SUPPLEMENTAL INFORMATION

Supplementary Table 1

Multicopy suppressors of *AAC2*^{A128P}-induced degenerative cell death

Functional group	Gene	Function of gene product
Tor signaling	*DOT6*	Protein involved in rRNA and ribosome biogenesis under the control of the Tor1 kinase; subunit of the RPD3L histone deacetylase complex; paralog of Tod6
	FHL1	Regulator of ribosomal protein transcription
	RPD3	Histone deacetylase
	TOD6	Protein involved in rRNA and ribosome biogenesis; subunit of the RPD3L histone deacetylase complex; paralog of Dot6
mRNA turnover /silencing	*CDC33*	mRNA cap binding protein and translation initiation factor eIF4E; component of cytoplasmic stress granules
	DCP2	Catalytic subunit of the Dcp1p-Dcp2p decapping enzyme complex; component of cytoplasmic mRNA processing body (P-body)
	EDC3	Enhancer of mRNA decapping; component of cytoplasmic mRNA processing body (P-body)
	NAM7	ATP-dependent RNA helicase of the SFI superfamily involved in nonsense mediated mRNA decay
	PBP1	Involved in P-body-dependent granule assembly; ortholog of human ataxin-2
	PRT1	eIF3b subunit of the core complex of translation initiation factor 3 (eIF3); component of cytoplasmic stress granules
	PSP2	Asn rich cytoplasmic protein that contains the RNA-binding RGG motifs; component of P-bodies
	TIF3	Translation initiation factor eIF-4B; constituent of stress granules
	TIF4632	Translation initiation factor eIF4G; subunit of the mRNA cap-binding protein complex (eIF4F) that also contains eIF4E (Cdc33p); involved in stress granule assembly
Ribosomal function /protein translation	*REB1*	RNA polymerase I enhancer binding protein
	RPL38	Ribosomal 60S subunit protein L38
	RPL40A	Ubiquitin-ribosomal 60S subunit protein L40A fusion protein; cleaved to yield ubiquitin and ribosomal protein L40A
	RPL40B	Ubiquitin-ribosomal 60S subunit protein L40B fusion protein; cleaved to yield ubiquitin and ribosomal protein L40B
	RPL43A	Ribosomal 60S subunit protein L43A
	RPP0	Conserved ribosomal protein P0 of the ribosomal stalk

	RPS6B	Ribosomal 40S subunit protein S6B
	RPS30B	Ribosomal 40S subunit protein S30B
	SNR3	H/ACA box small nucleolar RNA (snoRNA)
tRNA methylation	*TRM9*	tRNA methyltransferase; catalyzes modification of wobble bases in tRNA anticodons to 2, 5-methoxycarbonylmethyluridine and 5-methoxycarbonylmethyl-2-thiouridine
	TRM11	Catalytic subunit of an adoMet-dependent tRNA methyltransferase complex (Trm11p-Trm112p), required for the methylation of the guanosine nucleotide at position 10 (m2G10) in tRNAs
Cytosolic protein chaperoning /degradation	*MMS2*	Ubiquitin-conjugating enzyme variant
	POC4	Component of a heterodimeric Poc4p-Irc25p chaperone involved in assembly of alpha subunits into the 20S proteasome
	SAF1	F-Box protein involved in proteasome-dependent protein degradation
	SSB1	Cytoplasmic ATPase that is a ribosome-associated molecular chaperone; functions with J-protein partner Zuo1p
	SSB2	Cytoplasmic ATPase that is a ribosome-associated molecular chaperone; functions with J-protein partner Zuo1p
	UBP3	Ubiquitin-specific protease
	UMP1	Short-lived chaperone required for correct maturation of the 20S proteasome
	ZUO1	Ribosome-associated chaperone; contains a DnaJ domain and functions as a J-protein partner for Ssb1p and Ssb2p
Ungrouped	*HRR25*	Protein kinase involved in diverse functions such as ribosomal biogenesis and tRNA modification
	KIN2	Serine/threonine protein kinase
	RGI1	YER067W, protein of unknown function; possibly involved in energy metabolism under respiratory conditions
	SDD1	YEL057C, protein of unknown function
	SDD2	YMR074C, protein with homology to human PDCD5 involved in programmed cell death
	SDD3	YOL098C, putative metalloprotease
	SDD4	YPR022C, putative transcription factor
	SSY5	Serine protease of SPS plasma membrane amino acid sensor system

Supplementary Table 2

Comparison of cytosolic proteomes between *AAC2*^{A128P} and wild type cells as revealed by iTRAQ analysis

(The data are shown in a separate Source Data file)

Cytosolic protein samples from two biological replicates of wild type cells were labeled with the 114- and 115-tags and two biological replicates of *AAC2*^{A128P}-expressing cells were labeled with the 116- and 117-tags. The ratios of particular proteins between the mutant and the wild type were calculated by using the 114 and 115 signals as denominators. The final mutant/WT ratio was the average of the 116/114, 117/114, 116/115 and 117/115 ratios.

