Supplementary information:

Figure S1. Heatmap and unsupervised cluster analysis. Normalized gene expression levels of biological replicates of control and treated samples in ML017 and ML017/ET. Rows represent genes. Sample names are reported at the bottom of the heatmap; replicate numbers are indicated in Roman numerals. Unsupervised cluster analysis is shown at the top.

Figure S2. Sanger sequencing on ML017 and ML017/ET.
No mutations were found in either model compared to the human reference. Electropherograms show one of the four binding sites of DDIT3, with no difference between ML017 and ML017/ET. The other three binding sites showed the same concordant sequence (data not shown).

Figure S3. Antitumor activity of cisplatin in ML017 and ML017/ET xenografts.
When tumour weight reached about 300 mg mice were randomized to receive cisplatin 5 mg/kg q7dx3 or saline (arrows). No significant reduction of tumor growth was observed in either the resistant or the sensitive models, suggesting that mutations of NER proteins are not involved in the mechanism of resistance.

Table S1. Primer sequences used for ChIP, RT-PCR and gene sequence regions for ddPCR primers and probe design.

Table S2. Genes involved in the pathways of adipogenesis, fatty acid metabolism, neutral lipid metabolism and lipid storage. ES, enrichment score. Columns headed in orange refer to the ML017 model, in blue to the ML017/ET model.

Table S3. Genes of the TC-NER pathway as reported by the REPAIRtoire Database (Milanowska *et al*, 2011). UVSSA was added manually to the list. Gene annotation with David (Huang *et al*, 2009).

Table S4. SNV in ML017/ET. Somatic SNV with genomic coordinates (hg19 genome build) are described using the HGVS notation.

References

Huang DW, Sherman BT, Lempicki RA (2009) Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc* **4**: 44–57, doi:10.1038/nprot.2008.211.

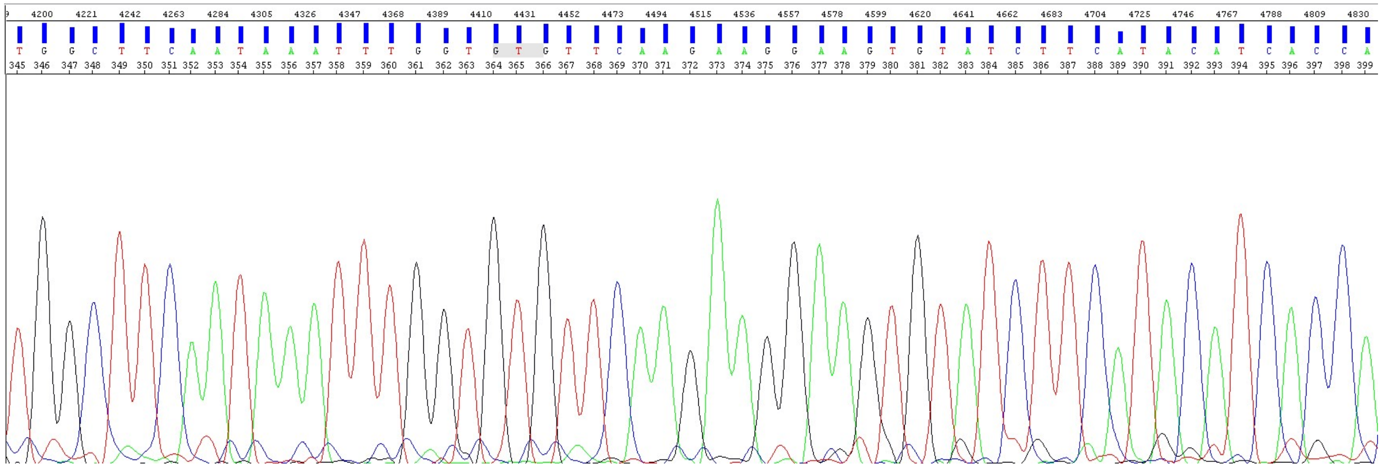
Milanowska K, Krwawicz J, Papaj G, Kosinski J, Poleszak K, Lesiak J, Osinska E, Rother K, Bujnicki JM (2011) REPAIRtoire--a database of DNA repair pathways. *Nucleic Acids Res* **39**: D788-792, doi:10.1093/nar/gkq1087.

