Supplemental Table 1. Severe insulin resistance syndromes

Condition	Gene, inheritance pattern	Pathogenetic mechanisms	Clinical features	Treatment considerations
Defects of insulin signaling				
Donohue syndrome (leprechaunism) (OMIM 246200)	*INSR* (AR)	Impaired insulin receptors and abnormal signal transduction	Congenital onset, death usually during infancy, delayed vertical growth, hyperinsulinemia without dyslipidemia, thick skin without subcutaneous fat, acanthosis nigricans, distended abdomen, enlarged genitalia in males, cystic ovaries in females; elfin facies with prominent eyes, thick lips, upturned nostrils, and low-set posterior rotated ears; hypertrophic cardiomyopathy	rhIGF-1; considering concentrated insulins
Rabson-Mendenhall syndrome (OMIM 262190)	*INSR* (AR)	Impaired insulin receptors and abnormal signal transduction	Congenital onset, growth retardation, abnormal dentition, hyperinsulinemia without dyslipidemia, lack of subcutaneous fat, wasting of muscles, polycystic ovaries, genital enlargement, acanthosis nigricans, widely spaced eyes, broad nose, large low-set ears	
Type A insulin resistance syndrome (OMIM 147670)	*INSR* (AR)	Impaired insulin receptors and abnormal signal transduction	Typical presentation in adolescence or adulthood; acanthosis nigricans, acromegaloid features, hyperandrogenism, hirsutism, oligomenorrhea, polycystic ovaries	
Type B insulin resistance syndrome (ORPHAcode 2298)	NA	Autoantibody against insulin receptor	Presents in adulthood; acanthosis nigricans, markedly enlarged ovaries, hyperandrogenism, features associated with autoimmunity	No specific therapy; perhaps immunoglobulins, immunosuppressive therapy, plasmapheresis
Lipodystrophies				
Congenital generalized lipodystrophy				
CGL1 (OMIM 608594)	*AGPAT2* (AR)	AGPAT2 is involved in the acylation process of lysophosphatidic acid to phosphatidic acid production, which is involved in biosynthesis of triacylglyceride and glycerophospholipids. AGPAT2 deficiency is associated with impaired signaling of PI3K/AKT and PPARγ, affecting adipogenesis and reducing the levels of stored triglycerides.	Generalized lack of metabolically active adipose tissue and generalized lipoatrophy since birth, dyslipidemia, fatty liver	Metreleptin; strenuous exercise should be avoided in patients with cardiomyopathy (i.e., CGL4)
CGL2 (OMIM 269700)	*BSCL2* (AR)	BSCL2 participates in the biosynthesis of glycerophospholipids and triacylglycerides. BSCL2 mutations may impair adipogenesis, the expression of several enzymes (AGPAT2, DGAT2, and lipin-1), and lipogenic transcription factors (PPARγ, C/EBP-α).	Generalized lack of both metabolically active and mechanical adipose tissue since birth, mild mental retardation, dyslipidemia, fatty liver, cardiomyopathy	
CGL3 (OMIM 612526)	*CAV1* (AR)	*CAV1* mutations affect caveolin-1 function. Caveolin-1 is involved in PKA-mediated phosphorylation of perilipin, which regulates lipolysis. Loss of caveolin-1 is associated with decreased de novo lipid droplet accumulation and white adipose tissue atrophy. Caveolin-1 may have a dual role, functional and structural, in the modulation of lipid droplet biogenesis, accumulation, and metabolism.	Generalized lipoatrophy from birth, dyslipidemia, fatty liver, short stature	
CGL4 (OMIM 613327)	*PTRF* (AR)	PTRF regulates caveolin-1 and -3 expression and affects caveolae formation and stability, adipocyte differentiation, and adipose tissue expandability.	Generalized lipoatrophy and congenital muscular dystrophy, modest metabolic phenotype, hypertriglyceridemia, cardiomyopathy, cardiac fibrosis, QT interval prolongation, life-threatening cardiac arrhythmias, atlantoaxial instability, gastrointestinal disorders, acromegaloid characteristics	
Congenital partial lipodystrophies				
FPLD1 (Köbberling type) (OMIM 608600)	Polygenic (NA)	Little is known about the underlying pathophysiological mechanisms.	Distal lipoatrophy, visceral adiposity	No specific therapy
