Supplementary Table 1. shRNA sequences used for *LRPPRC* knockdown.

LRPPRC kd	Clone Name	Sequence (5'➔ 3')
kd1	NM_133259.2-1441s1c1	CCTCAAAGGAATGCAAGAATT
kd2	NM_133259.2-2443s1c1	CGCAGCTTTAAGAGGTGAAAT
kd3	NM_133259.2-3384s1c1	GCCTCATCATAACGCAAGTTA
kd4	NM_133259.2-4626s1c1	CCGTGAACTTTCTAACGCATA
kd5	NM_133259.2-868s1c1	CCTCGCATTATTGAATGCATA
kd6	NM_133259.x-163s1c1	ATGTGAGTCACTATAATGCT
kd7	NM_133259.x-4007s1c1	ACCATAACTCTGTGCACTTG

Supplementary Table 2. Probe and primer sequences of mitochondrial mRNA, rRNA, and polycistronic RNA (pre-RNA) for qRT-PCR Taqman assay.

Gene ID	Probe	Forward Primer	Reverse Primer
MT-ND1	CACCGCCCCGACCTT	CCCTAAAACCCGCCACATCT	GGCTAGAATAAATAGGAGGCCTAGGT
MT-ND2	TTGCAGGCACACTCATC	AACCCGTCATCTACTCTACCATCT	GCTTCTGTGGAACGAGGGTTTATTT
MT-ND3	TCGAAGCCGCACTCGT	CCACAACTCAACGGCTACATAGAAA	GGGTAAAAGGAGGGCAATTTCTAGA
MT-ND4	CTCCTGAGCCAACAAC	TCACAACACCCTAGGCTCACTAA	GGGAGTCATAAGTGGAGTCCGT
MT-ND4L	CTCAACACCCACTCCC	TCCTCCCTACTATGCCTAGAAGGA	CTTCGCAGGCGGCAAA
MT-ND5	TCGCTGTCACTTTCC	CGGAAGCCTATTCGCAGGATT	GTAGTTGAGGTCTAGGGCTGTTAGA
MT-ND6	CCACCACCCCATCATAC	GGTTAGCGATGGAGGTAGGATTG	AAAGCCCCCGCACCAATA
MT-CYB	CCCTCGGCTTACTTCT	TCACCTCCCATTCCGATAAAATCAC	GGGTTGGCTAGGGTATAATTGTCTG
MT-CO1	TAGCTGCTGGCATCACT	CAGCAGTCCTACTTCTCCTATCTCT	GGGTCGAAGAAGGTGGTGTT
MT-CO2	CCCGCCATCATCCTAG	GCCCTTTTCCTAACACTCACAACAA	GTAAAGGATGCGTAGGGATGGG
MT-CO3	ACCCTCCTACAAGCCTC	TCACCTGAGCTCACCATAGTCTAAT	GCCGTCGGAAATGGTGAAG
MT-ATP6	ACTGCAGGCCACCTAC	CGTACGCCTAACCGCTAACATT	GCGACAGCGATTTCTAGGATAGT
MT-ATP8	CCCACCATAATTACCC	GCCCCAACTAAATACTACCGTATGG	GGCTTTGGTGAGGGAGGTA
MT-12S	ATCACTGCTGTTTCCC	ATGCAGCTCAAAACGCTTAGC	GCTGGCACGAAATTGACCAA
MT-16S	CAAAGCGCCTTCCCC	CCCTGTACGAAAGGACAAGAGAAAT	TCTTGGGTGGGTGTGGGTATAAT
Pre-RNA	ACGGGAAGGGTATAACC	CCTGCAAAGATGGTAGAGTAGATGAC	GGGCCCATACCCCGAAAAT

Supplementary Table 3. A list of previous studies on mitochondrial genes showing biochemical defects in human primary skin fibroblasts.