Figure S1


20
16
12
8
4
ML017_CTRL_III
ML017_ET_15d_III
ML017_ET_15d_I
ML017_ET_15d_II
ML017/ET_ET_24h_III
ML017/ET_ET_24h_IV
ML017_ET_24h_I
ML017_ET_24h_II
ML017_ET_24h_III
ML017_ET_24h_IV
ML017_CTRL_I
ML017_CTRL_II
ML017/ET_ET_15d_I
ML017/ET_ET_15d_IV
ML017/ET_ET_15d_II
ML017/ET_ET_15d_III
ML017/ET_CTRL_I
ML017/ET_CTRL_II
ML017/ET_CTRL_III
ML017/ET_ET_24h_I
ML017/ET_ET_24h_II

Figure S2

ML017



ML017/ET

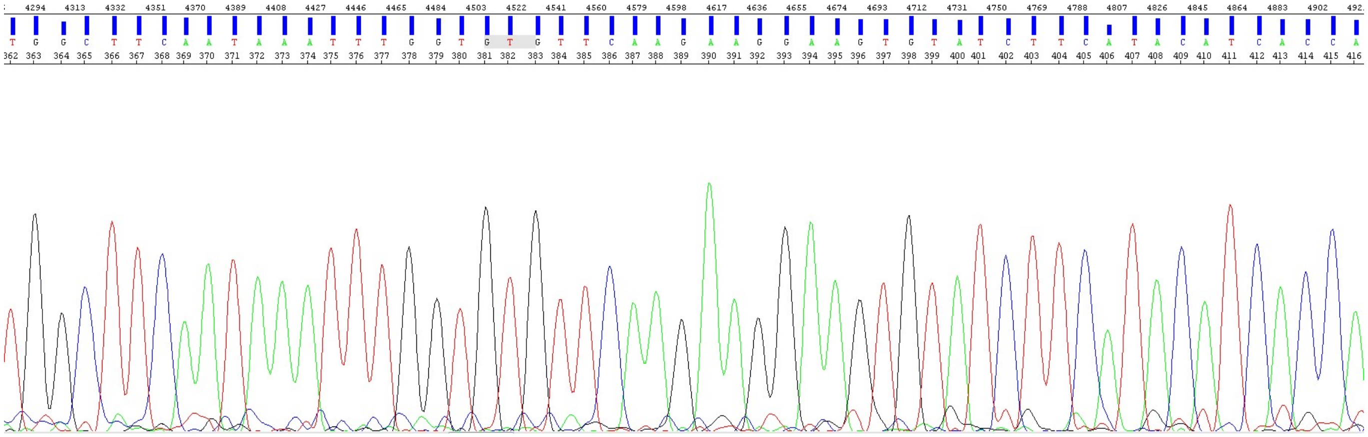
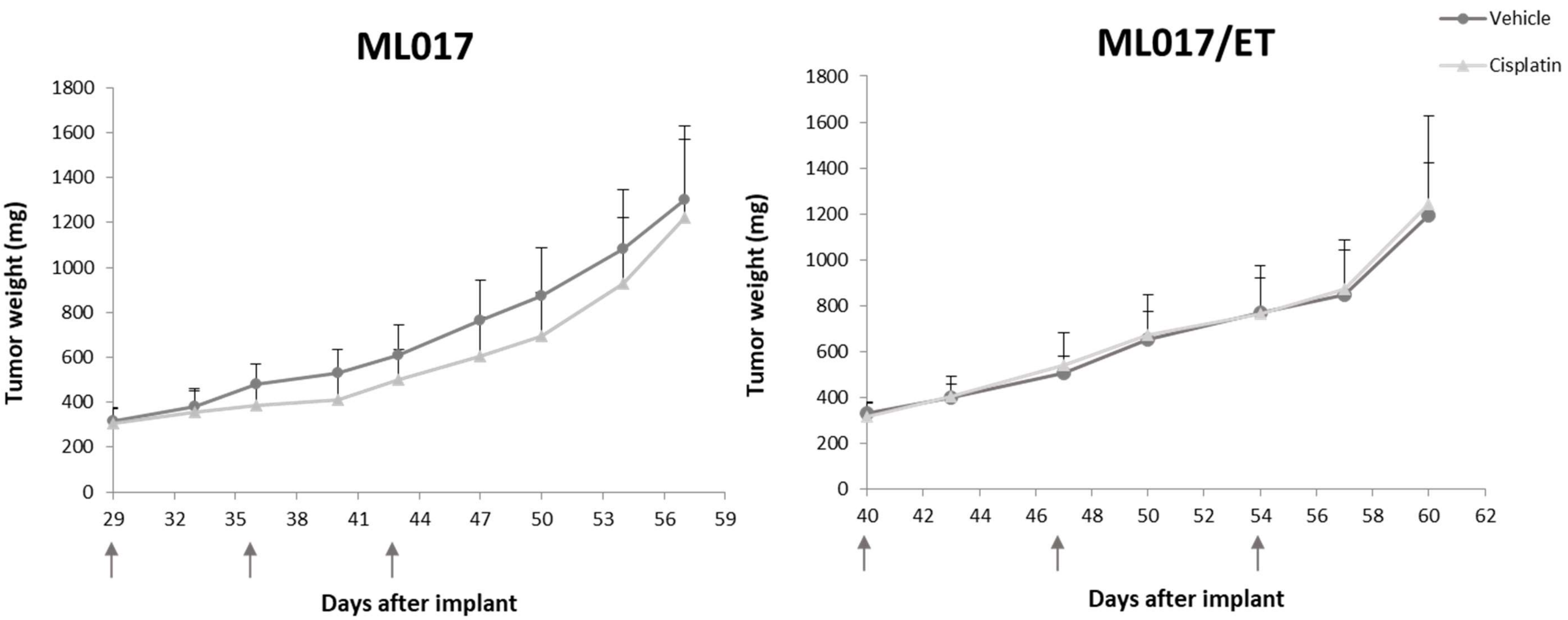


