Lipodystrophies

Disorders characterized by selective loss of adipose tissue.
Metabolic Complications of Lipodystrophies

- Insulin resistance, Premature DM
- Hypertriglyceridemia, low HDL cholesterol
- Polycystic ovarian syndrome
- Acanthosis nigricans
- Hepatic Steatosis
- Hypertension (rare)

Etiological Classification

GENETIC
- Autosomal recessive
- Autosomal dominant
- De novo mutations

ACQUIRED
- Autoimmune
- HAART-induced in HIV-infected patients
- Others

HAART: Highly active antiretroviral therapy
HIV: Human Immunodeficiency virus
Phenotypic Classification

GENERALIZED LIPODYSTROPHY
- Congenital generalized lipodystrophy (CGL)
- Acquired generalized lipodystrophy (AGL)

PARTIAL LIPODYSTROPHY
- Familial partial lipodystrophy (FPL)
- Acquired partial lipodystrophy (APL)
- HAART-induced in HIV-infected patients (LD-HIV)

LOCALIZED LIPODYSTROPHY

Genetic Lipodystrophies

Autosomal Recessive
- Congenital generalized lipodystrophy (CGL)
- Mandibuloacral dysplasia (MAD)-associated
- Autoinflammmatory (JMP)
- Other types
  - FPL
  - SHORT syndrome
  - Neonatal Progeroid syndrome
  - MDP syndrome

Autosomal Dominant
- Familial partial lipodystrophy (FPL)
- Atypical progeroid syndrome
- Hutchinson-Gilford progeria syndrome
- SHORT syndrome

Congenital Generalized Lipodystrophy (Berardinelli-Seip Syndrome)

- Autosomal recessive
- Prevalence < 1 in 10 million
- Reported in ~300 patients of various ethnicities

Congenital Generalized Lipodystrophy (Clinical Characteristics)

- Generalized lack of body fat and extreme muscularity from birth (essential criterion)
- Acanthosis nigricans
- Hepatomegaly due to steatosis
- Acromegaloïd features, umbilical hernia
- Clitoromegaly and hirsutism in women
- Lytic lesions in appendicular skeleton

Characterization of CGL Phenotype
(Laboratory Characteristics)

- Fasting or postprandial hyperinsulinemia
- Marked insulin resistance
- IGT or DM during teenage years
- Hypertriglyceridemia and low HDL cholesterol
- Characteristic body fat distribution on MRI
- Markedly reduced leptin and adiponectin levels

Simha & Garg. JCEM, 2003;88(11):5433-7
Haque et al. JCEM 2002;87:2395-2398
Garg et al. Diabetes Care 1995
DM in CGL Patients

- Hyperinsulinemia at or shortly after birth
- IGT during childhood
- DM usually in teenage years (onset 1-37 y)
- Severe amyloidosis of islets (90% affected) with β cell atrophy
- Resistant to ketosis
- Requires high dose of insulin (100-3000 u/d)

Garg et al. Diabetes Care 1995
Garg A. N Engl J Med 350; 1220-34, 2004

Serum Leptin Levels in CGL

Haque et al. JCEM 87:2395-8, 2002
CGL
Molecular Basis

Subtype   | Gene
----------|-------
CGL1      | AGPAT2
CGL2      | BSCL2
CGL3      | CAV1
CGL4      | PTRF

AGPAT2 mutations in CGL, type 1
(TG biosynthetic pathway)
**BSCL2 Mutations in CGL, Type 2**

- **BSCL2** located on chromosome 11q13
- Encodes a 462 amino acid transmembrane ER protein, seipin
- Seipin has a CAAX motif at C-terminal and an N-glycosylation site
- Role in lipid droplet formation and adipocyte differentiation

Magre et al. Nat Genet 2001;28:365-70  
Szymanski et al. PNAS 104:20890-20895, 2007  

**Seipin Deficiency Impairs Lipid Droplet Fusion**

Phenotypic Differences in CGL Patients with AGPAT2 and BSCL2 Mutations

<table>
<thead>
<tr>
<th></th>
<th>CGL1 (AGPAT2)</th>
<th>CGL2 (BSCL2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Retardation</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Lytic bone lesions</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Loss of Mechanical Fat</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Metabolic Abnormalities</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Agarwal, Simha et al. JCEM 2003; 88:4940-47

Caveolin 1 mutation in CGL, Type 3

- 22-year-old F from Brazil
- Homozygous p.Glu38X mutation
- Poor growth, short stature
- Generalized lipodystrophy, hepato-splenomegaly, HTG, acanthosis and hirsutism
- Diabetes mellitus – age 13
- Vitamin D resistance
- Amenorrhea - age 20

Kim, CA et al. JCEM 2008;93:1129-1134
Garg and Agarwal, JCEM 2008;93:1183-1185
CGL, Type 4