Gene	Reference
TAZ	Vreken, P. et al. 2000
BCS1L	de Lonlay, P. et al. 2001
COX15	Antonicka, H. et al. 2003
TK2	Vila, M. R. et al. 2003
DGUOK	Taanman, J. W. et al. 2003
COX10	Antonicka, H. et al. 2003
SCO1	Williams, S. L. et al. 2004
SURF1	Williams, S. L. et al. 2004
ETHE1	Tiranti, V. et al. 2004
ATPAF2	De Meirleir, L. et al. 2004
LRPPRC	Xu, F. et al. 2004
SCO2	Leary, S. C. et al. 2004
FXN	Sturm, B. et al. 2005
SDHA	Briere, J. J. et al. 2005

Vreken, P. , Valianpour, F. , Nijtmans, L. G., Grivell, L. A. , Plecko, B. , Wanders, R. J. , and Barth, P. G. (2000) *Biochem Biophys Res Commun* **279**(2), 378-382

de Lonlay, P. , Valnot, I. , Barrientos, A. , Gorbatyuk, M. , Tzagoloff, A. , Taanman, J. W. , Benayoun, E. , Chretien, D. , Kadhom, N. , Lombes, A. , de Baulny, H. O. , Niaudet, P. , Munnich, A. , Rustin, P. , and Rotig, A. (2001) *Nat Genet* **29**(1), 57-60

Antonicka, H. , Mattman, A. , Carlson, C. G. , Glerum, D. M. , Hoffbuhr, K. C. , Leary, S. C. , Kennaway, N. G. , and Shoubridge, E. A. (2003) *Am J Hum Genet* **72**(1), 101-114

Vila, M. R. , Segovia-Silvestre, T. , Gamez, J. , Marina, A. , Naini, A. B. , Meseguer, A. , Lombes, A. , Bonilla, E. , DiMauro, S. , Hirano, M. , and Andreu, A. L. (2003) *Neurology* **60**(7), 1203-1205

Taanman, J. W. , Muddle, J. R. , and Muntau, A. C. (2003) *Hum Mol Genet* **12**(15), 1839-1845

Antonicka, H. , Leary, S. C. , Guercin, G. H. , Agar, J. N. , Horvath, R. , Kennaway, N. G. , Harding, C. O. , Jaksch, M. , and Shoubridge, E. A. (2003) *Hum Mol Genet.* **12**(20), 2693-2702

Williams, S. L. , Valnot, I. , Rustin, P. , and Taanman, J. W. (2004) *J Biol Chem* **279**(9), 7462-7469

Tiranti, V. , D'Adamo, P. , Briem, E. , Ferrari, G. , Mineri, R. , Lamantea, E. , Mandel, H. , Balestri, P. , Garcia-Silva, M. T. , Vollmer, B. , Rinaldo, P. , Hahn, S. H. , Leonard, J. , Rahman, S. , Dionisi-Vici, C. , Garavaglia, B. , Gasparini, P. , and Zeviani, M. (2004) *Am J Hum Genet* **74**(2), 239-252

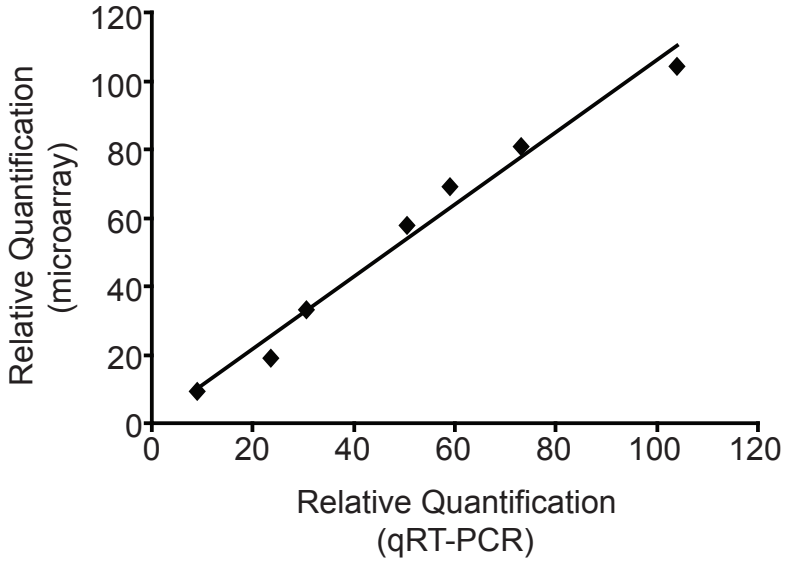
De Meirleir, L. , Seneca, S. , Lissens, W. , De Clercq, I. , Eyskens, F. , Gerlo, E. , Smet, J. , and Van Coster, R. (2004) *J Med Genet* **41**(2), 120-124

