

Loss-of-function variants affecting the STAGA complex component *SUPT7L* cause a developmental disorder with generalized lipodystrophy

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Supplementary Tables 1-4

Supplementary Table 1. Oligo sequences

Primer name	Sequence 5' -> 3'
SUPT7L gRNA FWD	CACCGCAATAAGGTTGCGAAGACGT
SUPT7L gRNA REV	AAACACGTCTTCGCAACCTTATTGC
SUPT7L_E03 F	TCCTCAGTTTCCTCGCATGA
SUPT7L_E03 R	AGTGGTCACAAATAGCCTACTTTT
hSupt7l_ex2_Fwd	GACACAGAATGCCTGGCATT
hSupt7l_ex4_Rev	GTGCCACATCAGTTAGGGTCT
hSupt7l_ex2-3_Fwd	ATGGACAATGAATCTGCAAAGA
hSupt7l_ex4_Rev	GTGCCACATCAGTTAGGGTCT
hSupt7l_ex3-4_Fwd	GAGTGACTTTTATCGTGGGA
hSupt7l_ex6_Rev	TCTTGCAGCGCTGGTTGAAA
hSUPT7L_ex4_Fwd	CCGCATCAAGGACTATCACAGT
hSUPT7L_ex5_Rev	GGCCTTCTCAGGATTGACAATC
hGAPDH_Fwd	CTGCACCACCAACTGCTTAG
hGAPDH_Rev	ACAGTCTTCTGGGTGGCAGT

CRISPR/Cas9 Guide	Sequence 5' -> 3'	PAM
SUPT7L sgRNA	CAATAAGGTTGCGAAGACGT	CGG

Supplementary Table 1: Primer and sgRNA sequences.

Supplementary Table 2. Gene set enrichment analysis - results for database Co-expression gene sets (tmod)

ID	Title	N1	AUC	P.Value	adj.P.Val
LI.M4.0	cell cycle and transcription	261	0.78	2.60E-36	1.60E-33
LI.M4.1	cell cycle (I)	141	0.87	2.40E-32	7.20E-30
DC.M3.3	Cell Cycle	46	0.87	2.10E-12	4.20E-10
LI.M4.2	PLK1 signaling events	33	0.87	2.80E-09	4.30E-07
LI.M4.4	mitotic cell cycle - DNA replication	30	0.87	4.80E-09	5.80E-07
LI.M6	mitotic cell division	29	0.89	1.60E-08	0.0000016
LI.M4.5	mitotic cell cycle in stimulated CD4 T cells	29	0.86	3.70E-08	0.0000032
LI.M10.0	E2F1 targets (Q3)	30	0.78	3.20E-07	0.000022
DC.M6.11	Cell Cycle	18	0.91	3.20E-07	0.000022
DC.M7.7	Undetermined	99	0.67	3.90E-07	0.000023
LI.M103	cell cycle (III)	51	0.73	4.30E-07	0.000024
LI.M10.1	E2F1 targets (Q4)	20	0.82	0.0000013	0.000067
LI.M4.6	cell division in stimulated CD4 T cells	22	0.84	0.0000043	0.0002
LI.M46	cell division stimulated CD4+ T cells	24	0.8	0.0000069	0.0003
LI.M76	DNA repair	21	0.87	0.0000084	0.00034
LI.M4.12	C-MYC transcriptional network	12	0.86	0.000012	0.00043
DC.M9.42	Cell Cycle	15	0.83	0.000012	0.00043
LI.M4.8	cell division - E2F transcription network	19	0.85	0.000043	0.0015
DC.M6.16	Cell Cycle	26	0.79	0.000058	0.0018
LI.M4.9	mitotic cell cycle in stimulated CD4 T cells	16	0.86	0.000059	0.0018
LI.M8	E2F transcription factor network	16	0.85	0.00011	0.0033
LI.M81	enriched in myeloid cells and monocytes	24	0.74	0.00013	0.0035
LI.M4.10	cell cycle (II)	14	0.79	0.00014	0.0035
LI.M22.0	mismatch repair (I)	27	0.77	0.00014	0.0035
LI.M4.7	mitotic cell cycle	20	0.8	0.00021	0.005
DC.M3.6	Cytotoxic/NK Cell	13	0.7	0.00026	0.0058
LI.M113	golgi membrane (I)	8	0.72	0.00065	0.013
LI.M49	transcription regulation in cell development	34	0.66	0.0011	0.021
LI.M141	TBA	7	0.78	0.0015	0.026
DC.M3.4	Interferon	43	0.66	0.0024	0.036
LI.M122	enriched for cell migration	11	0.72	0.0034	0.049