- ~ 30 patients reported
- Generalized loss of fat
- Congenital myopathy, elevated serum creatine kinase levels
- Percussion induced muscle mounding
- Congenital pyloric stenosis
- Long QT interval, arrhythmias, sudden death
- Atlanto-axial instability


PTRF mutations in CGL, type 4

- PTRF encodes polymerase I and transcript release factor
- PTRF contributes to caveolae formation
- PTRF Induces expression of caveolins 1 and 3
- All reported mutations are null
- Loss of PTRF results in mislocalization of caveolins in skeletal muscles

Familial Partial Lipodystrophy

- SC fat loss from the extremities resulting in extreme musculature
- Fat accumulation in the neck, face & intra-abdominal area
- Acanthosis nigricans
- Fasting or postprandial hyperinsulinemia
- Predisposition to DM, HTG and hepatic steatosis
- Low HDL cholesterol levels


FPL
Molecular Basis

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPL1</td>
<td>Unknown</td>
</tr>
<tr>
<td>FPL2</td>
<td>LMNA</td>
</tr>
<tr>
<td>FPL3</td>
<td>PPARG</td>
</tr>
<tr>
<td>FPL4</td>
<td>PLIN1</td>
</tr>
<tr>
<td>FPL5</td>
<td>AKT2</td>
</tr>
<tr>
<td>FPL6</td>
<td>CIDEC</td>
</tr>
</tbody>
</table>
Familial Partial Lipodystrophy, Type 2 (Dunnigan type)

- Autosomal dominant
- Prevalence < 1 in 10 million
- Described in ~ 300 patients mainly of European ancestry
Lamin A/C Mutations in FPLD

* Cardiomyopathy  † Emery-Dreifuss Muscular Dystrophy  ‡ Limb Girdle Muscular Dystrophy  § Mild Myopathy  ¶ Mild Lipodystrophy

Structure of Nuclear Lamina

Pathogenesis of lipodystrophy in FPLD patients

• *LMNA* mutations induce nuclear dysfunction resulting in premature death or apoptosis of adipocytes
• Why fat loss spares the face, neck and intra-abdominal region?

**PPARG** Mutations in FPL, type 3

• PPARγ is essential transcription factor for adipogenesis
• Milder phenotype than Dunnigan variety
• More fat loss from distal extremities
• ~40 patients reported

Agarwal & Garg. JCEM 2002; 87: 408-11
Hegele et al. Diabetes 2002;51:3586-90
Savage et al. Diabetes 2003; 52:910-17

Garg A. N Engl J Med 350; 1220-34, 2004
**FPL, type 4: PLIN1 mutations**

- Perilipin 1 is required for optimal lipid incorporation and release from the lipid droplets
- Three pedigrees reported with heterozygous null mutations
- Partial lipodystrophy, severe dyslipidemia, and insulin-resistant diabetes
- More uniform reduction in all fat depots
- Small-sized adipocytes
- Pattern of fat distribution remains unclear

Gandotra et al. NEJM 364, 740-8; 2011

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**FPL, type 5: AKT2 mutations**

- AKT2 encodes a phosphatidyl inositol-dependent Serine-Threonine protein kinase
- Single family reported
- R274H heterozygous mutation in a pedigree with lipodystrophy, DM and insulin resistance
- Pattern of fat loss unknown
- R274H mutation causes reduced fat accumulation in 3T3-L1 preadipocytes

George S, et al. Science 304; 1325-28, 2004
Role of AKT2 in Insulin Signaling

![Diagram of AKT2 in Insulin Signaling](image)


Autosomal recessive FPL, type 6 (CIDE6 mutation)

- 19-y-old Ecuadorian girl
- Recurrent diabetic ketoacidosis
- Homozygous p.E186X mutation
- CIDE6 required for unilocular lipid droplet formation

![Perilipin Staining](image)

Mandibuloacral Dysplasia (MAD) (Clinical characteristics)

- Skeletal abnormalities
  - Mandibular and clavicular hypoplasia
  - Acro-osteolysis
- Progeroid manifestations
  - Cutaneous atrophy with prominent superficial vasculature and mottled hyperpigmentation
  - Thin beaked nose
  - Hair loss
- Delayed dentition and closure of cranial sutures, crowded teeth
- Joint stiffness
- Lipodystrophy: partial (type A) or generalized (type B)


Mandibuloacral Dysplasia (Laboratory characteristics)

- Diabetes, glucose intolerance, insulin resistance
- Mild hypertriglyceridemia and low levels of HDL cholesterol have been reported in some patients with MAD

MAD
Molecular Basis

Subtype          Gene
• MAD A          LMNA
• MAD B          ZMPSTE24

Role of ZMPSTE24 in Post-translational Processing of Prelamin A

Phenotypic Differences in MAD type A and B with \textit{LMNA} and \textit{ZMPSTE24} Mutations