FPLD2 (Dunnigan type) (OMIM 151660)	*LMNA* (AD)	Defects in lamina proteins lamin A and C may result in adipocyte apoptosis and premature death. Prelamin A accumulation may interfere with the main adipocyte transcription factors or regulators (i.e., SREBP1, PPARγ), resulting in disrupted adipogenesis.	Distal and truncal lipoatrophy, "cushingoid" appearance due to excess fat accumulation in face and neck, skeletal and cardiac muscular dystrophy	
FPLD3 (OMIM 604367)	*PPARG* (AD)	Impaired adipocyte differentiation and adipogenesis	Distal lipoatrophy, gluteofemoral fat loss, visceral adiposity, cardiovascular disease, severe hypertriglyceridemia and hypertension	
FPLD4 (OMIM 613877)	*PLIN1* (AD)	*PLIN1* encodes perilipin-1, a main component of lipid droplet membranes. Perilipin-1 participates in lipid storage and lipolysis via the regulation of HSL and ATGL, which catalyze the hydrolysis of diacylglycerol and triacylglycerol into monoacylglycerol and fatty acids.	Limb and gluteofemoral fat loss, facial acromegaloid features, muscular hypertrophy	
FPLD5 (OMIM 615238)	*CIDEC* (AR)	*CIDEC* is involved in the differentiation of adipocytes and lipid and glucose metabolism. *CIDEC* mutations may impair adipocyte differentiation and lipid droplet accumulation.	Peripheral lipoatrophy, visceral adiposity, multilocular small lipid droplets, ketosis-prone insulin resistance	
FPLD6 (OMIM 615980)	*LIPE* (AR)	*LIPE* encodes HSL, which is associated with adipocyte function, lipolysis, and lipid and glucose homeostasis.	Distal lipoatrophy, visceral adiposity, muscular dystrophy	

Mandibuloacral dysplasia type A (OMIM 248370)	*LMNA* (AR)	*LMNA* encodes lamin A and C nuclear lamina proteins. Mutations may affect nuclear function resulting in premature cell death in adipose and skeletal tissue.	Distal and truncal lipoatrophy, skeletal anomalies, mandibular and clavicular hypoplasia, acroosteolysis, delayed dentition, progeroid features	No specific therapy
Mandibuloacral dysplasia type B (OMIM 608612)	*ZMPSTE24* (AR)	*ZMPSTE24* regulates posttranslational processing of prelamin A to mature lamin A. Therefore, accumulation of the toxic farnesylated form of prelamin A may disrupt nuclear function in several tissues.	Skeletal anomalies, mandibular and clavicular hypoplasia, acroosteolysis, delayed dentition, generalized loss of fat, premature renal failure (segmental glomerulosclerosis), progeroid features	
SHORT syndrome (OMIM 269880)	*PIK3R1* (AD)	*PIK3R1* encodes regulatory p85a subunit, which is involved in the activation of AKT signaling pathway, which regulates a wide range of cellular functions (differentiation, growth, cell survival, glucose transporter type 4 trafficking, and glucose utilization).	Short stature, joint hyperextensibility, ocular depression, Rieger anomaly, teething delay, facial, truncal, and upper-extremity lipoatrophy	No specific therapy
Acquired generalized lipodystrophy	NA	The pathogenic mechanism of AGL is not fully clarified; an immune-mediated loss of adipose tissue has been suggested. Antiadipocyte antibodies against perilipin-1, complement activation, and proinflammatory cytokines may contribute to AGL development by impairing fat uptake, adipocyte differentiation, adipogenesis, or increased adipocyte and preadipocyte apoptosis.	Generalized loss of fat associated with autoimmune or inflammatory diseases; severe hypertriglyceridemia, hepatic steatosis, diabetes mellitus, acanthosis nigricans, polycystic ovary syndrome	Metreleptin
Acquired partial lipodystrophy (Barraquer-Simons syndrome) (OMIM 608709)	NA	The etiology of the syndrome is still uncertain. However, the presence of circulating autoantibody (C3 nephritic factor) and low complement component 3 levels suggest an autoimmune-mediated loss of adipose tissue.	Progressive loss of adipose tissue from face, neck, arms, thorax, and upper abdomen, while fat may be preserved or increased over the lower abdomen, thighs, and gluteal region. Membranoproliferative glomerulonephritis or autoimmune disease may exist. Metabolic disorders such as insulin resistance and related complications are less frequent in comparison with the other lipodystrophic syndromes.	No specific therapy