Figure S3


ML017
Tumor weight (mg)
1800
1600
1400
1200
1000
800
600
400
200
0
29
32
35
38
41
44
47
50
53
56
59
Days after implant
ML017/ET
Vehicle
Cisplatin
Tumor weight (mg)
1800
1600
1400
1200
1000
800
600
400
200
0
40
42
44
46
48
50
52
54
56
58
60
62
Days after implant

Supplementary Table 1

Experiment	**Gene**		**EntrezID**	**Primer Sequence**	
Chip	FN-1		2335	FW	CTTCGCTTCACACAAGTCCA
				RV	GCAGCGAACAAAAGAGATGC
	Control satellite		/	FW	CAATTATCCCTTCGGGGAATCGG
				RV	GGCGACCAATAGCCAAAAAAGTGAG
Real-time PCR	UVSSA		57654	FW	CCCTTCTTTCCCCGAGTAG
				RV	ATCCATATCTGGTGGGATGAG
	B2M		567	FW	AAGCAGCATCATGGAGGTTT
				RV	AGCAAGCAAGCAGAATTTGG
	G6PD		2539	FW	TGCCCCCGACCGTCTAC
				RV	ATGCGGTTCCAGCCTATCTG
ddPCR	CNV assay	RPP 30	10556	Region	ATGAGGAACCTGAAACTTCATGTTAAGTAACTTGTAAGTGGTAGTGCATAGACTTTAAATCAGGCAGACTGACACTAGAGTTCACATTCATAACCACTCCTCAAATGTCCTCCTACTCTTGAC
		EIF2C	26523		GAGGGCTACTACCACCCGCTGGGGGGTGGGCGCGAGGTCTGGTTCGGCTTTCACCAGTCTGTGCGCCCTGCCATGTGGAAGATGATGCTCAACATTGATGGTGAGTGGGGAGAGCTATGGAGC
		UVSSA	57654		TCCGGGCAGGCTGCCTCCGTTAGGGCCGCCCCTGCTCTCCGGACGCGACTTTTCATTGGTCTCAGAATTTCTTGGCTCCTCTTGGCCTCTGCAGCCTTGCTGGAGGCTGCCCTGCGGAATCTG
	Mutational assay	UVSSA	57654		TGGAGGAACTCTTCGTCAGGTCTCACCAGTTCCGGATGCTGGTTGTTTCCAACTTCCAGGA[GTTCCT/-]GGAGCTCACGCTGGGCACAGACCCCGCACAGCCTCTGCCGCCCCCCAGGGAGGCGGCACAG