<table>
<thead>
<tr>
<th></th>
<th>MAD A (LMNA)</th>
<th>MAD B (ZMPSTE24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>2-4 y</td>
<td>&lt;2 y</td>
</tr>
<tr>
<td>Progeroid features</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Premature at birth</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>SC calcified nodules</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>


Mandibular Hypoplasia, Deafness and Progeroid (MDP) Syndrome

- Generalized loss of subcutaneous fat
- Mandibular hypoplasia
- Short stature
- Joint contractures
- Sclerodermatous skin with mottled pigmentation
- Hypogonadism and undescended testes in males
- Molecular genetic basis unknown

Mandibular Hypoplasia, Deafness and Progeroid (MDP) Syndrome

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>MAD (LMNA) n=28</th>
<th>MAD (ZMPSTE24) n=8</th>
<th>MDP n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandibular hypoplasia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sclerodermatous skin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>Partial</td>
<td>Partial</td>
<td>Partial/generalized</td>
</tr>
<tr>
<td>Clavicular hypoplasia</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Acro-osteolysis</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Deafness</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Undescended testes, male hypogonadism</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>


Atypical Progeroid Syndrome due to LMNA mutations

- Progeroid features
  - Short stature, beaked nose, premature graying, partial alopecia, high-pitched voice, skin atrophy over the hands and feet
- Diabetes
- Partial or generalized lipodystrophy
- Skin pigmentation
- Mandibular hypoplasia

Garg et al. JCEM, 94(12), 4971-83 (2009)
Joint Contractures, Microcytic Anemia, and Panniculitis-induced (JMP) Autoinflammatory Lipodystrophy

- Severe panniculitis-induced lipodystrophy (face, arms, thorax)
- No acanthosis nigricans or hyperinsulinemia
- Mild hypertriglyceridemia
- Low HDL cholesterol
- Mild elevations of liver enzymes
- Limb muscle atrophy, joint contractures (hands and feet)
- Microcytic hypochromic anemia
- Hypergammaglobulinemia

Garg et al. JCEM, 95, E58-63 (2010)

PSMB8 mutations in JMP syndrome
(Nakajo-Nishimura or Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature [CANDLE] syndromes)

- PSMB8 encodes β5i subunit of immunoproteasomes
- Immunoproteasomes are induced by γ interferon in lymphoid tissues
- Abnormal processing of autoantigens for MHC-class 1 presentation
- Altered immune response to a common pathogen triggering autoinflammation

Agarwal et al. AJHG 2010;87:866-72.
Liu et al. (2012) Arthritis & Rheumatism, 64(3), 895–907
Kitamura et al. (2011) JCI, 121(10), 4150–4160
Arima K et al. (2011) PNAS, 108, 14914-14919
SHORT Syndrome
Autosomal dominant and recessive

- Short stature
- Hyperextensibility of joints
- Ocular depression
- Rieger anomaly
- Teething delay
- Premature onset of DM
- Lipodystrophy

Neonatal Progeroid Syndrome
(Wiedemann-Rautenstrauch)

- Premature birth
- Oligoohydroamnios and IUGR
- Dry, deeply wrinkled skin
- Large, low set ears, and beaked nose
- Generalized loss of SC fat sparing gluteal region
- Normal glucose and lipids
- 25 patients reported, early death

Lipodystrophies
Disorders of Adipose Tissue Development, Differentiation and Death


Lipid droplet formation in adipocytes and lipodystrophy genes

Lipodystrophy in HIV-infected patients (LD-HIV)

- Loss of sc fat from the extremities and face
- ↑ Fat deposition in the neck and abdomen
- ↑↑ TG and ↓ HDL cholesterol
- ↑ Insulin levels

Lipodystrophy in HIV-infected Patients (MRI images of fat distribution)
Risk Factors for Lipodystrophy in HIV-infected Patients

- HIV-1 protease inhibitors (PIs)
- Nucleoside Reverse Transcriptase inhibitors (NRTIs)
- Duration of HIV infection
- Others
  - Aging
  - Total body fat mass, nutritional status
  - Previous viral load, AIDS

Lipodystrophy in HIV+ Patients

- Characterization of phenotype of PI-induced lipodystrophy
- Characterize NRTI-induced fat loss and its associations
- Identify molecular mechanisms underlying these syndromes
- Development of new antiretrovirals not associated with development of lipodystrophy
Acquired Generalized Lipodystrophy

- About 80 cases reported
- Onset in childhood or adolescence
- Female-to-male ratio: 3:1
- Autoimmune mechanism

