSMB8 may trigger an autoinflammatory response that results in panniculitis and other clinical manifestations.

*Short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Reiger anomaly and teething delay (SHORT) Syndrome*

A total of 30 patients have been reported with SHORT syndrome. The pedigrees reveal both autosomal recessive and dominant modes of transmission. Reiger anomaly consists of eye abnormalities such as iris hypoplasia, Schwalbe ring, iridocorneal synechiae, micro- or megalo-cornea and dental anomalies such as hypodontia (missing teeth), microdontia (teeth smaller than normal), incomplete or underdevelopment of enamel and atypical teeth. Other clinical features include intrauterine growth retardation, failure to thrive, delayed speech development, small head circumference, bilateral clinodactyly (fifth finger bending towards adjacent 4th finger) and sensorineural hearing loss. Different patterns of fat loss have been reported. In many patients, lipodystrophy affects the face, upper extremities and sometimes the trunk, with relative sparing of the lower extremities. Others had lipodystrophy affecting only the face, gluteal region and elbows. Diabetes occurs as early as the second and third decade of life. The molecular basis of SHORT syndrome remains unknown.

*Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome)*

This is an autosomal recessive syndrome with a total of approximately 25 reported cases. Newborns with this syndrome have a triangular, old-looking face with relatively large skull (progeroid appearance), prominent veins on the scalp, sparse scalp hair, large anterior fontanelle and generalized lipodystrophy. However, sc fat in the sacral and gluteal areas is spared. Approximately 50 percent of patients reportedly die before the age of 6 years but patients surviving up to the age of 16 years have been reported. Recently, two patients who also manifested clinical features of Marfan syndrome were reported to harbor de novo heterozygous mutations in fibrillin 1 (FBN1) gene. No patient has been reported to develop diabetes.
Acquired Lipodystrophies

Acquired lipodystrophies are caused by medications, autoimmune mechanisms or other unknown mechanisms. These include highly active antiretroviral therapy (HAART) induced lipodystrophy in HIV-infected patients (LD-HIV), acquired generalized lipodystrophy (AGL), acquired partial lipodystrophy (APL) and localized lipodystrophy. Acquired lipodystrophies do not have a direct genetic basis. Rather, many mechanisms may be involved.

Despite recognition of acquired lipodystrophies for more than a century, progress in understanding underlying pathogenetic mechanisms has been slow. Acquired partial lipodystrophy (APL) has been reported in approximately 250 cases of various ethnicities with male to female ratio of 1:4 and acquired generalized lipodystrophy (AGL) in approximately 100 cases, mostly Caucasians with a male to female ratio of 1:3. LD-HIV is estimated to affect more than 100,000 patients in the United States and many more in other countries.

Acquired Generalized Lipodystrophy (AGL, Lawrence syndrome)

Even though the onset of loss of sc fat in patients with AGL occurs during childhood, the exact mechanisms of fat loss are not known. The pattern and extent of fat loss is quite variable. Most of the patients have generalized loss of fat, but in a few of them, some areas of the body such as intraabdominal fat and bone marrow fat are spared. However, patients develop extremely severe hepatic steatosis and fibrosis, diabetes, and hypertriglyceridemia, which are difficult to manage. The panniculitis–associated AGL usually presents with less severe fat loss and metabolic complications than the autoimmune or idiopathic subtypes. Some patients with AGL have been reported to have chronic hepatitis with autoimmune features and low serum complement 4 levels, suggesting involvement of the classical complement pathway in the pathogenesis of fat loss.

Acquired Partial Lipodystrophy (APL, Barraquer-Simons syndrome)

APL develops in most patients before age 15. Patients lose sc fat gradually in a symmetric fashion, first affecting the face and then spreading downward. Most of them present with fat loss from the face, neck, upper extremities, and trunk with sparing of sc abdominal fat and lower extremities. Metabolic complications are usually not seen. However, approximately one fifth of the patients develop membranoproliferative glomerulonephritis, and later on some of them develop drusen (yellow or
white extracellular material buildup in the membrane of eye). There is strong
evidence to suggest that fat loss involves autoimmune-mediated destruction
of adipocytes because more than 80% of the patients have low serum levels
of complement 3 and a circulating autoantibody called complement 3-
nephrit factor that blocks degradation of the enzyme C3 convertase. .