Supplementary Table 3

Gene Ontology Analysis Showing Cytosolic Processes that are Down-regulated by >2 in Response to Mitochondrial Inner Membrane Damage

Gene Ontology Term	**Cluster Frequency**	***P* value**
Oxidoreductase activity	30 out of 107 genes, 28.0%	3.20e-16
Oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor	10 out of 107 genes, 9.3%	6.79e-06
Oxidoreductase activity, acting on NAD(P)H	7 out of 107 genes, 6.5%	1.08e-05
Oxidoreductase activity, acting on CH-OH group of donors	10 out of 107 genes, 9.3%	1.92e-05
Oxidoreductase activity, acting on the aldehyde or oxo group of donors	6 out of 107 genes, 5.6%	0.00015
Transferase activity, transferring hexosyl groups	9 out of 107 genes, 8.4%	0.00016
Oxidoreductase activity, acting on a sulfur group of donors	6 out of 107 genes, 5.6%	0.00046
Oxidoreductase activity, acting on the aldehyde or oxo group of donors, NAD or NADP as acceptor	5 out of 107 genes, 4.7%	0.00076
Transferase activity, transferring glycosyl groups	9 out of 107 genes, 8.4%	0.00101
Transferase activity, transferring alkyl or aryl (other than methyl) groups	6 out of 107 genes, 5.6%	0.00184
UDP-glucosyltransferase activity	4 out of 107 genes, 3.7%	0.00264
Alditol:NADP+ 1-oxidoreductase activity	3 out of 107 genes, 2.8%	0.00276
Aldehyde dehydrogenase (NAD) activity	3 out of 107 genes, 2.8%	0.00546
Disulfide oxidoreductase activity	4 out of 107 genes, 3.7%	0.00649
Glucosyltransferase activity	3 out of 107 genes, 2.8%	0.00945
Glutathione transferase activity	3 out of 107 genes, 2.8%	0.00945
Alcohol dehydrogenase (NADP+) activity	3 out of 107 genes, 2.8%	0.00945

Supplementary Table 4

Proteins that are up-regulated for >2 fold in the cytosol of *AAC2*^{A128P}-expressing cells

Category	**Protein**	**Function**	**Remarks**
Mitochondria	Idh2	Subunit of mitochondrial NAD(+)-dependent isocitrate dehydrogenase	
	Idh1	Subunit of mitochondrial NAD(+)-dependent isocitrate dehydrogenase	
	Mss116	DEAD-box protein required for efficient splicing of mitochondrial Group I and II introns	
	Hsp10	Mitochondrial matrix co-chaperonin that inhibits the ATPase activity of Hsp60p	
	Ssc1	Hsp70 family ATPase in mitochondria	
	Mnp1	Putative mitochondrial ribosomal protein	
	Hsp60	Mitochondrial chaperonin	
	Cpr3	Mitochondrial peptidyl-prolyl cis-trans isomerase (cyclophilin)	
	Shm1	Mitochondrial serine hydroxymethyltransferase	
	Tuf1	Mitochondrial translation elongation factor Tu	
	Aco1	Mitochondrial aconitase	
	Mmf1	Mitochondrial protein required for transamination of isoleucine	
	Leu4	Alpha-isopropylmalate synthase (2-isopropylmalate synthase) localized to both mitochondria and cytosol	
	Arg7	Mitochondrial ornithine acetyltransferase, catalyzes arginine biosynthesis	
	Cox17	Copper metallochaperone in mitochondria	
	Idp1	Mitochondrial NADP-specific isocitrate dehydrogenase	
	Pdb1	E1 beta subunit of the pyruvate dehydrogenase (PDH) complex in mitochondria	
	Pda1	E1 alpha subunit of the pyruvate dehydrogenase (PDH) complex in mitochondria	

	Bat1	Mitochondrial branched-chain amino acid (BCAA) aminotransferase	
	Ilv5	Bifunctional acetohydroxyacid reductoisomerase and mtDNA binding protein in mitochondria	
	Pim1	ATP-dependent Lon protease in mitochondria	
	Kgd1	Subunit of the mitochondrial alpha-ketoglutarate dehydrogenase complex	
	Nfu1	Protein involved in iron metabolism in mitochondria	
	Aac2	Major ADP/ATP carrier of the mitochondrial inner membrane	Mitochondrial inner membrane protein
Cytosolic ribosome associated proteins	Tma7	Protein of unknown that associates with ribosomes	A highly conserved ribosome associated protein
	Gis2	Translational activator for mRNAs with internal ribosome entry sites	Ortholog of human ZNF9/CNBP involved in type 2 myotonic dystrophy
	Nog2	GTPase required for the nuclear export of pre-60S ribosomal subunit	Ortholog of human nucleostemins
Methylation	Sam1	*S*-adenosylmethionine synthetase	
	Sam2	*S*-adenosylmethionine synthetase	
Others	His3	Histidine biosynthesis	
	Guk1	Guanylate kinase, converts GMP to GDP	
	YPR172W	Protein of unknown function, transcriptionally activated by Yrm1p along with genes involved in multidrug resistance	
	Gyl1	Putative GTPase activating protein (GAP)	
	Pno1	Also known as Rrp20, involved in pre-18S rRNA processing by recruiting the 18S rRNA dimethyltransferase Dim1p	A point mutation is known to cause ρ^o-lethality [35]
	Bni1	Formin, nucleates the formation of linear actin filaments	
	Hem13	Coproporphyrinogen III oxidase involved in heme biosynthetic pathway	
	YMR102C	Protein of unknown function; transcriptionally activated by paralogous transcription factors Yrm1p and Yrr1p along with genes involved in multidrug resistance	