Xu, F. , Morin, C. , Mitchell, G. , Ackerley, C. , and Robinson, B. H. (2004) *Biochem J* **382**(1), 331-336

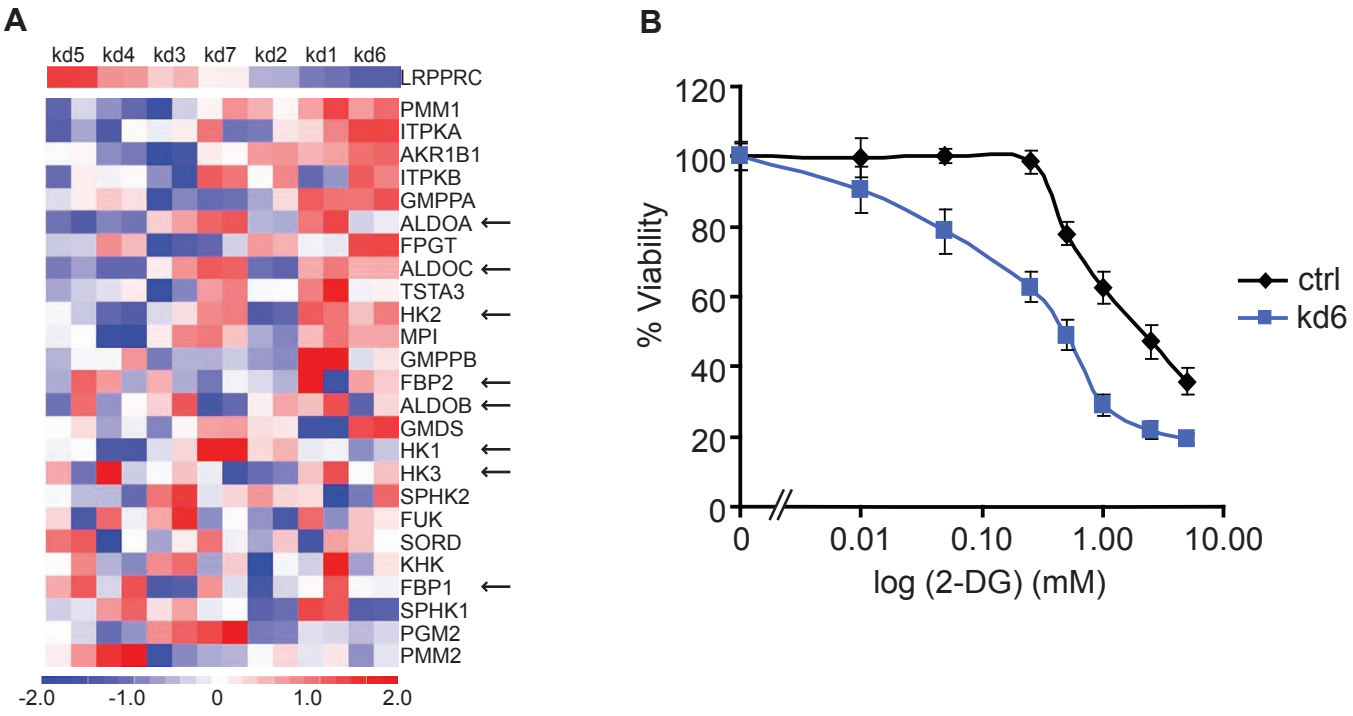
Leary, S. C. , Kaufman, B. A. , Pellecchia, G. , Guercin, G. H. , Mattman, A. , Jaksch, M. , and Shoubridge, E. A. (2004) *Hum Mol Genet* **13**(17), 1839-1848