Supplementary Table 2: Transcriptome analysis of fibroblasts from individual II-1 compared to unaffected controls. Shown are all deregulated gene sets with an area under the curve (AUC)>0.65 and p<0.05. N1: Number of genes in gene set.

Supplementary Table 3. Clinical and genetic characterization

Clinical manifestations	SUPT7L related lipodystrophy	Wiedemann-Rautenstrauch syndrome	PYCR1 related cutis laxa	Fontaine progeroid syndrome	Berardinelli-Seip congenital lipodystrophy
Growth					
IUGR	+	+	+	+	-
Failure to thrive	+	+	+/-	+	-
Skin & hair					
Thin skin	+	+	+	+	-
Sparse hair	+	+	+	+	-
Sparse eyebrows	+	+	+	-	-
Facial appearance					
Triangular face	+	+	+	+	+
Broad forehead	+	+	+	+	-
Microcephaly	+	-	+	+/-	-
Downslanting palpebral fissures	+	+	+	+	-
Hypertelorism	+	+	-	+	-
Low-set ears	+	-	-	+	-
Physical abnormalities					
Neonatal tooth	+	+	-	-	-
Delayed fontanel closure	+	+	+	+	-
Craniosynostosis	-	-	-	+	-
Short stature	+	+	+	+	-
Hernias	+	-	+	+	+
Hepatomegaly	+	-	-	-	+
Asymmetric kidneys	+	-	-	-	-
Neurological					
Intellectual disability	+	+	+/-	-	+/-
Developmental delay	+	+	+	+	-
Muscle weakness	+	+	+	+/-	-
Eyes					
Congenital cataracts	+	-	+	-	-
Metabolic abnormalities					
Lipodystrophy	+	+	+	+/-	+
Hypothyroidism	+	-	-	-	-
Elevated triglycerides	+	+	-	-	+
Genetic alteration affecting:	<i>SUPT7L</i>	<i>POLR3A</i>	<i>PYCR1</i>	<i>SLC25A24</i>	<i>BSCL2</i>

Supplementary Table 3: Clinical and genetic characterization of different differential diagnoses of the *SUPT7L* related lipodystrophy.

Supplementary Table 4. Lipodystrophy genes Panel ID: R158

<u>Gene Symbol</u>	<u>Phenotypes</u>	<u>Omim</u>
AGPAT2	Lipodystrophy, congenital generalized, type 1, 608594	603100
BSCL2	Lipodystrophy, congenital generalized, type 2, OMIM:269700;Encephalopathy, progressive, with or without lipodystrophy, OMIM:615924	606158
CAV1	?Lipodystrophy, congenital generalized, type 3, 612526;Lipodystrophy, familial partial, type 7, 606721	601047
CAVIN1	Lipodystrophy, congenital generalized, type 4, 613327	603198
FBN1	Marfan lipodystrophy syndrome, OMIM:616914	134797
INSR	Diabetes mellitus, insulin-resistant, with acanthosis nigricans, OMIM:610549	147670
KCNJ6	Keppen-Lubinsky syndrome, OMIM:614098;Keppen-Lubinsky syndrome, MONDO:0013572	600877
LIPE	Lipodystrophy, familial partial, type 6, 615980	151750
LMNA	Lipodystrophy, familial partial, 2, 151660	150330
MTX2	Mandibuloacral dysplasia;lipodystrophy;arterial calcification	608555
OTULIN	Autoinflammation, panniculitis, and dermatosis syndrome, OMIM:617099	615712
PLIN1	Lipodystrophy, familial partial, type 4, 613877	170290
POLD1	Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome, 615381	174761
PPARG	Insulin resistance, severe, digenic 604367;Lipodystrophy, familial partial, type 3 604367	601487
ZMPSTE24	Mandibuloacral dysplasia with type B lipodystrophy, 608612	606480