Supplementary Table 2

Legend	
Rank metric score	Score associated to the position of the gene in the ranked list of the gene enrichment analysis.
Running ES	The enrichment score at this point in the ranked list of genes as computed by the enrichement analysis.
🟧	ML017
🟦	ML017/ET

Adipogenesis					
Gene Symbol	**Description**	**Rank metric score**	**Running ES**	**Rank metric score**	**Running ES**
ADIPOQ	adiponectin, C1Q and collagen domain containing	0.75	0.04	/	/
MRAP	melanocortin 2 receptor accessory protein	0.56	0.07	/	/
SLC1A5	solute carrier family 1 member 5	0.39	0.08	/	/
RETSAT	retinol saturase	0.36	0.10	/	/
CIDEA	cell death-inducing DFFA-like effector a	0.33	0.12	/	/
UCP2	uncoupling protein 2	0.32	0.13	/	/
LIPE	lipase E, hormone sensitive type	0.30	0.15	/	/
LEP	leptin	0.29	0.16	/	/
CDKN2C	cyclin dependent kinase inhibitor 2C	0.28	0.17	/	/
CD151	CD151 molecule (Raph blood group)	0.28	0.19	/	/
PEMT	phosphatidylethanolamine N-methyltransferase	0.27	0.20	/	/
C3	complement C3	0.26	0.21	/	/
FAH	fumarylacetoacetate hydrolase	0.25	0.22	/	/
ABCA1	ATP binding cassette subfamily A member 1	0.25	0.23	/	/

SLC25A1	solute carrier family 25 member 1	0.25	0.25	/	/
GADD45A	growth arrest and DNA damage inducible alpha	0.24	0.26	/	/
ME1	malic enzyme 1	0.24	0.27	/	/
GPX3	glutathione peroxidase 3	0.23	0.28	/	/
GBE1	1,4-alpha-glucan branching enzyme 1	0.23	0.29	/	/
PRDX3	peroxiredoxin 3	0.23	0.30	/	/
MGLL	monoglyceride lipase	0.22	0.31	/	/
ESYT1	extended synaptotagmin 1	0.21	0.32	/	/
REEP6	receptor accessory protein 6	0.21	0.33	/	/
DRAM2	DNA damage regulated autophagy modulator 2	0.19	0.33	/	/
AIFM1	apoptosis inducing factor mitochondria associated 1	0.19	0.34	/	/
MGST3	microsomal glutathione S-transferase 3	0.19	0.35	/	/
LTC4S	leukotriene C4 synthase	0.19	0.36	/	/
DHRS7B	dehydrogenase/reductase 7B	0.19	0.37	/	/
DGAT1	diacylglycerol O-acyltransferase 1	0.18	0.37	/	/
PDCD4	programmed cell death 4	0.18	0.38	/	/
CYC1	cytochrome c1	0.18	0.39	/	/
DECR1	2,4-dienoyl-CoA reductase 1	0.17	0.39	/	/
ADCY6	adenylate cyclase 6	0.17	0.40	/	/
POR	cytochrome p450 oxidoreductase	0.16	0.40	/	/
FABP4	fatty acid binding protein 4	0.16	0.41	/	/
SORBS1	sorbin and SH3 domain containing 1	0.16	0.42	/	/
SLC19A1	solute carrier family 19 member 1	0.16	0.42	/	/
CPT2	carnitine palmitoyltransferase 2	0.15	0.43	/	/
SDHB	succinate dehydrogenase complex iron sulfur subunit B	0.15	0.44	/	/
PGM1	phosphoglucomutase 1	0.15	0.44	/	/
IDH3A	isocitrate dehydrogenase 3 (NAD(+)) alpha	0.15	0.45	/	/
AGPAT3	1-acylglycerol-3-phosphate O-acyltransferase 3	0.15	0.46	/	/
PHYH	phytanoyl-CoA 2-hydroxylase	0.15	0.47	/	/
SNCG	synuclein gamma	0.14	0.47	/	/
ARL4A	ADP ribosylation factor like GTPase 4A	0.14	0.47	/	/