Acquired Generalized Lipodystrophy
Clinical Features and Metabolic Abnormalities

<table>
<thead>
<tr>
<th>Variables</th>
<th>Panniculitis Variety</th>
<th>Autoimmune Disease Variety</th>
<th>Idiopathic Variety</th>
</tr>
</thead>
<tbody>
<tr>
<td>M : F</td>
<td>7 : 11</td>
<td>5 : 14</td>
<td>9 : 33</td>
</tr>
<tr>
<td>Age (y)</td>
<td>3 - 59</td>
<td>6 - 36</td>
<td>2 - 60</td>
</tr>
<tr>
<td>Age of onset (y)</td>
<td>0.2 - 29</td>
<td>2 - 47*</td>
<td>0.6 - 28</td>
</tr>
<tr>
<td>Prevalence of DM (%)</td>
<td>44*</td>
<td>89</td>
<td>87.5</td>
</tr>
<tr>
<td>Age of onset of DM (y)</td>
<td>15.8 ±11.4</td>
<td>18.8 ±10.0</td>
<td>15.8 ±9.1</td>
</tr>
<tr>
<td>Acanthosis nigricans (%)</td>
<td>45</td>
<td>61.5</td>
<td>63</td>
</tr>
<tr>
<td>Hirsutism (%)</td>
<td>50</td>
<td>33</td>
<td>55</td>
</tr>
<tr>
<td>Hepatomegaly (%)</td>
<td>71</td>
<td>100</td>
<td>84</td>
</tr>
<tr>
<td>Hypertriglyceridemia (%)</td>
<td>59*</td>
<td>87.5</td>
<td>91</td>
</tr>
<tr>
<td>Elevated ALT (%)</td>
<td>45</td>
<td>82</td>
<td>56</td>
</tr>
</tbody>
</table>

* P < 0.05


Acquired Partial Lipodystrophy
(Barraquer-Simons syndrome)

- Progressive fat loss from face, neck, trunk and arms
- Normal or excess fat in hips and legs
- Preceding viral infection
- Duration of fat loss - 18 months to 6 year
- ~250 patients reported

Misra et al. Medicine 83; 18-34, 2004
Acquired Partial Lipodystrophy

Age of Onset ~10 Years
Female to Male Ratio 4:1
Low Serum C3 72%
C3NeF Positive 83%
Autoimmune Diseases 11%
Membrano-proliferative
Glomerulonephritis (MPGN) 19%

Misra et al. Medicine 83; 18-34, 2004

Clinical Features of APL

<table>
<thead>
<tr>
<th>Variable</th>
<th>Present Report</th>
<th>Literature Review</th>
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</thead>
<tbody>
<tr>
<td>Age of onset (yr)</td>
<td>10 ± 9.3</td>
<td>10.4 ± 7.5</td>
</tr>
<tr>
<td>Reporting age (yr)</td>
<td>29.9 ± 16.4</td>
<td>24.8 ± 13.9</td>
</tr>
<tr>
<td>Female:male ratio</td>
<td>7.8:1</td>
<td>3.5:1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>13.6</td>
<td>11.8</td>
</tr>
<tr>
<td>Low serum complement 3 (%)</td>
<td>66.6</td>
<td>73.6</td>
</tr>
<tr>
<td>Positive serum complement 3 nephritic factor (%)</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>Associated autoimmune disease (%)</td>
<td>20</td>
<td>9.1</td>
</tr>
<tr>
<td>MPGN (%)</td>
<td>3</td>
<td>27</td>
</tr>
</tbody>
</table>

Misra et al. Medicine, 83(1), 18-34, 2004
Localized Lipodystrophies

- Drug-induced
- Pressure-induced
- Panniculitis
- Centrifugal
- Idiopathic
Lipodystrophies
(When to suspect)

• “lean or nonobese” patients with:
  – Premature diabetes
  – Insulin resistant diabetes
  – Severe hypertriglyceridemia
  – Hepatic steatosis
  – Acanthosis nigricans
  – Polycystic ovarian syndrome

Generalized Lipodystrophies
(Differential Diagnosis)

• Malnutrition, starvation
• Anorexia nervosa
• Uncontrolled diabetes mellitus
• Thyrotoxicosis
• Adrenocortical insufficiency
• Cancer cachexia
• HIV-associated wasting
• Chronic infections
• Diencephalic Syndrome
Partial Lipodystrophies  
(Differential Diagnosis)

• Cushing’s syndrome  
• Truncal obesity  
• Multiple symmetric lipomatosis  
  (Madelung’s disease)

Conclusions

• Adipose tissue serves an important role as an endocrine organ  
• Loss of adipose tissue either due to a genetic or acquired disorders can lead to several metabolic complications  
• The resulting loss of adipocyte-derived hormone leptin is a key contributor to lipodystrophy associated insulin resistance and lipotoxicity