<u>Lipodystrophy genes according to Isabelle Jéru and further candidates</u>		<u>Omim</u>
AGPAT2	Lipodystrophy, congenital generalized, type 1	603100
BSCL2	Lipodystrophy, congenital generalized, type 2	606158
CAV1	Lipodystrophy, congenital generalized, type 3; Lipodystrophy, familial partial, type 7	601047
CAVIN1	Lipodystrophy, congenital generalized, type 4	603198
LIPE	Lipodystrophy, familial partial, type 6	151750
LMNA	Lipodystrophy, familial partial, 2	150330
PLIN1	Lipodystrophy, familial partial, type 4	170290
POLD1	Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome	174761
PPARG	Insulin resistance, severe, digenic 604367;Lipodystrophy, familial partial, type 3	601487
ZMPSTE24	Mandibuloacral dysplasia with type B lipodystrophy	606480
ADRA2A	No OMIM number;familial partial lipodystrophy	104210
AKT2	Diabetes mellitus, type II ;Hypoinsulinemic hypoglycemia with hemihypertrophy ;Partial lipodystrophy	164731
CIDEC	Lipodystrophy, familial partial, type 5	612120
BANF1	Nestor-Guillermo progeria syndrome	614008
BLM	Bloom Syndrome	210900
ERCC6	Cockayne syndrome type B	133540
ERCC8	Cockayne syndrome type A	216400
FBN1	Marfan lipodystrophic syndrome	616914
KCNJ6	Keppen-Lubinsky syndrome	614098
LMNA	Hutchinson-Gilford progeria syndrome; Dunnigan disease or FPLD; Mandibulo-acral dysplasia type A	176670
MFN2	Multiple symmetric lipomatosis	248370
MTX2	Mandibuloacral dysplasia progeroid syndrome	619127
OPA3	Optic atrophy 3 with cataract	165300
OTULIN	Autoinflammation, panniculitis, and dermatosis syndrome	617099
PCYT1A	Spondylometaphyseal dysplasia with cone-rod dystrophy	608940

PIK3R1	SHORT syndrome	269880
POLR3A	Wiedemann-Rautenstrauch syndrome	264090
POLR3B	Wiedemann-Rautenstrauch syndrome	--
POMP	PRASS2	618048
PSMA3	--	--
PSMB4	PRASS3	617591
PSMB8	PRASS1	256040
PSMB9	PRASS3	617591
PSMG2	PRASS4	619183
PTPN11	LEOPARD syndrome 1	151100
SLC25A24	Fontaine syndrome	612289
SLC29A3	Histiocytosis-lymphadenopathy plus syndrome	602782
SPRTN	Ruijs-Aalfs syndrome	616200
WRN	Werner syndrome	277700
BUD13	Systemic lipodystrophy	--
LEMD2	Marbach-Rustad progeroid syndrome	619322
ALDH18A1	Cutis laxa, autosomal dominant 3, Cutis laxa, autosomal recessive, type IIIA	219150
PYCR1	Cutis laxa, autosomal recessive, type IIB; Cutis laxa, autosomal recessive, type IIIB	614438

Supplementary Table 4: Lipodystrophy genes Panel ID: R158. Genomics England PanelApp (Green), Lipodystrophy - childhood onset (Version 4.50)