SUCLG1	succinate-CoA ligase alpha subunit	0.14	0.47	/	/
TKT	transketolase	0.14	0.48	/	/
ACADS	acyl-CoA dehydrogenase, C-2 to C-3 short chain	0.13	0.48	/	/
ACAA2	acetyl-CoA acyltransferase 2	0.13	0.48	/	/
ITIH5	inter-alpha-trypsin inhibitor heavy chain family member 5	0.12	0.48	/	/
DHRS7	dehydrogenase/reductase 7	0.12	0.48	/	/
ACO2	aconitase 2	0.12	0.49	/	/
GPX4	glutathione peroxidase 4	0.12	0.49	/	/
MYLK	myosin light chain kinase	0.12	0.50	/	/
UCK1	uridine-cytidine kinase 1	0.12	0.50	/	/
SCP2	sterol carrier protein 2	0.11	0.50	/	/
NDUFB7	NADH:ubiquinone oxidoreductase subunit B7	0.11	0.49	/	/
LIFR	LIF receptor alpha	0.11	0.50	/	/
HADH	hydroxyacyl-CoA dehydrogenase	0.10	0.50	/	/
STAT5A	signal transducer and activator of transcription 5A	0.10	0.50	/	/
IDH1	isocitrate dehydrogenase (NADP(+)) 1, cytosolic	0.10	0.50	/	/
SAMM50	SAMM50 sorting and assembly machinery component	0.10	0.51	/	/
APOE	apolipoprotein E	0.10	0.51	/	/
CS	citrate synthase	0.10	0.51	/	/
ARAF	A-Raf proto-oncogene, serine/threonine kinase	0.10	0.51	/	/
UQCR10	ubiquinol-cytochrome c reductase, complex III subunit X	0.10	0.52	/	/
IDH3G	isocitrate dehydrogenase 3 (NAD(+)) gamma	0.09	0.52	/	/
TOB1	transducer of ERBB2, 1	0.09	0.53	/	/
PQLC3	PQ loop repeat containing 3	0.09	0.52	/	/
RAB34	RAB34, member RAS oncogene family	0.09	0.52	/	/
ADIPOR2	adiponectin receptor 2	0.08	0.52	/	/
RREB1	ras responsive element binding protein 1	0.08	0.52	/	/
TST	thiosulfate sulfurtransferase	0.08	0.52	/	/
ALDOA	aldolase, fructose-bisphosphate A	0.08	0.52	/	/
BAZ2A	bromodomain adjacent to zinc finger domain 2A	0.08	0.53	/	/

