The National Organization for Rare Disorders

NORD Guides for Physicians

The Physician's Guide to
Lipodystrophy Disorders

Visit website at:
nordphysicianguides.org/Lipodystrophies/

NORD
National Organization for Rare Disorders

For more information about NORD's programs and services, contact:
National Organization for Rare Disorders (NORD)
PO Box 1968
Danbury, CT 06813-1968
Phone: (203) 744-0100
Toll free: (800) 999-NORD
Fax: (203) 798-2291
Website: www.rarediseases.org Email: orphan@rarediseases.org

NORD's Rare Disease Database and Organizational Database may be accessed at www.rarediseases.org.

Contents ©2012 National Organization for Rare Disorders®

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, acromegaloid 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. Table1 shows various distinguishing features of each subtype of CGL.

Table 1: Clinical Features of Various Types of Congenital Generalized Lipodystrophy (CGL)

	CGL subtype (gene)			
Clinical features	**CGL1** *(AGPAT2)*	**CGL2** *(BSCL2)*	**CGL3** *(CAV1*	**CGL4** *(PTRF)*
Loss of metabolically active adipose tissue	+++	+++	++	++
Loss of mechanical adipose tissue	-	+	-	-
Bone marrow fat	-	-	+	+
Mild intellectual disability	-	+	-	-
Acanthosis nigricans	+++	+++	++	+/-
Hepatomegaly	+	+	+	+
Diabetes mellitus	+	+	+	+
Hypertriglyceridemia	+	+	+	+
Hyperinsulinemia	+	+	+	+
Cardiomyopathy	-	+	-	+
Cardiac arrhythmias and sudden death	-	-	-	+
Congenital myopathy	-	-	-	+

* – * 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.

FPLType 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-nephritic 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-1protease 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 I c, 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.

Table 2: Classification, Clinical Features, and Pathogenetic Basis of Acquired Lipodystrophies.

Type	Subtype	Clinical features	Pathogenetic basi
Lipodystrophy in HIV infected patients	•PI-induced •NRTI-induced	Loss of sc fat from the face and extremities and excess fat deposition in the neck and abdomen.	PIs may inhibit ZMPSTE24 and/ or cause dysregulation of transcription factors involved in adipogenesis. NRTIs may inhibit mitochondrial polymerase- *γ* and cause mitochondrial toxicity.
Acquired partial lipodystrophy	•Autoimmune •MPGN-associated •Idiopathic	Loss of sc fat from the face, neck, upper limbs, and trunk, sparing the lower abdomen and lower limbs.	Low serum complement 3 levels and presence of an autoantibody, C3 nephritic factor in most patients suggest autoimmune –mediated loss of adipose tissue.
Acquired generalized lipodystrophy	•Autoimmune •Panniculitis-associated •Idiopathic	Generalized loss of fat associated with tender sc nodules, autoimmune or other diseases.	Panniculitis preceding the loss of sc fat and association of autoimmune diseases suggest immune-mediated loss of adipose tissue.
Localized lipodystrophy	•Drug •Panniculitis-induced •Pressure-induced •Centrifugal •Idiopathic	Loss of sc fat from small areas of the body.	Multiple mechanisms involved.

Key

PIs (Protease inhibitors)
NRTIs (Nucleoside reverse transcriptase inhibitors)
ZMPSTE24 , (Zinc metalloproteinase)

MGPN , (Membranoproliferative glomerulonephritis)

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, CIDEC, 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

