Supplemental Table 1. Baseline Characteristics

	Total (n = 122)	Michigan (n = 83)	Turkey (n = 39)	*P* value
Current age, y	49 (38-59)	51 (39-61)	44 (30-53)	0.011
Sex, Female	101 (83)	68 (82)	33 (85)	0.802
BMI, kg/m^2	27.2 (22.6-32.4)	30.0 (24.1-34.4)	24.6 (20.6-26.2)	<0.001
Ethnicity, Non-Hispanic	115 (94)	76 (92)	39 (100)	0.096
Race				0.175
Caucasian	115 (94)	76 (92)	39 (100)	
African American	5 (4)	5 (6)	0	
Asian	2 (2)	2 (2)	0	
Variants identified				NA
LMNA	60 (49)	33 (40)	27 (69)	
PPARG	8 (7)	4 (5)	4 (10)	
POLD1	2 (2)	2 (2)	0	
MFN2	1 (1)	1 (1)	0	
VUS in novel genes	15 (12)	15 (18)	0	
Negative targeted sequencing[†]	17 (14)	9 (11)	8 (21)	
Negative WES	19 (16)	19 (23)	0	
Diabetes Mellitus	108 (89)	76 (92)	32 (82)	0.138
Hypertension	82 (67)	60 (72)	22 (56)	0.099
Pancreatitis	35 (29)	30 (36)	5 (13)	0.010
Glucose, mg/dL	147 (102-195)	149 (106-202)	137 (93-189)	0.396
HbA1c, %	7.8 (6.2-8.9)	7.9 (6.6-8.9)	7.5 (5.8-8.9)	0.346
Triglycerides, mg/dL	320 (198-544)	320 (224-644)	325 (169-544)	0.560
Total cholesterol, mg/dL	212 (166-254)	212 (164-248)	210 (176-259)	0.544
LDL, mg/dL	97 (64-130)	92 (58 -124)	106 (84-135)	0.047
HDL, mg/dL	36 (30-44)	36 (30-43)	34 (29-44)	0.800
Non-HDL cholesterol, mg/dl	165 (130-210)	163 (129-212)	169 (137-207)	0.782
AST, IU/L	26 (19-36)	28 (22-42)	19 (16-26)	<0.001
ALT, IU/L	29 (21-45)	34 (25-53)	21 (15-26)	<0.001
Creatinine, mg/dL	0.70 (0.60-0.89)	0.71 (0.60-0.89)	0.66 (0.59-0.90)	0.361
Leptin[‡], ng/mL	7.4 (2.4-16.0)	11.0 (4.4-19.0)	3.5 (1.5-7.0)	<0.001

Values are median (interquartile range) or n (%). [†]7 patients from Michigan were negative for *LMNA*482 and T10I, 1 patient negative for 13 genes (*AKT2, CAV1, CIDEC, LIPE, LMNA, LMNB2, PIK3R1, PLN1, POLD1, PPARG, PSMB8, TBC1D4,* and *ZMPSTE24*), and 9 Turkish patients were negative for *LMNA* and *PPARG*. BMI indicates body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase; HbA1c, hemoglobin A1c; VUS. variant of unknown significance; WES, whole-exome sequencing. [‡]Leptin levels are before metreleptin treatment closest to cardiac evaluation.