ANGPTL4	angiopoietin like 4	0.08	0.53	/	/
PREB	prolactin regulatory element binding	0.08	0.53	/	/
APLP2	amyloid beta precursor like protein 2	0.08	0.53	/	/
HSPB8	heat shock protein family B (small) member 8	0.07	0.53	/	/
ATP5O	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	0.07	0.53	/	/
SLC27A1	solute carrier family 27 member 1	0.073522	0.53612494	/	/
Fatty acid metabolism					
Gene	**Description**	**Rank metric score**	**Running ES**	**Rank metric score**	**Running ES**
EPHX1	epoxide hydrolase 1	0.49	0.03	0.18	0.39
ACSL5	acyl-CoA synthetase long-chain family member 5	0.37	0.06	0.34	0.26
RETSAT	retinol saturase	0.36	0.08	0.21	0.36
CBR3	carbonyl reductase 3	0.35	0.11	0.16	0.43
CA2	carbonic anhydrase 2	0.35	0.13	0.57	0.13
CIDEA	cell death-inducing DFFA-like effector a	0.33	0.18	0.52	0.24
HPGD	hydroxyprostaglandin dehydrogenase 15-(NAD)	0.25	0.23	0.32	0.29
ME1	malic enzyme 1	0.24	0.26	0.23	0.33
REEP6	receptor accessory protein 6	0.21	0.31	0.28	0.31
LTC4S	leukotriene C4 synthase	0.19	0.34	0.17	0.40
MLYCD	malonyl-CoA decarboxylase	0.15	0.37	0.16	0.44
ALDH9A1	aldehyde dehydrogenase 9 family member A1	0.15	0.38	0.13	0.45
MAOA	monoamine oxidase A	0.14	0.43	0.54	0.19
ACAA2	acetyl-CoA acyltransferase 2	0.13	0.44	0.11	0.45
IL4I1	interleukin 4 induced 1	0.10	0.50	0.20	0.38
PSME1	proteasome activator subunit 1	0.35	0.16	/	/
ACSL1	acyl-CoA synthetase long-chain family member 1	0.32	0.20	/	/
GPD1	glycerol-3-phosphate dehydrogenase 1	0.30	0.22	/	/
AOC3	amine oxidase, copper containing 3	0.24	0.24	/	/
INMT	indolethylamine N-methyltransferase	0.22	0.27	/	/
MGLL	monoglyceride lipase	0.22	0.28	/	/
G0S2	G0/G1 switch 2	0.21	0.30	/	/

LGALS1	galectin 1	0.20	0.32	/	/
FMO1	flavin containing monooxygenase 1	0.20	0.33	/	/
DECR1	2,4-dienoyl-CoA reductase 1	0.17	0.34	/	/
UBE2L6	ubiquitin conjugating enzyme E2 L6	0.17	0.35	/	/
TP53INP2	tumor protein p53 inducible nuclear protein 2	0.16	0.36	/	/
CPT2	carnitine palmitoyltransferase 2	0.15	0.36	/	/
HSDL2	hydroxysteroid dehydrogenase like 2	0.14	0.39	/	/
GRHPR	glyoxylate and hydroxypyruvate reductase	0.14	0.40	/	/
BCKDHB	branched chain keto acid dehydrogenase E1 subunit beta	0.14	0.40	/	/
SUCLG1	succinate-CoA ligase alpha subunit	0.14	0.41	/	/
S100A10	S100 calcium binding protein A10	0.14	0.42	/	/
ACADS	acyl-CoA dehydrogenase, C-2 to C-3 short chain	0.13	0.43	/	/
HADHB	hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit	0.13	0.44	/	/
ECI1	enoyl-CoA delta isomerase 1	0.12	0.45	/	/
BPHL	biphenyl hydrolase like	0.12	0.45	/	/
PDHA1	pyruvate dehydrogenase (lipoamide) alpha 1	0.12	0.46	/	/
ACO2	aconitase 2	0.12	0.47	/	/
ACOT8	acyl-CoA thioesterase 8	0.12	0.47	/	/
HSD17B4	hydroxysteroid 17-beta dehydrogenase 4	0.12	0.48	/	/
ACAA1	acetyl-CoA acyltransferase 1	0.11	0.48	/	/
IDH3B	isocitrate dehydrogenase 3 (NAD(+)) beta	0.11	0.49	/	/
HMGCL	3-hydroxymethyl-3-methylglutaryl-CoA lyase	0.11	0.48	/	/
ADSL	adenylosuccinate lyase	0.10	0.49	/	/
HADH	hydroxyacyl-CoA dehydrogenase	0.10	0.49	/	/
IDH1	isocitrate dehydrogenase (NADP(+)) 1, cytosolic	0.10	0.49	/	/
ALAD	aminolevulinate dehydratase	0.10	0.50	/	/