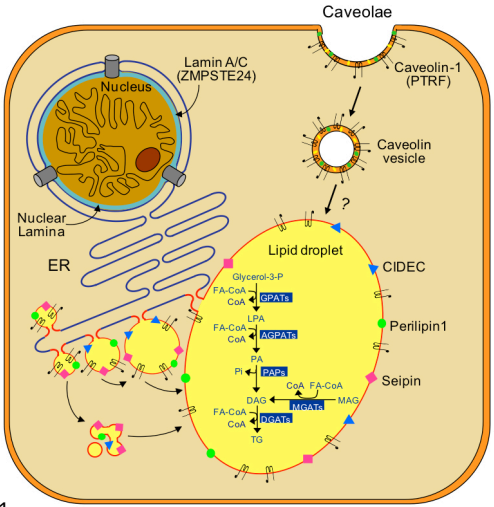

Figure 1

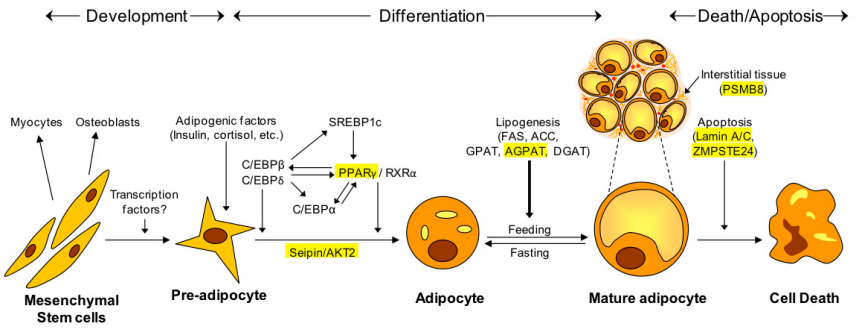

Figure 2

Figure Legends:

Fig. 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.

REFERENCES

1. Garg A 2000 Lipodystrophies. Am J Med 108:143-152.

2. Garg A 2004 Acquired and inherited lipodystrophies. N Engl J Med 350:1220-1234.

3. Berardinelli W 1954 An undiagnosed endocrinometabolic syndrome: report of 2 cases. J Clin Endocrinol Metab 14:193-204.

4. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA 1998 A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 12:F51-58.

5. Garg A, Misra A 2004 Lipodystrophies: rare disorders causing metabolic syndrome. Endocrinol Metab Clin North Am 33:305-331.

6. Seip M 1959 Lipodystrophy and gigantism with associated endocrine manifestations: a new diencephalic syndrome? Acta Paediatrica 48:555-574.

7. Van Maldergem L, Magre J, Khallouf TE, Gedde-Dahl T, Jr., Delepine M, Trygstad O, Seemanova E, Stephenson T, Albott CS, Bonnici F, Panz VR, Medina JL, Bogalho P, Huet F, Savasta S, Verloes A, Robert JJ, Loret H, De Kerdanet M, Tubiana-Rufi N, Megarbane A, Maassen J, Polak M, Lacombe D, Kahn CR, Silveira EL, D'Abronzo FH, Grigorescu F, Lathrop M, Capeau J, O'Rahilly S 2002 Genotype-phenotype relationships in Berardinelli-Seip congenital lipodystrophy. J Med Genet 39:722-733.

8. Agarwal AK, Simha V, Oral EA, Moran SA, Gorden P, O'Rahilly S, Zaidi Z, Gurakan F, Arslanian SA, Klar A, Ricker A, White NH, Bindl L, Herbst K, Kennel K, Patel SB, Al-Gazali L, Garg A 2003 Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. J Clin Endocrinol Metab 88:4840-4847.

9. Pardini VC, Victoria I, M., Rocha SM, Andrade DG, Rocha AM, Pieroni FB, Milagres G, Purisch S, Velho G 1998 Leptin levels, beta-cell function, and insulin sensitivity in families with congenital and acquired generalized lipoatrophic diabetes. J Clin Endocrinol Metab 83:503-508.

10. Magre J, Delepine M, Van Maldergem L, Robert JJ, Maassen JA, Meier M, Panz VR, Kim CA, Tubiana-Rufi N, Czernichow P, Seemanova E, Buchanan CR, Lacombe D, Vigouroux C, Lascols O, Kahn CR, Capeau J, Lathrop M 2003 Prevalence of mutations in AGPAT2 among human lipodystrophies. Diabetes 52:1573-1578.