Sturm, B. , Bistrich, U. , Schranzhofer, M. , Sarsero, J. P. , Rauen, U. , Scheiber-Mojdehkar, B. , de Groot, H. , Ioannou, P. , and Petrat, F. (2005) *J Biol Chem* **280**(8), 6701-6708

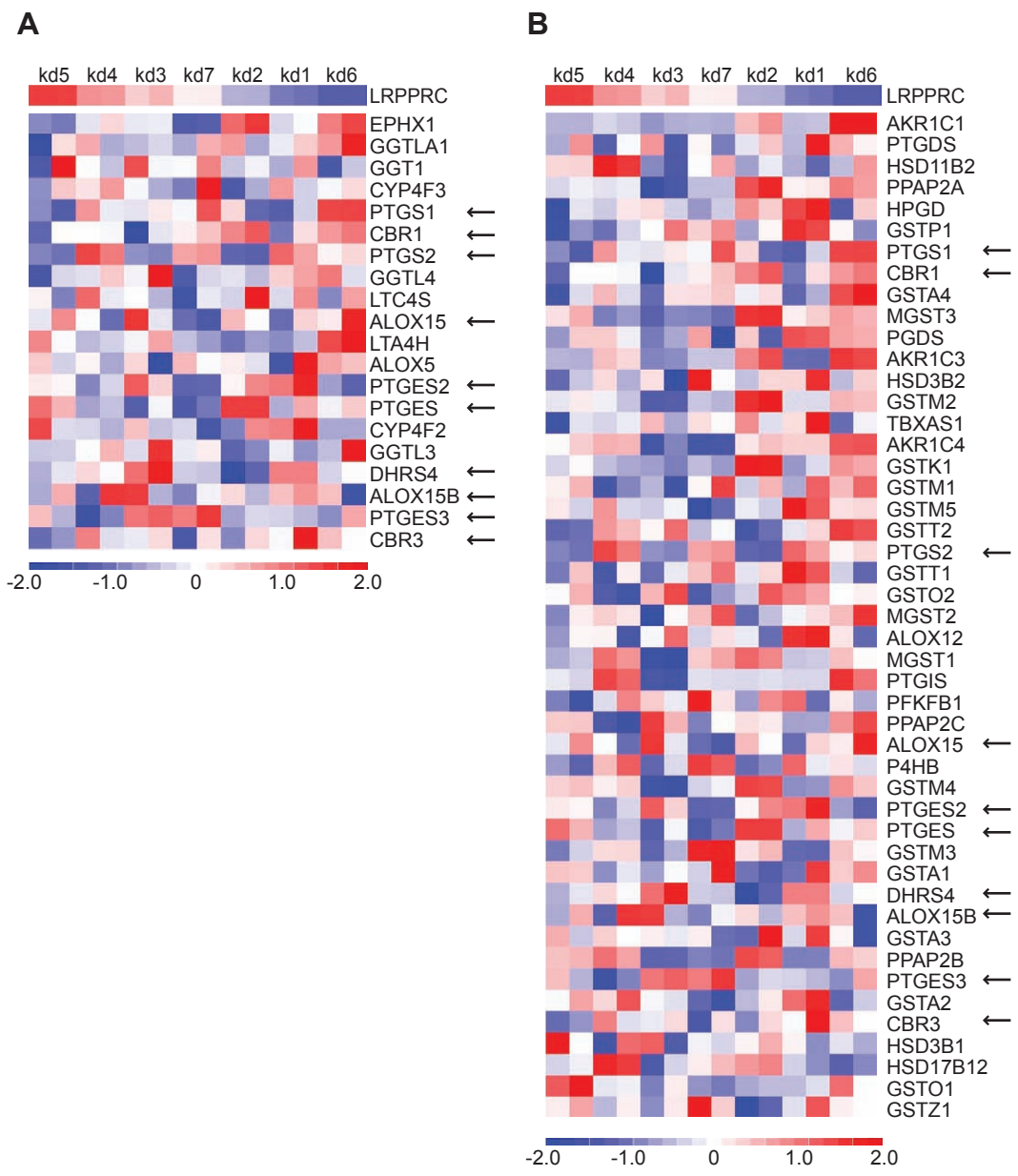
Briere, J. J. , Favier, J. , Benit, P. , El Ghouzzi, V. , Lorenzato, A. , Rabier, D. , Di Renzo, M. F. , Gimenez-Roqueplo, A. P. , and Rustin, P. (2005) *Hum Mol Genet* **14**(21), 3263-3269