IDH3G	isocitrate dehydrogenase 3 (NAD(+)) gamma	0.09	0.50	/	/
PTPRG	protein tyrosine phosphatase, receptor type G	0.09	0.50	/	/
SERINC1	serine incorporator 1	0.09	0.51	/	/
SUCLA2	succinate-CoA ligase ADP-forming beta subunit	0.09	0.51	/	/
HCCS	holocytochrome c synthase	0.09	0.51	/	/
NSDHL	NAD(P) dependent steroid dehydrogenase-like	0.08	0.51	/	/
NBN	nibrin	0.08	0.52	/	/
ADIPOR2	adiponectin receptor 2	0.08	0.52	/	/
ALDOA	aldolase, fructose-bisphosphate A	0.08	0.52	/	/
UROS	uroporphyrinogen III synthase	0.08	0.52	/	/
PCBD1	pterin-4 alpha-carbinolamine dehydratase 1	0.08	0.53	/	/
ACSS1	acyl-CoA synthetase short-chain family member 1	0.08	0.53	/	/
FASN	fatty acid synthase	0.08	0.53	/	/
ERP29	endoplasmic reticulum protein 29	0.07	0.54	/	/
LDHA	lactate dehydrogenase A	0.07	0.54	/	/
HMGCS2	3-hydroxy-3-methylglutaryl-CoA synthase 2	/	/	0.75	0.07
ACSM3	acyl-CoA synthetase medium-chain family member 3	/	/	0.21	0.34
EHHADH	enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase	/	/	0.17	0.42
ACSL4	acyl-CoA synthetase long-chain family member 4	/	/	0.13	0.42
ACADM	acyl-CoA dehydrogenase, C-4 to C-12 straight chain	/	/	0.13	0.44
HSD17B7	hydroxysteroid 17-beta dehydrogenase 7	/	/	0.11	0.44
Neutral lipid metabolism					
Gene	**Description**	**Rank metric score**	**Running ES**	**Rank metric score**	**Running ES**
DGAT2	diacylglycerol O-acyltransferase 2	0.45	0.07	0.40	0.30
CAV1	caveolin 1	0.37	0.13	0.20	0.48
LIPE	lipase E, hormone sensitive type	0.30	0.23	0.17	0.57
CAV3	caveolin 3	0.28	0.37	0.40	0.22