11. Garg A, Wilson R, Barnes R, Arioglu E, Zaidi Z, Gurakan F, Kocak N, O'Rahilly S, Taylor SI, Patel SB, Bowcock AM 1999 A gene for congenital generalized lipodystrophy maps to human chromosome 9q34. J Clin Endocrinol Metab 84:3390-3394.

12. Agarwal AK, Arioglu E, de Almeida S, Akkoc N, Taylor SI, Bowcock AM, Barnes RI, Garg A 2002 AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. Nat Genet 31:21-23.

13. Magre J, Delepine M, Khallouf E, Gedde-Dahl T, Jr., Van Maldergem L, Sobel E, Papp J, Meier M, Megarbane A, Bachy A, Verloes A, d'Abronzo FH, Seemanova E, Assan R, Baudic N, Bourut C, Czernichow P, Huet F, Grigorescu F, de Kerdanet M, Lacombe D, Labrune P, Lanza M, Loret H, Matsuda F, Navarro J, Nivelon-Chevalier A, Polak M, Robert JJ, Tric P, Tubiana-Rufi N, Vigouroux C, Weissenbach J, Savasta S, Maassen JA, Trygstad O, Bogalho P, Freitas P, Medina JL, Bonnicci F, Joffe BI, Loyson G, Panz VR, Raal FJ, O'Rahilly S, Stephenson T, Kahn CR, Lathrop M, Capeau J 2001 Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13. Nat Genet 28:365-370.

14. Kim CA, Delepine M, Boutet E, El Mourabit H, Le Lay S, Meier M, Nemani M, Bridel E, Leite CC, Bertola DR, Semple RK, O'Rahilly S, Dugail I, Capeau J, Lathrop M, Magre J 2008

Association of a homozygous nonsense caveolin-1 mutation with Berardinelli-Seip congenital lipodystrophy. J Clin Endocrinol Metab 93:1129-1134.

15. Hayashi YK, Matsuda C, Ogawa M, Goto K, Tominaga K, Mitsuhashi S, Park YE, Nonaka I, Hino-Fukuyo N, Haginoya K, Sugano H, Nishino I 2009 Human PTRF mutations cause secondary deficiency of caveolins resulting in muscular dystrophy with generalized lipodystrophy. J Clin Invest 119:2623-2633.

16. Shastry S, Delgado MR, Dirik E, Turkmen M, Agarwal AK, Garg A 2010 Congenital generalized lipodystrophy, type 4 (CGL4) associated with myopathy due to novel PTRF mutations. Am J Med Genet A 152A:2245-2253.

17. Rajab A, Straub V, McCann LJ, Seelow D, Varon R, Barresi R, Schulze A, Lucke B, Lutzkendorf S, Karbasiyan M, Bachmann S, Spuler S, Schuelke M 2010 Fatal cardiac arrhythmia and long-QT syndrome in a new form of congenital generalized lipodystrophy with muscle rippling (CGL4) due to PTRF-CAVIN mutations. PLoS Genet 6:e1000874.

18. Takeuchi K, Reue K 2009 Biochemistry, physiology, and genetics of GPAT, AGPAT, and lipin enzymes in triglyceride synthesis. Am J Physiol Endocrinol Metab 296:E1195-1209.

19. Agarwal AK, Garg A 2010 Enzymatic activity of the human 1-acylglycerol-3-phosphate-O-acyltransferase isoform 11: upregulated in breast and cervical cancers. J Lipid Res 51:2143-2152.

20. Agarwal AK, Garg A 2003 Congenital generalized lipodystrophy: significance of triglyceride biosynthetic pathways. Trends Endocrinol Metab 14:214-221.

21. Szymanski KM, Binns D, Bartz R, Grishin NV, Li WP, Agarwal AK, Garg A, Anderson RG, Goodman JM 2007 The lipodystrophy protein seipin is found at endoplasmic reticulum lipid droplet junctions and is important for droplet morphology. Proc Natl Acad Sci U S A 104:20890-20895.