Supplemental Table 2. List of pathogenic variants

Pathogenic variants	n	Site	MITER probability (predictions of pathogenicity)
LMNA			
LMNA p.R482Q (c.1445G>A)	20	Michigan: 15; Turkey: 5	
LMNA p.R482W (c.1444C>T)	16	Michigan: 4; Turkey: 12	
LMNA p.R349W (c.1045C>T)	5	Michigan: 2; Turkey: 3	
LMNA p.R482L (c.1445G>T)	2	Michigan: 2; Turkey: 0	
LMNA p.D47N (c.139G>A)	1	Michigan: 0; Turkey: 1	
LMNA p.R60G (c.178C>G)	1	Michigan: 1; Turkey: 0	
LMNA p.R62G (c.184C>G)	1	Michigan: 1; Turkey: 0	
LMNA p.T10I (c.29C>T)*	1	Michigan: 1; Turkey: 0	
LMNA p.R225X (c.673C>T)	1	Michigan: 0; Turkey: 1	
LMNA p.D300N (c.898G>A)	1	Michigan: 1; Turkey: 0	
LMNA p.G412W (c.1234G>T)	1	Michigan: 0; Turkey: 1	
LMNA p.R453W (c.1357C>T)	1	Michigan: 1; Turkey: 0	
LMNA p.K486E (c.14565A>G)	1	Michigan: 0; Turkey: 1	
LMNA p.T528M (c.1583C>T)	1	Michigan: 0; Turkey: 1	
LMNA p.G535Q (c.1604G>A)	1	Michigan: 1; Turkey: 0	
LMNA p.R541P (c. 1622G>C)	1	Michigan: 1; Turkey: 0	
LMNA p.R582C (c 1744 C>T)	1	Michigan: 1; Turkey: 0	
LMNA p.R582H (c.1745G>A)	1	Michigan: 0; Turkey: 1	
LMNA p.R584H (c.1751 G>A)	1	Michigan: 1; Turkey: 0	
LMNA p.R624PfsX50 (c.1870dup)	1	Michigan: 0; Turkey: 1	
LMNA, intron 8	1	Michigan: 1; Turkey: 0	
PPARG			
PPARG p.Y151C (c.452A>G)	4	Michigan: 0; Turkey: 4	99.9% - pathogenic
PPARG p.A261V (c.782C>T)	1	Michigan: 1; Turkey: 0	65.7% - pathogenic
PPARG p.E352K (c.1054G>A)	1	Michigan: 1; Turkey: 0	98.2% - pathogenic
PPARG p.G161V (c.482G>T)	1	Michigan: 1; Turkey: 0	99.7% - pathogenic
PPARG p.R194Q (c.581G>A)	1	Michigan: 1; Turkey: 0	99.9% - pathogenic
POLD1			
POLD1 p.E1067K (c.3199G>A)	2	Michigan: 2; Turkey: 0	
MFN2			
MFN2 homozygous p.R707W (c.2119C>T)	1	Michigan: 1; Turkey: 0	

*Phenotype consistent with generalized lipodystrophy.
Predictions of *PPARG* pathogenicity (at disease prevalence 0.2; i.e., 1 in 5 patients who visits the clinic have lipodystrophy) http://miter.broadinstitute.org/

Supplemental Table 3. List of medications

	Total	*LMNA*	Non-*LMNA*	*P* value
	122	60	55	
Glucose lowering				
Insulin	59 (48)	20 (33)	35 (64)	0.001
Daily insulin dose	125 (60-225)	80 (41.5-192)	135 (70-225)	0.27
Insulin U300/U500	24 (19.67)	7 (12)	16 (29)	0.034
Secretagogue	9 (7)	5 (8)	3 (6)	0.719
Metformin	76 (62)	35 (58)	36 (66)	0.450
Glitazone	30 (25)	17 (28)	11 (20)	0.385
GLP1 agonist	11 (9)	7 (12)	4 (8)	0.533
DPP4 inhibitor	12 (10)	7 (12)	4 (8)	0.533
SGLT2 inhibitor	14 (12)	6 (10)	7 (13)	0.771
Alpha glucosidase inhibitor	1 (1)	1 (2)	0	1.000
Lipid lowering				
Statin	45 (37)	21 (35)	19 (35)	1.000
High dose statin†	21 (17)	5 (8)	14 (26)	0.022
Fibrate	50 (41)	22 (37)	26 (47)	0.263
Niacin	1 (1)	0	1 (2)	0.478
Ezetimibe	2 (2)	0	2 (4)	0.227
Fish oil/Omega3 fatty acid	33 (27)	14 (23)	15 (27)	0.671
Antihypertensive				
ACE inhibitor/ARB	82 (67)	39 (65)	38 (69)	0.694
Calcium channel blocker	18 (15)	8 (13)	9 (16)	0.794
Beta blocker	36 (30)	15 (25)	17 (31)	0.536
Spironolactone	13 (11)	9 (15)	4 (7)	0.245
Thiazide	14 (12)	5 (8)	9(16)	0.256
Other antihypertensive	5 (4)	1 (2)	4 (7)	0.192
Other				
Antiplatelet	40 (33)	16 (27)	22 (40)	0.165
Anticoagulant	9 (7)	8 (13)	1 (2)	0.033
Synthetic thyroxine	21 (17)	8 (13)	11 (20)	0.452
Nitrate	12 (10)	3 (5)	8 (15)	0.114
Furosemide	13 (11)	8 (13)	5 (9)	0.563

