Lipodystrophy: Metabolic and Clinical Aspects

Resource Room Slide Series

THE ENDOCRINE SOCIETY
T-DEG
Genetic Basis of Lipodystrophies

Abhimanyu Garg, MD
Professor of Internal Medicine
Chief, Division of Nutrition and Metabolic Diseases
Distinguished Chair in Human Nutrition Research
University of Texas Southwestern Medical Center
Dallas, TX
There are no relevant financial relationships to disclose.
Learning Objectives

• Identify major subtypes of genetic lipodystrophies to establish starting points for diagnosis
• Define the molecular genetic basis of major subtypes of genetic lipodystrophies to better classify disease subtypes
• Describe mechanisms of metabolic complications in genetic lipodystrophies to target treatment appropriately
• Describe genotype-phenotype relationships among genetic lipodystrophies to provide an initial framework for clinical diagnosis
Lipodystrophies:

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

- Insulin resistance, premature diabetes
- Hypertriglyceridemia, low HDL cholesterol
- Polycystic ovarian syndrome
- Acanthosis nigricans
- Hepatic steatosis
- Hypertension (rare)
Genetic Lipodystrophies

Autosomal recessive:
- Congenital generalized lipodystrophy (CGL)
- Mandibuloacral dysplasia (MAD)-associated
- Joint contractures, microcytic anemia, and panniculitis-induced (JMP) autoinflammatory lipodystrophy
- Other types
  - Familial partial lipodystrophy (FPL)
  - SHORT syndrome
  - Neonatal progeroid syndrome
  - Mandibular hypoplasia, deafness, and progeroid (MDP) syndrome

Autosomal dominant:
- FPL
- Atypical progeroid syndrome
- Hutchinson-Gilford progeria syndrome
- SHORT syndrome

Congenital Generalized Lipodystrophy (CGL; Berardinelli-Seip Syndrome)

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

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

CGL Phenotype (Laboratory Characteristics)

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

Diabetes in CGL Patients

- Hyperinsulinemia at or shortly after birth
- IGT during childhood
- Diabetes usually in teenage years (onset 1-37 years of age)
- Severe amyloidosis of islets (90% affected) with β-cell atrophy
- Resistant to ketosis
- Requires high dose of insulin (100-3,000 units/day)

<table>
<thead>
<tr>
<th>Subtype:</th>
<th>Gene:</th>
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<tbody>
<tr>
<td>CGL1</td>
<td>AGPAT2</td>
</tr>
<tr>
<td>CGL2</td>
<td>BSCL2</td>
</tr>
<tr>
<td>CGL3</td>
<td>CAV1</td>
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<tr>
<td>CGL4</td>
<td>PTRF</td>
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</table>
Serum Leptin Levels in CGL

AGPAT2 Mutations in CGL Type 1 (Triglyceride Biosynthetic Pathway)
BSCL2 Mutations in CGL Type 2

- **BSCL2** gene located on chromosome 11q13
- Encodes a 462 amino acid transmembrane ER protein, seipin
- Seipin has a role in lipid droplet fusion and adipocyte differentiation
- CGL type 2 patients have loss of both mechanical and metabolically active adipose tissue

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>
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<tbody>
<tr>
<td>Mental retardation</td>
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<td>Cardiomyopathy</td>
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<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>
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Caveolin 1 Mutation in CGL Type 3

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

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 (FPL)

- Subcutaneous fat loss from the extremities resulting in extreme muscularity
- Fat accumulation in the neck, face, and intra-abdominal area
- Acanthosis nigricans
- Fasting or postprandial hyperinsulinemia
- Predisposition to diabetes, hypertriglyceridemia, and hepatic steatosis
- Low HDL cholesterol levels

<table>
<thead>
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<th>Subtype:</th>
<th>Gene:</th>
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<tbody>
<tr>
<td>FPL1</td>
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</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>CIDE C</td>
</tr>
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</table>
FPL Type 2
(Dunnigan Type; FPLD)

http://www.utsouthwestern.edu/media/files/2400/Familial-Partial-Dunnigan.pdf
FPLD, cont.

- Autosomal dominant
- Prevalence <1 in 10 million
- Described in ~300 patients mainly of European ancestry
LMNA (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 does fat loss spare 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

FPL Type 4: \textit{PLIN1} Mutations

- Perilipin 1 (\textit{PLIN1}) 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

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, diabetes, and insulin resistance
- Pattern of fat loss unknown
- R274H mutation causes reduced fat accumulation in 3T3-L1 preadipocytes

Role of AKT2 in Insulin Signaling

Autosomal Recessive FPL Type 6 (CIDE-C Mutation)

- 19-year-old Ecuadorian girl
- Recurrent diabetic ketoacidosis
- Homozygous p.E186X mutation
- CIDE-C required for unilocular lipid droplet formation

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)

MAD: Laboratory Characteristics

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

## MAD: Molecular Basis

<table>
<thead>
<tr>
<th>Subtype:</th>
<th>Gene:</th>
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<tbody>
<tr>
<td>MAD A</td>
<td>LMNA</td>
</tr>
<tr>
<td>MAD B</td>
<td>ZMPSTE24</td>
</tr>
</tbody>
</table>
Role of ZMPSTE24 in Post-Translational Processing of Prelamin A

### Phenotypic Differences in MAD Types A and B with *LMNA* and *ZMPSTE24* Mutations

<table>
<thead>
<tr>
<th>Trait</th>
<th>MAD A <em>(LMNA)</em></th>
<th>MAD B <em>(ZMPSTE24)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>2-4 years</td>
<td>&lt;2 years</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>
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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

# MDP Syndrome: Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>MAD (LMNA) n = 28</th>
<th>MAD (ZMPSTE24) n = 8</th>
<th>MDP n = 7</th>
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<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

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

Panniculitis in JMP Syndrome

**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

SHORT Syndrome
Autosomal Dominant and Recessive

- **S**hort stature
- **H**yperextensibility of joints
- **O**cular depression
- **R**ieger anomaly
- **T**eething delay
- Premature onset of diabetes
- Lipodystrophy
Neonatal Progeroid Syndrome (Wiedemann-Rautenstrauch)

• Premature birth
• Oligohydramnios and intrauterine growth restriction
• Dry, deeply wrinkled skin
• Large, low-set ears and beaked nose
• Generalized loss of subcutaneous 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

Future Directions

- To identify additional lipodystrophy genes
- To understand the role of these genes in adipocyte biology
- To understand the pathogenesis of metabolic complications in genetic syndromes of lipodystrophy
- To develop novel targeted therapies for various syndromes