22. Fei W, Shui G, Gaeta B, Du X, Kuerschner L, Li P, Brown AJ, Wenk MR, Parton RG, Yang H 2008 Fld1p, a functional homologue of human seipin, regulates the size of lipid droplets in yeast. J Cell Biol 180:473-482.

23. Payne VA, Grimsey N, Tuthill A, Virtue S, Gray SL, Dalla Nora E, Semple RK, O'Rahilly S, Rochford JJ 2008 The human lipodystrophy gene BSCL2/seipin may be essential for normal adipocyte differentiation. Diabetes 57:2055-2060.

24. Garg A, Agarwal AK 2008 Caveolin-1: a new locus for human lipodystrophy. J Clin Endocrinol Metab 93:1183-1185.

25. Simha V, Garg A 2003 Phenotypic heterogeneity in body fat distribution in patients with congenital generalized lipodystrophy due to mutations in the AGPAT2 or Seipin genes. J Clin Endocrinol Metab 88:5433-5437.

26. Simha V, Agarwal AK, Aronin PA, Iannaccone ST, Garg A 2008 Novel subtype of congenital generalized lipodystrophy associated with muscular weakness and cervical spine instability. Am J Med Genet A 146A:2318-2326.

27. Simha V, Agarwal AK, Oral EA, Fryns JP, Garg A 2003 Genetic and phenotypic heterogeneity in patients with mandibuloacral dysplasia-associated lipodystrophy. J Clin Endocrinol Metab 88:2821-2824.

28. Freidenberg GR, Cutler DL, Jones MC, Hall B, Mier RJ, Culler F, Jones KL, Lozzio C, Kaufmann S 1992 Severe insulin resistance and diabetes mellitus in mandibuloacral dysplasia. Am J Dis Child 146:93-99.

29. Novelli G, Muchir A, Sangiuolo F, Helbling-Leclerc A, D'Apice MR, Massart C, Capon F, Sbraccia P, Federici M, Lauro R, Tudisco C, Pallotta R, Scarano G, Dallapiccola B, Merlini L,

Bonne G 2002 Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. Am J Hum Genet 71:426-431.

30. Agarwal AK, Fryns JP, Auchus RJ, Garg A 2003 Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia. Hum Mol Genet 12:1995-2001.

31. Agarwal AK, Zhou XJ, Hall RK, Nicholls K, Bankier A, Van Esch H, Fryns J-P, Garg A 2006 Focal segmental glomerulosclerosis in patients with mandibuloacral dysplasia due to zinc metalloproteinase deficiency. J Investig Med 54:208-213.

32. Ahmad Z, Zackai E, Medne L, Garg A 2010 Early onset mandibuloacral dysplasia due to compound heterozygous mutations in ZMPSTE24. Am J Med Genet A 152A:2703-2710.

33. Garg A, Hernandez MD, Sousa AB, Subramanyam L, Martinez de Villarreal L, dos Santos HG, Barboza O 2010 An autosomal recessive syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy. J Clin Endocrinol Metab 95:E58-63.

34. Horikoshi A, Iwabuchi S, Iizuka Y, Hagiwara T, Amaki I 1980 [A case of partial lipodystrophy with erythema, dactylic deformities, calcification of the basal ganglia, immunological disorders and low IQ level (author's transl)]. Rinsho Shinkeigaku – Clinical Neurology 20:173-180.

35. Tanaka M, Miyatani N, Yamada S, Miyashita K, Toyoshima I, Sakuma K, Tanaka K, Yuasa T, Miyatake T, Tsubaki T 1993 Hereditary lipo-muscular atrophy with joint contracture, skin eruptions and hyper-gamma-globulinemia: a new syndrome. Intern Med 32:42-45.

36. Agarwal AK, Xing C, DeMartino GN, Mizrachi D, Hernandez MD, Sousa AB, Martinez de Villarreal L, dos Santos HG, Garg A 2010 PSMB8 encoding the beta5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. Am J Hum Genet 87:866-872.