MOGAT1	monoacylglycerol O-acyltransferase 1	0.24	0.40	0.30	0.36
SNCA	synuclein alpha	0.21	0.46	0.65	0.14
ABHD12	abhydrolase domain containing 12	0.21	0.50	0.13	0.56
SLC22A4	solute carrier family 22 member 4	0.17	0.53	0.21	0.44
ACSL1	acyl-CoA synthetase long-chain family member 1	0.32	0.18	/	/
GPD1	glycerol-3-phosphate dehydrogenase 1	0.30	0.28	/	/
ANG	angiogenin	0.29	0.33	/	/
MGLL	monoglyceride lipase	0.22	0.43	/	/
DGAT1	diacylglycerol O-acyltransferase 1	0.18	0.51	/	/
FABP4	fatty acid binding protein 4	0.16	0.55	/	/
AGPAT3	1-acylglycerol-3-phosphate O-acyltransferase 3	0.15	0.57	/	/
ABHD2	abhydrolase domain containing 2	0.14	0.58	/	/
PNPLA2	patatin like phospholipase domain containing 2	0.13	0.58	/	/
PNPLA3	patatin like phospholipase domain containing 3	0.12	0.60	/	/
LPIN1	lipin 1	0.12	0.62	/	/
GPD1L	glycerol-3-phosphate dehydrogenase 1-like	0.11	0.62	/	/
PLCE1	phospholipase C epsilon 1	0.11	0.64	/	/
AGMO	alkylglycerol monooxygenase	/	/	0.25	0.40
PCK1	phosphoenolpyruvate carboxykinase 1	/	/	0.17	0.50
FABP9	fatty acid binding protein 9	/	/	0.17	0.53
PCSK9	proprotein convertase subtilisin/kexin type 9	/	/	0.13	0.59
ACSL4	acyl-CoA synthetase long-chain family member 4	/	/	0.13	0.61
Lipid storage					
Gene	**Description**	**Rank metric score**	**Running ES**	**Rank metric score**	**Running ES**
DGAT2	diacylglycerol O-acyltransferase 2	0.45	0.12	0.40	0.30
PLIN5	perilipin 5	0.41	0.23	0.22	0.59
IL1B	interleukin 1 beta	0.37	0.34	0.34	0.54
CAV1	caveolin 1	0.37	0.44	0.20	0.65
ACVR1C	activin A receptor type 1C	0.35	0.54	0.38	0.43

CIDEA	cell death-inducing DFFA-like effector a	0.33	0.63	0.52	0.17
NRIP1	nuclear receptor interacting protein 1	0.31	0.71	0.15	0.68
ABHD4	abhydrolase domain containing 4	0.25	0.77	/	/
HEXB	hexosaminidase subunit beta	0.23	0.83	/	/
DGAT1	diacylglycerol O-acyltransferase 1	0.18	0.85	/	/
STAT5B	signal transducer and activator of transcription 5B	/	/	0.13	0.70

Supplementary Table 3

Gene	Gene Name
CSA	also known as ERCC8, ERCC excision repair 8, CSA ubiquitin ligase complex subunit
CSB	also known as ERCC6, ERCC excision repair 6, chromatin remodeling factor
CUL4A	cullin 4A
DDB1	damage specific DNA binding protein 1
DDB2	damage specific DNA binding protein 2
ERCC1	ERCC excision repair 1, endonuclease non-catalytic subunit
GTF2H1	general transcription factor IIH subunit 1
GTF2H2	general transcription factor IIH subunit 2
GTF2H3	general transcription factor IIH subunit 3
GTF2H4	general transcription factor IIH subunit 4
GTF2H5	general transcription factor IIH subunit 5
LIG1	DNA ligase 1
MMS19	MMS19 homolog, cytosolic iron-sulfur assembly component
PCNA	proliferating cell nuclear antigen
POLD1	DNA polymerase delta 1, catalytic subunit
POLE	DNA polymerase epsilon, catalytic subunit
RAD23B	RAD23 homolog B, nucleotide excision repair protein
RFC1	replication factor C subunit 1
RPA1	eplication protein A1
XPA	XPA, DNA damage recognition and repair factor
XPB	also known as ERCC3, ERCC excision repair 3, TFIIH core complex helicase subunit
XPC	XPC complex subunit, DNA damage recognition and repair factor
XPD	also known as ERCC2, ERCC excision repair 2, TFIIH core complex helicase subunit
XPF	also known as ERCC4, ERCC excision repair 4, endonuclease catalytic subunit
XPG	also known as ERCC5, ERCC excision repair 5, endonuclease
UVSSA	UV stimulated scaffold protein A

Supplementary Table 4

chrom	chr4
start	1343466
end	1343473
gene	*UVSSA*
ref	AGTTCCT
alt	**A**
type	indel
subtype	del
impact	inframe_deletion
codon change	c.256_261del
aa change	p.Phe86_Leu87del
impact severity	MED
median depth	30
mutated fraction	100