HAART-induced lipodystrophy in HIV–infected patients (LD-HIV)
LD-HIV usually appears after receiving HIV-1 protease inhibitor-containing
HAART for 2 years or more. Most patients gradually lose sc fat from the
arms, legs, and face. Some areas of the body are spared, and some patients
accumulate excess fat in these areas manifesting as buffalo hump, double
chin, and increased waist circumference. It is also observed that the fat
loss progressively gets worse with ongoing HAART therapy and does not
reverse on discontinuation of protease inhibitors. Many patients develop
hypertriglyceridemia, but only a few develop diabetes mellitus.

In many patients, protease inhibitors and nucleoside reverse transcriptase
inhibitors are implicated in causing lipodystrophy. Protease inhibitors may
cause lipodystrophy by inhibiting ZMPSTE24, resulting in accumulation
of prelamin A. Other mechanisms may include protease inhibitor-induced
alteration of expression of key transcription factors involved in lipogenesis
and adipocyte differentiation such as sterol regulatory element-binding
protein 1c, and PPAR . Protease inhibitors may also induce insulin resistance
by inhibiting glucose transporter 4 expressions. Since protease inhibitors or
nucleoside reverse transcriptase inhibitors are usually given together as part
of the HAART, the individual effects of these drugs on the phenotype remain
unclear.

Localized Lipodystrophy
Localized lipodystrophy can occur due to sc injection of various drugs,
panniculitis, pressure, and other mechanisms. It present with sc fat loss from
a focal region resulting in a dimple or a crater with overlying skin usually
unaffected. In some patients, large contiguous or anatomically distinct areas
on any region of the body may be involved.
Diagnosis

Lipodystrophies should be suspected in differential diagnosis of “lean or non-obese” patients presenting with early diabetes, severe hypertriglyceridemia, hepatic steatosis, hepatosplenomegaly, acanthosis nigricans, and polycystic ovarian syndrome. These patients should be examined carefully for evidence of loss of sc fat especially from the hips and thighs and muscular prominence. Some patients may present with excess sc fat deposition in various anatomic regions and may resemble patients with Cushing’s syndrome and truncal obesity. Patients with lipodystrophy should also be differentiated from those with anorexia nervosa, cachexia, starvation, diencephalic...
syndrome, multiple symmetric lipomatosis and other rare progeroid syndromes and disorders affecting growth and development.

History

If a lipodystrophy phenotype is discovered at or shortly after birth, CGL should be considered; otherwise the patient may have acquired lipodystrophy. In those suspected of having genetic lipodystrophies, an in-depth pedigree analysis should be conducted. Patients should be asked about the age of onset and progression of lipodystrophy and other associated manifestations. Taking a detailed family history, including the history of consanguinity, is very important to understand the mode of inheritance. Diagnosis of APL, atypical progeroid syndrome, and AGL can be delayed in children for several years until they see a specialist. Associated autoimmune diseases, especially juvenile dermatomyositis, should be considered in patients with acquired lipodystrophies. Those with localized lipodystrophies should be asked about local injections, trauma, pressure, or other insults.

Complications

Some patients with generalized lipodystrophies are predisposed to developing extreme hypertriglyceridemia and chylomicronemia, which result in acute pancreatitis and even death. Many patients with FPL develop coronary heart disease and other atherosclerotic vascular complications. Hepatic steatosis can lead to cirrhosis, necessitating liver transplantation. Some patients with MAD die during childhood of unknown reasons, and patients with APL who develop membranoproliferative glomerulonephritis may eventually succumb to renal failure. Sudden death has been reported during childhood in CGL, type 4, likely due to arrhythmias.