HALS	NA	Usually in patients treated with HAART. Protease inhibitors may suppress adipogenesis, inhibit (pre)adipocyte differentiation, increase apoptosis, or induce dysregulation of adipogenic transcription factors (PPARγ, SREBP1, C/EBP-α, and C/EBP-β). NRTI may suppress mitochondrial polymerase and cause mitochondrial toxicity.	Loss of subcutaneous fat from the face and upper and lower extremities, excess fat deposition in the neck and abdomen; impaired metabolic profile including severe insulin resistance, diabetes mellitus, liver steatosis, dyslipidemia, i.e., hypertriglyceridemia, and increased levels of small, dense LDL particles and lipoprotein(a)	Growth hormone–releasing hormone (GHRH)
Other complex syndromes				
Alström syndrome (OMIM 203800)	*ALMS1* (AR)	Loss of ALMS1 expression has been associated with pancreatic hyperplasia and partial β cell degranulation along with decreased proliferation and increased apoptosis.	Photoreceptor dystrophy, progressive sensorineural hearing loss, hyperandrogenism, dilated cardiomyopathy, or congestive heart failure; severe insulin resistance, hyperinsulinemia, fatty liver, hyperlipidemia, diabetes mellitus, truncal obesity, and acanthosis nigricans	No specific therapy
Werner syndrome (OMIM 277700)	*WRN* (AR)	WRN protein deficiency causes genomic instability, accumulation of somatic mutations, aberrant telomere maintenance, and cell dysfunction in various cell lines.	Progeroid features, short stature, scleroderma-like skin atrophy, graying and loss of hair, indolent ulcerations around Achilles tendons; increased overall risk of malignancy; truncal obesity, severe insulin resistance, and diabetes	
Bloom syndrome (OMIM 210900)	*BLM* (AR)	*BLM* encodes a RecQ helicase. Loss of function of RecQ helicase leads to excess chromosomal instability.	Telangiectasia, photosensitivity, immunodeficiency, increased susceptibility to cancer, recurrent infection; severe fatty liver, dyslipidemia, impaired glucose tolerance, diabetes, prenatal and postnatal growth deficiency, short stature, photosensitive skin changes	
Microcephalic osteodysplastic primordial dwarfism type II (OMIM 210720)	*PCNT* (AR)	PCNT is involved in chromosome segregation, cytokinesis, and cell division. PCNT, a critical centrosomal protein, regulates γ-tubulin ring complex, which initiates assembly of the mitotic spindle apparatus. Dysfunction or absence of PCNT can lead to missegregated chromosomes and disorganized mitotic spindles, causing growth hormone resistance.	Osteodysplasia with severe growth retardation, short stature (adult height usually < 110 cm), abnormal dentition, microcephaly, increased risk for cerebrovascular disease, absent or mild mental retardation, insulin resistance, acanthosis nigricans, severe fatty liver and dyslipidemia	

Note that the more specific treatments presented in the table should be combined with lifestyle modification tailored to the individual patient, as well as management of all coexisting cardiometabolic risk factors and diseases. See "Treatment strategies" in the main text for a more detailed approach to these syndromes. AD, autosomal dominant; AGL, acquired generalized lipodystrophy; AR, autosomal recessive; ATGL, adipose tissue triglyceride lipase; C/EBP-α, CCAAT/enhancer-binding protein-α; CGL, congenital generalized lipodystrophy; FPLD, familial partial lipodystrophy; HAART, highly active antiretroviral therapy; HALS, HIV-associated lipodystrophy syndrome; HSL, hormone-sensitive lipase; INSR, insulin receptor; NRTI, nucleoside reverse transcriptase inhibitor; rhIGF-1, recombinant human IGF-1; SREBP1, sterol response element–binding protein 1.