Values are median (interquartile range) or n (%). GLP1 indicates Glucagon like peptide 1; DPP4, dipeptidyl peptidase 4 inhibitor; SGLT2, sodium-glucose cotransporter 2; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. †High dose statin includes atorvastatin or simvastatin > 40mg, or rosuvastatin > 10mg. Seven patients with no complete gene sequencing for *LMNA* are excluded from the comparison (*LMNA* vs. non-*LMNA*).

Supplemental Table 4. Comparison of patients with pathogenic variants in *LMNA* gene codon 482 to patients without any pathogenic *LMNA* variants

	Codon 482 LMNA **(n = 38)**	**Non-*LMNA*** **(n = 55)**	***P* value**
Cardiac exam age, y	47 (33-57)	51 (36-57)	0.708
Sex, Female	31 (82)	46 (84)	0.788
BMI, kg/m2	24.8 (21.9-28.3)	31.5 (25.9-35.6)	< 0.001
Diabetes Mellitus	31 (82)	52 (95)	0.085
Hypertension	27 (71)	36 (66)	0.655
Pancreatitis	6 (16)	20 (36)	0.036
Glucose, mg/dL	142 (101-184)	165 (128-239)	0.148
HbA1c, %	7.7 (6-8.7)	8.3 (7.1-9.2)	0.083
Triglycerides, mg/dL	323 (196-485)	342 (246-896)	0.832
Total cholesterol, mg/dL	193 (160-226)	226 (174-293)	0.031
LDL cholesterol, mg/dL	93 (63-125)	106 (65-145)	0.443
HDL cholesterol, mg/dL	36 (30-44)	33 (29-42)	0.492
Non-HDL cholesterol, mg/dL	149 (116-187)	187 (138-254)	0.013
Leptin†, ng/mL	3.12 (1.40-7.42)	12 (5.29-18.50)	0.002
Ischemic heart disease	8 (21)	16 (29)	0.473
Stroke	2 (5)	7 (13)	0.301
Arrhythmia	13 (34)	12 (22)	0.236
Atrial fib/flutter	3 (8)	2 (4)	0.396
PVC	5 (13)	1 (2)	0.040
PAC/SVPC	2 (5)	2 (4)	1.000
Sinus arrhythmia	6 (16)	7 (13)	0.796
Conduction abnormality	5 (13)	7 (13)	1.000
Axis deviation	1 (3)	3 (6)	0.642
Prolonged QT	7 (18)	10 (18)	1.000
Cardiomyopathy	2 (5)	3 (6)	1.000
Congestive heart failure	3 (8)	7 (13)	0.519
LV hypertrophy‡	10 (32)	16 (40)	0.621
Diastolic dysfunction‡	4 (13)	12 (30)	0.151
Valvular heart disease‡	10 (32)	9 (23)	0.423

Values are median (interquartile range) or n (%). BMI indicates body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; HbA1c, hemoglobin A1c; PVC, premature ventricular complex; PAC, premature atrial complex; SVPC, supraventricular premature complex. †Leptin levels are before metreleptin treatment closest to cardiac evaluation. ‡Echocardiogram is available in 71 patients (31 codon 482 *LMNA* and 40 non-*LMNA*). Seven patients with no complete gene sequencing for *LMNA* are excluded.

Supplemental video 1: Optical mapping video of mature functional syncytium of cardiomyocytes differentiated from a patient carrying a variant (*LMNA* R349W) causative of familial partial lipodystrophy type 2 (FPLD2). Syncytium presents regular normal rhythm of spontaneous depolarization that is succeeded by an early afterdepolarization (second 35) followed by spontaneous quiescence (second 43) followed by tachyarrhythmia (second 51).