Laboratory Tests

The diagnosis of various types of lipodystrophies is mainly clinical. Laboratory test depends upon the type of lipodystrophy and may provide additional supportive evidence. Except for patients with localized lipodystrophies, a serum chemistry profile for glucose, lipids, liver enzymes, and uric acid should be obtained. Measurement of serum leptin does not help diagnostically but may predict response to investigational metreleptin replacement therapy. Patients with APL should be tested for serum C3 and C3-nephritic factor and urinalysis for proteinuria should be conducted on these patients. Radiographs can show the presence of lytic lesions in appendicular bones in patients with CGL and skeletal defects in those
with MAD. Skin biopsy is useful for patients with localized lipodystrophy or panniculitis-associated varieties. Holter monitoring, echocardiography, and stress test should be conducted for patients suspected of having cardiomyopathy or coronary heart disease.

Distinction between various types of lipodystrophy can be made by physical examination. Skinfold thickness measurement, dual–energy X-ray absorptiometry, and a whole body T-1 weighted magnetic resonance imaging can provide information on the pattern of fat loss. For genetic lipodystrophies whose molecular basis is known, genetic testing, including prenatal diagnosis, is available for AGPAT2, BSCL2, LMNA, ZMPSTE24, and PPARG in clinical laboratories. Genotyping for other lipodystrophy genes such as CAV1, PTRF, AKT2, CIDE, PLIN1 and PSMB8 is available on a research basis.

**Treatment**

Treatment of various types of lipodystrophies is quite challenging. Proper counseling of parents is critical for preventing unwanted stress and psychological sequelae in children affected with lipodystrophy. Because reversal of the lost adipose tissue is not possible, cosmetic surgery to improve appearance and management of metabolic complications are the only therapeutic options. Unwanted excess adipose tissue can be surgically excised or removed by liposuction. Those with severe facial lipodystrophy can undergo reconstructive facial surgery including fascial grafts from thighs, free flaps from anterolateral thigh, anterior abdomen, or temporalis muscle.

For the lack of clinical trial evidence, all patients are advised to consume high carbohydrate, low–fat diets. These diets can improve chylomicronemia in patients presenting with acute pancreatitis however, it may also raise very low density lipoprotein triglyceride concentration. Reduction of energy intake and increased physical activity is important in patients with FPL to avoid excess fat deposition in nonlipodystrophic regions. Many patients with FPL have increased risk of coronary heart disease and they should limit intake of saturated and trans-unsaturated fats and dietary cholesterol. However, whether such diet will be beneficial in the long term to reduce hepatic steatosis, serum triglycerides and improve glycemic control remains unclear.

**Investigative Therapies**

No controlled clinical trials have been conducted to help guide drug
therapy for metabolic complications. Since many patients have extreme insulin resistance, they may require high doses of insulin. However, some patients can achieve good glycemic control with oral hypoglycemic drugs such as metformin and sulfonylureas. Metformin can improve insulin sensitivity, reduce appetite and induce ovulation in patients with polycystic ovarian syndrome. Thiazolidinediones can also be used; however, they can induce unwanted growth of adipose tissue in nonlipodystrophic regions in patients with FPL. Although patients with PPARG mutations and FPL should respond better to thiazolidinediones, there is not much data to support this. For many patients with generalized lipodystrophy, insulin therapy is needed. Subcutaneous metreleptin replacement therapy has been shown to improve diabetes control, hepatic steatosis, and hypertriglyceridemia in markedly hypoleptinemic patients with generalized lipodystrophies, but its effects in patients with FPL so far have been modest. Metreleptin therapy remains investigational and is not yet approved by the U.S. Food and Drug Administration (FDA).

Information on current clinical trials is posted at www.clinicaltrials.gov

All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials sponsored by private sources, contact: www.centerwatch.com