Supplementary Figure 1. *LRPPRC* transcript levels measured by qRT-PCR and microarray show strong correlation.
Total cellular RNA was extracted from *LRPPRC* knockdown cell lines. *LRPPRC* transcipt level was measured for the same samples by qRT-PCR and microarray. The average of two biological replicaetes is shown.

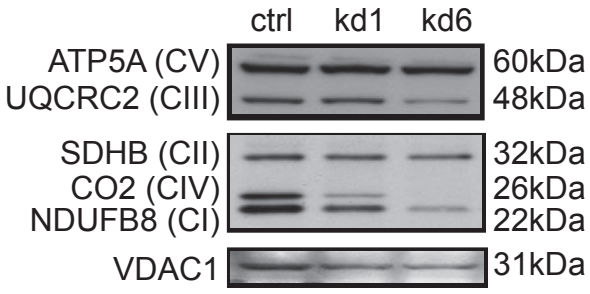


Supplementary Figure 2. Up-regulation of key glycolytic genes included in the "fructose and mannose metabolism" gene set could be an adaptive nuclear response.
(A) The expression of genes included in "fructose and mannose metabolism" gene set in *LRPPRC* knockdown cells. Glycolytic genes included in this pathway are indicated by arrows. Two replicates for each knockdown are shown adjacent to each other. (B) MCH58 cells infected with pLKO.1 (ctrl) or shLRPPRC6 (kd6) were grown in the presence of increasing concentrations of the glycolytic inhibitor, 2-deoxyglucose for 72 hours. Cell viability was measured by calcein asay Data is normalized to untreated cells. (n=5; error bars represent standard deviation from the mean value).



Supplementary Figure 3. Gene expression profile of gene sets that are anti-correlated to *LRPPRC* expression

(A) Expression of genes included in the "putative anti-inflammatory metabolite formation from eicosapentanoic acid" gene set in *LRPPRC* knockdown cells. (B) Expression of genes included in the "prostaglandin formation from arachidonate" gene set in *LRPPRC* knockdown cells. Genes were ordered by their correlation to *LRPPRC* expression profile (shown separately on top), with genes showing strongest anti-correlation at top and weakest anti-correlation at the bottom. Two replicates for each knockdown are shown adjacent to each other. Arrows indicate overlapping genes included in both gene sets.



Supplementary Figure 4. *LRPPRC* knockdown results in a depletion of multiple mitochondrial respiratory chain complexes.
Western blot assay of whole cell lysate harvested from MCH58 fibroblasts infected either with an empty vector or one of the two most potent shRNAs against *LRPPRC*. Blotted proteins are indicated to the left of the image with the respective mitochondrial respiratory chain complex in parentheses. VDAC1 was used as a loading control.