37. Rivett AJ, Hearn AR 2004 Proteasome function in antigen presentation: immunoproteasome complexes, Peptide production, and interactions with viral proteins. Curr Protein Pept Sci 5:153-161.

38. Torrelo A, Patel S, Colmenero I, Gurbindo D, Lendinez F, Hernandez A, Lopez-Robledillo JC, Dadban A, Requena L, Paller AS 2010 Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. J Am Acad Dermatol 62:489-495.

39. Ramot Y, Czarnowicki T, Maly A, Navon-Elkan P, Zlotogorski A 2010 Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature Syndrome: A Case Report. Pediatr Dermatol 5:538-41.

40. Dunnigan MG, Cochrane MA, Kelly A, Scott JW 1974 Familial lipoatrophic diabetes with dominant transmission. A new syndrome. Q J Med 43:33-48.

41. Kobberling J, Dunnigan MG 1986 Familial partial lipodystrophy: two types of an X linked dominant syndrome, lethal in the hemizygous state. J Med Genet 23:120-127.

42. Garg A, Peshock RM, Fleckenstein JL 1999 Adipose tissue distribution in patients with familial partial lipodystrophy (Dunnigan variety). J Clin Endocrinol Metab 84:170-174.

43. Garg A 2000 Gender differences in the prevalence of metabolic complications in familial partial lipodystrophy (Dunnigan variety). J Clin Endocrinol Metab 85:1776-1782.

44. Garg A, Speckman RA, Bowcock AM 2002 Multisystem dystrophy syndrome due to novel missense mutations in the amino-terminal head and alpha-helical rod domains of the lamin A/C gene. Am J Med 112:549-555.

45. Subramanyam L, Simha V, Garg A 2010 Overlapping syndrome with familial partial lipodystrophy, Dunnigan variety and cardiomyopathy due to amino-terminal heterozygous

missense lamin A/C mutations. Clin Genet 78:66-73.

46. Peters JM, Barnes R, Bennett L, Gitomer WM, Bowcock AM, Garg A 1998 Localization of the gene for familial partial lipodystrophy (Dunnigan variety) to chromosome 1q21-22. Nat Genet 18:292-295.

47. Cao H, Hegele RA 2000 Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan-type familial partial lipodystrophy. Hum Mol Genet 9:109-112.

48. Shackleton S, Lloyd DJ, Jackson SN, Evans R, Niermeijer MF, Singh BM, Schmidt H, Brabant G, Kumar S, Durrington PN, Gregory S, O'Rahilly S, Trembath RC 2000 LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. Nat Genet 24:153-156.

49. Speckman RA, Garg A, Du F, Bennett L, Veile R, Arioglu E, Taylor SI, Lovett M, Bowcock AM 2000 Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C. Am J Hum Genet 66:1192-1198.

50. Agarwal AK, Garg A 2002 A novel heterozygous mutation in peroxisome proliferator-activated receptor-g gene in a patient with familial partial lipodystrophy. J Clin Endocrinol Metab 87:408-411.

51. Hegele RA, Cao H, Frankowski C, Mathews ST, Leff T 2002 PPARG F388L, a transactivation-deficient mutant, in familial partial lipodystrophy. Diabetes 51:3586-3590.

52. Semple RK, Chatterjee VK, O'Rahilly S 2006 PPAR gamma and human metabolic disease. J Clin Invest 116:581-589.

53. George S, Rochford JJ, Wolfrum C, Gray SL, Schinner S, Wilson JC, Soos MA, Murgatroyd PR, Williams RM, Acerini CL, Dunger DB, Barford D, Umpleby AM, Wareham NJ, Davies HA, Schafer AJ, Stoffel M, O'Rahilly S, Barroso I 2004 A family with severe insulin resistance and diabetes due to a mutation in AKT2. Science 304:1325-1328.