*NORD does not endorse or recommend any particular studies.*

**Biochemistry**
Figure 1 The Role of Lipodystrophy Genes in Lipid Droplet formation in Adipocytes. Lipid droplets (LD) are organelles that store triglycerides (TG) intracellularly. They form as budding vesicles at the endoplasmic reticulum (ER) which fuse in adipocytes to form one large LD. Many proteins, such as cell death-inducing DNA fragmentation factor a-like effector c (CIDEC, shown in blue triangles), seipin (pink squares) and perilipin 1 (green circles) are present on the LD membrane. CIDEC and seipin may be involved in fusion of LDs to form a larger LD while perilipin 1 is essential for lipid storage and hormone mediated lipolysis. Caveolae are formed from lipid rafts on the cell surface which include cholesterol (yellow symbols), glycosphingolipids (green symbols) and caveolin-1 (black hair pin like symbols). Endocytosis of caveolae forms caveolin vesicles which may directly merge with lipid droplets and thus translocating fatty acids to LDs. Polymerase I and transcript release factor (PTRF) controls expression of caveolin 1 and 3 (not shown). The classical and alternative pathways involved in the biosynthesis of TG are shown inside the lipid droplet. In the adipose tissue, TG synthesis requires glycerol-3-phosphate as the initial substrate (classical pathway), whereas in the small intestine, synthesis of TG can occur via an alternative pathway using monoacylglycerol (MAG) as the initial substrate. Acylation of glycerol-3-phosphate using fatty acyl coenzyme A (FA-CoA) at the sn-1 position is catalyzed by glycerol-3-phosphate acyltransferases (GPATs) resulting in the formation of 1-acylglycerol-3-phosphate or lysophosphatidic acid (LPA). LPA is then acylated at the sn-2 position by 1-acylglycerol-3-phosphate acyltransferases (AGPATs) to yield phosphatidic acid (PA). Removal of phosphate group from PA by PA phosphatases (PAPs) produces diacylglycerol (DAG). Further acylation of DAG at the sn-3 position by diacylglycerol acyltransferases
(DGATs) finally produces TG. In the alternative pathway, MAG is acylated to DAG by monoacylglycerol acyltransferases (MGATs) which is then further converted to TG. Lamin A/C are integral components of nuclear lamina (shown in blue color) and interact with nuclear membrane proteins as well as chromatin. Zinc metalloproteinase (ZMPSTE24) is critical for post-translational processing of prelamin A to its mature form, lamin A. Published with permission from Garg A. Lipodystrophies: Genetic and acquired body fat disorders. JCEM: 2011; 96:3313-3325. Copyright 2011, The Endocrine Society.

Fig. 2 The Role of Lipodystrophy Genes in Pathways involved in the Development, Differentiation and Death of Adipocytes. The pluripotent mesenchymal stem cells can form preadipocytes, myocytes or osteoblasts depending upon the various cues. In response to various signals from hormones such as insulin and steroids and induction of adipogenic transcription factors, a series of changes are initiated in preadipocytes which lead to their differentiation to adipocytes. The transcription factors, CCAAT (cytidine-cytidine-adenosine-adenosine-thymidine)-enhancer-binding proteins (C/EBP) b/d are the first to be upregulated and then stimulate other transcription factors such as PPARg, C/EBPa, and sterol regulatory element-binding protein (SREBP) 1c. Some other genes such as preadipocyte factor 1 (Pref1), a known adipogenesis inhibitor are downregulated. Mature adipocytes are activated resulting in the overexpression of lipogenic genes like fatty acid synthase (FAS), acetyl coenzyme A carboxylase (ACC), GPATs, AGPATs, and DGATs for biosynthesis of triglycerides and phospholipids. The size of the lipid droplets is reduced upon fasting and increases with increased substrate availability. Available data suggest that the BSCL2-encoded protein, seipin, and v-AKT murine thymoma oncogene homolog 2 (AKT2) may be involved in adipocyte differentiation, whereas the AGPAT2 gene affects triglyceride synthesis. Clinical evidence from lipodystrophy patients harboring LMNA or ZMPSTE24 mutations suggests that nuclear dysfunction may accelerate apoptosis/death of mature adipocytes. Interstitial tissue may also play an important role in adipocyte survival. Mutations in PSMB8 which encodes 5i, a catalytic subunit of the immunoproteasomes may induce autoinflammatory syndrome resulting in infiltration of lymphocytes in adipose tissue (panniculitis) and death of nearby adipocytes. Published with permission from Garg A. Lipodystrophies: Genetic and acquired body fat disorders. JCEM: 2011; 96:3313-3325. Copyright 2011, The Endocrine Society.
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Resources

UT Southwestern Lipodystrophy website: www.lipodystrophy.info


Clinical Centers & Medical Experts

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- Grants and fellowships to encourage research on rare diseases
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- Publications for physicians and other medical professionals

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