Genetics of Lipodystrophy

Marissa Lightbourne, MD, MPH[a], Rebecca J. Brown, MD, MHSc[b,*]

KEYWORDS

• Lipodystrophy • Leptin • Berardinelli-Seip syndrome • Dunnigan syndrome
• Kobberling syndrome

KEY POINTS

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

BACKGROUND

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

The major subtypes of lipodystrophy include congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy

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[a] Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 10-CRC/1-3330, MSC 1103, 10 Center Drive, Bethesda, MD 20892, USA; [b] National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Building 10-CRC, Room 6-5942, 10 Center Drive, Bethesda, MD 20892, USA
* Corresponding author.
E-mail address: brownrebecca@mail.nih.gov

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(AGL), and acquired partial lipodystrophy (APL) (Fig. 1). There also are other systemic disorders associated with lipodystrophy, such as the progeroid disorders (Fig. 2) and autoinflammatory disorders. Localized forms of lipodystrophy and lipodystrophy in patients infected with the human immunodeficiency virus are the more

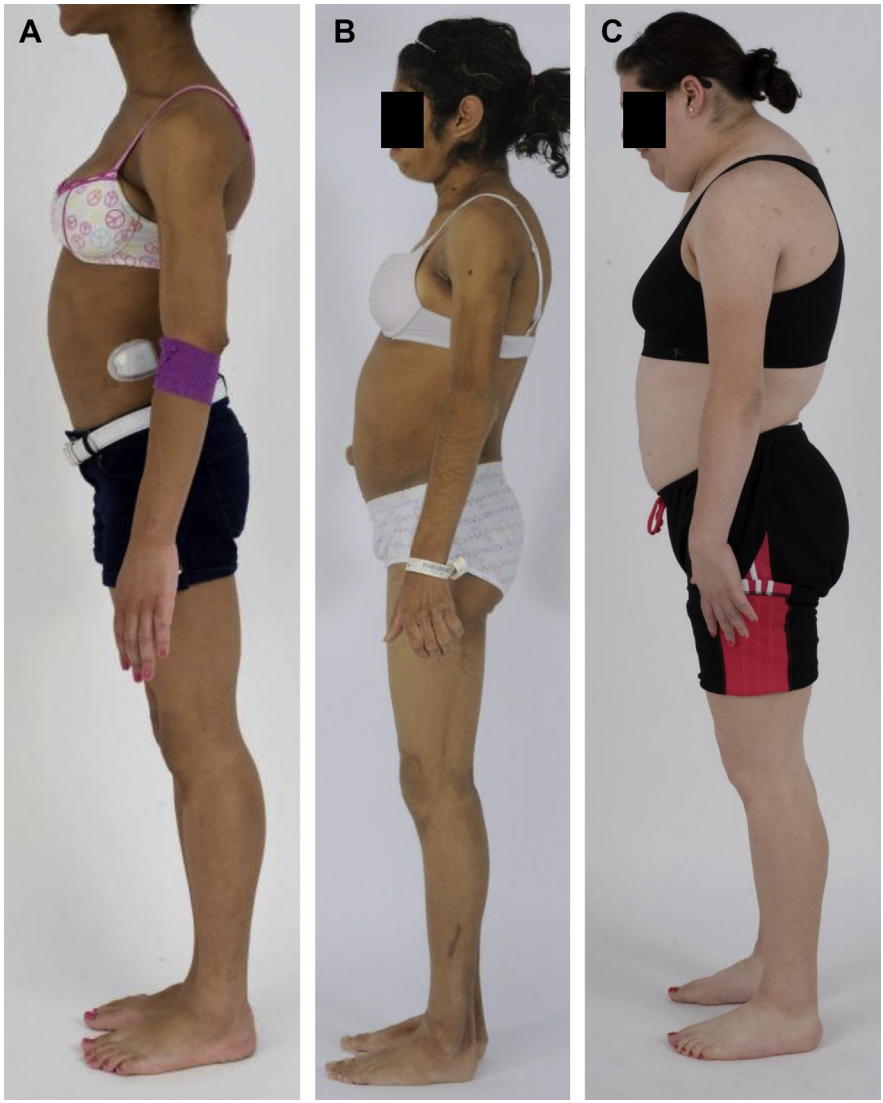

Fig. 1. Common genetic forms of lipodystrophy. (*A*) Adolescent with congenital generalized lipodystrophy due to recessive mutation in *AGPAT2*, demonstrating generalized lack of subcutaneous fat with prominent muscularity, acromegaloid hands and feet, and insulin pump use. (*B*) Adolescent with congenital generalized lipodystrophy due to recessive mutation in *BSCL2*, demonstrating generalized lack of fat, including the face, hands, and feet, prominent umbilicus, and severe acanthosis nigricans. (*C*) Adolescent with familial partial lipodystrophy due to *LMNA* mutation, demonstrating lack of fat in the buttocks and extremities, preserved truncal fat, and increased fat in the head, neck, and dorsocervical area.