54. Rubio-Cabezas O, Puri V, Murano I, Saudek V, Semple RK, Dash S, Hyden CS, Bottomley W, Vigouroux C, Magre J, Raymond-Barker P, Murgatroyd PR, Chawla A, Skepper JN, Chatterjee VK, Suliman S, Patch AM, Agarwal AK, Garg A, Barroso I, Cinti S, Czech MP, Argente J, O'Rahilly S, Savage DB 2009 Partial lipodystrophy and insulin resistant diabetes in a patient with a homozygous nonsense mutation in CIDEC. EMBO Mol Med 1:280-287.

55. Gandotra S, Le Dour C, Bottomley W, Cervera P, Giral P, Reznik Y, Charpentier G, Auclair M, Delepine M, Barroso I, Semple RK, Lathrop M, Lascols O, Capeau J, O'Rahilly S, Magre J, Savage DB, Vigouroux C 2011 Perilipin deficiency and autosomal dominant partial lipodystrophy. N Engl J Med 364:740-748.

56. Olofsson SO, Bostrom P, Andersson L, Rutberg M, Levin M, Perman J, Boren J 2008 Triglyceride containing lipid droplets and lipid droplet-associated proteins. Curr Opin Lipidol 19:441-447.

57. Nishino N, Tamori Y, Tateya S, Kawaguchi T, Shibakusa T, Mizunoya W, Inoue K, Kitazawa R, Kitazawa S, Matsuki Y, Hiramatsu R, Masubuchi S, Omachi A, Kimura K, Saito M, Amo T, Ohta S, Yamaguchi T, Osumi T, Cheng J, Fujimoto T, Nakao H, Nakao K, Aiba A, Okamura H, Fushiki T, Kasuga M 2008 FSP27 contributes to efficient energy storage in murine white adipocytes by promoting the formation of unilocular lipid droplets. J Clin Invest 118:2808-2821.

58. Caron M, Auclair M, Donadille B, Bereziat V, Guerci B, Laville M, Narbonne H, Bodemer C, Lascols O, Capeau J, Vigouroux C 2007 Human lipodystrophies linked to mutations in A-type lamins and to HIV protease inhibitor therapy are both associated with prelamin A accumulation, oxidative stress and premature cellular senescence. Cell Death Differ 14:1759-

1767.

59. Garg A, Vinaitheerthan M, Weatherall P, Bowcock A 2001 Phenotypic heterogeneity in patients with familial partial lipodystrophy (Dunnigan variety) related to the site of mis-sense mutations in Lamin A/C (LMNA) gene. J Clin Endocrinol Metab 86:59-65.

60. Al-Shali K, Cao H, Knoers N, Hermus AR, Tack CJ, Hegele RA 2004 A single-base mutation in the peroxisome proliferator-activated receptor gamma4 promoter associated with altered in vitro expression and partial lipodystrophy. J Clin Endocrinol Metab 89:5655-5660.

61. Garg A, Subramanyam L, Agarwal AK, Simha V, Levine B, D'Apice MR, Novelli G, Crow Y 2009 Atypical progeroid syndrome due to heterozygous missense LMNA mutations. J Clin Endocrinol Metab 94:4971-4983.

62. Shastry S, Simha V, Godbole K, Sbraccia P, Melancon S, Yajnik CS, Novelli G, Kroiss M, Garg A 2010 A novel syndrome of mandibular hypoplasia, deafness, and progeroid features associated with lipodystrophy, undescended testes, and male hypogonadism. J Clin Endocrinol Metab 95:E192-197.

63. Sensenbrenner JA, Hussels IE, Levin LS 1975 CC – A low birthweight syndrome, Rieger syndrome. Birth Defects 11:423-426.

64. Gorlin RJ, Cervenka J, Moller K, Horrobin M, Witkop J 1975 Rieger anomaly and growth retardation (The S-H-O-R-T Syndrome). Birth Defects 11:46-48.

65. O'Neill B, Simha V, Kotha V, Garg A 2007 Body fat distribution and metabolic variables in patients with neonatal progeroid syndrome. Am J Med Genet A 143:1421-1430.

66. Misra A, Peethambaram A, Garg A 2004 Clinical features and metabolic and autoimmune derangements in acquired partial lipodystrophy: report of 35 cases and review of the literature. Medicine (Baltimore) 83:18-34.

67. Misra A, Garg A 2003 Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature. Medicine 82:129-146;

68. Chen D, Misra A, Garg A 2002 Lipodystrophy in human immunodeficiency virus-infected patients. J Clin Endocrinol Metab 87:4845-4856.

69. Carr A 2000 HIV protease inhibitor-related lipodystrophy syndrome. Clinical Infectious Diseases 30 Suppl 2:S135-142.

70. Grinspoon S, Carr A 2005 Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med 352:48-62.

71. Savage DB, Semple RK, Clatworthy MR, Lyons PA, Morgan BP, Cochran EK, Gorden P, Raymond-Barker P, Murgatroyd PR, Adams C, Scobie I, Mufti GJ, Alexander GJ, Thiru S, Murano I, Cinti S, Chaudhry AN, Smith KG, O'Rahilly S 2009 Complement abnormalities in

acquired lipodystrophy revisited. J Clin Endocrinol Metab 94:10-16.

72. Hudon SE, Coffinier C, Michaelis S, Fong LG, Young SG, Hrycyna CA 2008 HIV-protease inhibitors block the enzymatic activity of purified Ste24p. Biochem Biophys Res Commun 374:365-368.

73. Bastard JP, Caron M, Vidal H, Jan V, Auclair M, Vigouroux C, Luboinski J, Laville M, Malachi M, Girard PM, Rozenbaum W, Levan P, Capeau J 2002 Association between altered expression of adipogenic factor SREBP1 in lipoatrophic adipose tissue from HIV-1-infected patients and abnormal adipocyte differentiation and insulin resistance. Lancet 359:1026-1031.

74. Murata H, Hruz PW, Mueckler M 2000 The mechanism of insulin resistance caused by HIV protease inhibitor therapy. J Biol Chem 275:20251-20254.

75. Carr A, Miller J, Law M, Cooper DA 2000 A syndrome of lipoatrophy, lactic acidaemia and

liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. AIDS 14:F25-32.

76. Lee H, Hanes J, Johnson KA 2003 Toxicity of nucleoside analogues used to treat AIDS and the selectivity of the mitochondrial DNA polymerase. Biochemistry 42:14711-14719.

77. Klopstock T, Naumann M, Seibel P, Shalke B, Reiners K, Reichmann H 1997 Mitochondrial DNA mutations in multiple symmetric lipomatosis. Molecular & Cellular Biochemistry 174:271-275.

78. Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman ML, Taylor SI, Gorden P, Garg A 2002 Leptin-replacement therapy for lipodystrophy. N Engl J Med 346:570-578.

79. Simha V, Szczepaniak LS, Wagner AJ, DePaoli AM, Garg A 2003 Effect of leptin replacement on intrahepatic and intramyocellular lipid content in patients with generalized lipodystrophy. Diabetes Care 26:30-35.

80. Park JY, Javor ED, Cochran EK, DePaoli AM, Gorden P 2007 Long-term efficacy of leptin replacement in patients with Dunnigan-type familial partial lipodystrophy. Metabolism 56:508-516.

81. Simha V, Subramanyam L, Szczpaniak L,Quittner C, Adams-HuetB, Snell P,Garg,A 2012 Comparison of efficacy and safety of leptin replacement therapy in moderately and severely hypoleptinemic patients with familial partial lipodystrophy of the Dunnigan variety. J Clin Endocrinol Metab 97(3): 785-92.

Resources

UT Southwestern Lipodystrophy website:
www.lipodystrophy.info

GeneTests website:
http://www.ncbi.nlm.nih.gov/sites/genetests/

Clinical Centers & Medical Experts

Abhimanyu Garg, M.D.
Professor of Internal Medicine,
Chief, Division of Nutrition and Metabolic Diseases,
Distinguished Chair in Human Nutrition Research
UT Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, K5.214
Dallas, TX 75390-8537

Phillip Gorden, M.D.

Clinical & Cellular Biology Section
NIDDK, National Institutes of Health
Building 10-CRC , Room 6-5952
10 Center Dr.
Bethesda, MD 20892-1770

Elif Ora, M.D.
Associate Professor, Endocrinology

University of Michigan
Internal Medicine Metabolism, Endocrinology & Diabetes
Domino's Farms
24 Frank Lloyd Wright Dr, GPS: 4000 Ave Maria Drive
Ann Arbor, MI 48109

Acknowledgements

NORD is grateful to the following medical expert for serving as author of this Physician Guide:

Abhimanyu Garg, M.D.
Professor of Internal Medicine,
Chief, Division of Nutrition and Metabolic Diseases,
Distinguished Chair in Human Nutrition Research
UT Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, K5.214
Dallas, TX 75390-8537

This NORD Physician Guide was made possible by an educational grant from Amylin Pharmaceuticals

Patient Support and Resources

National Organization for Rare Disorders (NORD)
55 Kenosia Avenue
PO Box 1968
Danbury, CT 06813-1968
Phone: (203) 744-0100
Toll free: (800) 999-NORD
Fax: (203) 798-2291

www.rarediseases.org
orphan@rarediseases.org

NORD is grateful to the following medical expert for serving as author of this Physician Guide:

Abhimanyu Garg, M.D.
Professor of Internal Medicine,
Chief, Division of Nutrition and Metabolic Diseases,
Distinguished Chair in Human Nutrition Research
UT Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, K5.214
Dallas, TX 75390-8537

This NORD Physician Guide was made possible by an educational grant from Amylin Pharmaceuticals

NORD Guides for Physicians

#1 The Pediatrician's Guide to Tyrosinemia Type 1

#2 The Pediatrician's Guide to Ornithine Transcarbamylase Deficiency...and other Urea Cycle Disorders

#3 The Physician's Guide to Primary Lateral Sclerosis

#4 The Physician's Guide to Pompe Disease

#5 The Physician's Guide to Multiple System Atrophy

#6 The Physician's Guide to Hereditary Ataxia

#7 The Physician's Guide to Giant Hypertrophic Gastritis and Menetrier's Disease

#8 The Physician's Guide to Amyloidosis

#9 The Physician's Guide to Medullary Thyroid Cancer

#10 The Physician's Guide to Hereditary Angioedema (HAE)

#11 The Physician's Guide to The Homocystinurias

#12 The Physician's Guide to Treacher Collins Syndrome

#13 The Physician's Guide to Urea Cycle Disorders

#14 The Physician's Guide to Myelofibrosis

#15 The Physician's Guide to Lipodystrophy Disorders

These booklets are available free of charge. To obtain copies, call or write to NORD or download the text from www.NORDPhysicianGuides.org.

For information on rare disorders and the voluntary health organizations that help people affected by them, visit NORD's web site at www.rarediseases.org or call (800) 999-NORD or (203) 744-0100.

NORD helps patients and families affected by rare disorders by providing:

- Physician-reviewed information in understandable language
- Referrals to support groups and other sources of help
- Networking with other patients and families
- Medication assistance programs
- Grants and fellowships to encourage research on rare diseases
- Advocacy for health-related causes that affect the rare-disease community
- Publications for physicians and other medical professionals

Contact NORD at orphan@rarediseases.org.

National Organization for Rare Disorders (NORD)
PO Box 1968
Danbury, CT 06813-1968
Phone: (203) 744-0100
Toll free: (800) 999-NORD
Fax: (203) 798-2291

This booklet was made possible through an educational grant from Amylin Pharmaceuticals.