	Cup1-2	Metallothionein	
	Tub3	Alpha-tubulin	
	Pdr5	Multidrug transporter on the plasma membrane	
	YCR087C-A	Putative protein of unknown function	
	YGL039W	Aldehyde reductase	
	Gpm3	Phosphoglycerate mutase, converts 3-phosphoglycerate to 2-phosphoglycerate in glycolysis	

Supplementary Table 5

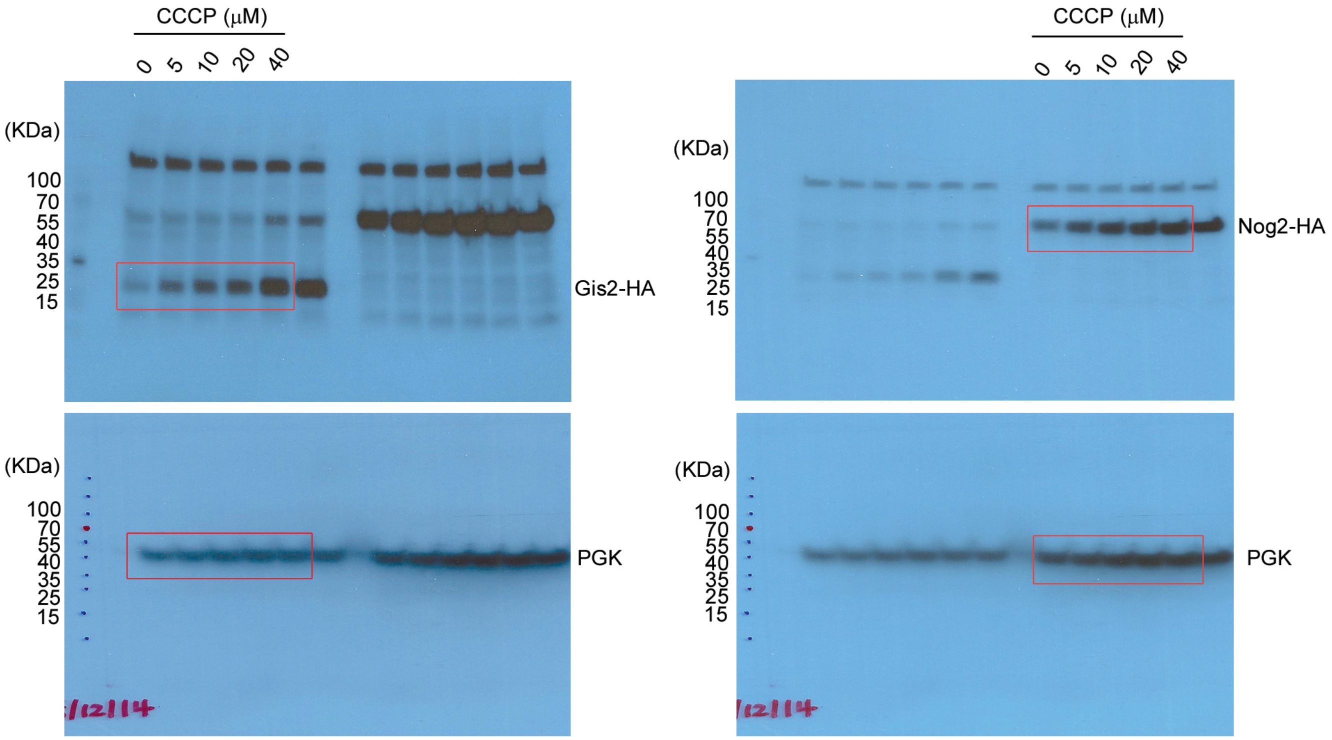
Anti-degenerative suppressors/pathways and their mammalian orthologs known to cause degenerative diseases

Yeast	Mammal	Diseases and References
Pbp1	Ataxin-2	Spinocerebellar ataxia type 2 and amyotrophic lateral sclerosis [36-39]
Tif4631 and Tif4632	eIF4G1	Associated with Parkinson's disease in humans [40]
Nog2	Nucleostemin	Osteoarthritis [41]
Hrr25	TTBK2	Spinocerebellar ataxia type 11 [42]
Rpl38	Rpl38	Conductive hearing impairment in mouse [43]
Nam7/Upf1	UPF3	Upf3 forms complex with Upf2 and Upf1 which is identified as an anti-degenerative protein in yeast. Mutations in Upf3 cause X-linked mental retardation in humans [44].
Gis2	ZNF9/CNBP	Myotonic dystrophy type 2 [45]
Sam1, Sam2	MAT1A	Mental retardation, dystonia, demylination and other neurological disorders [46]

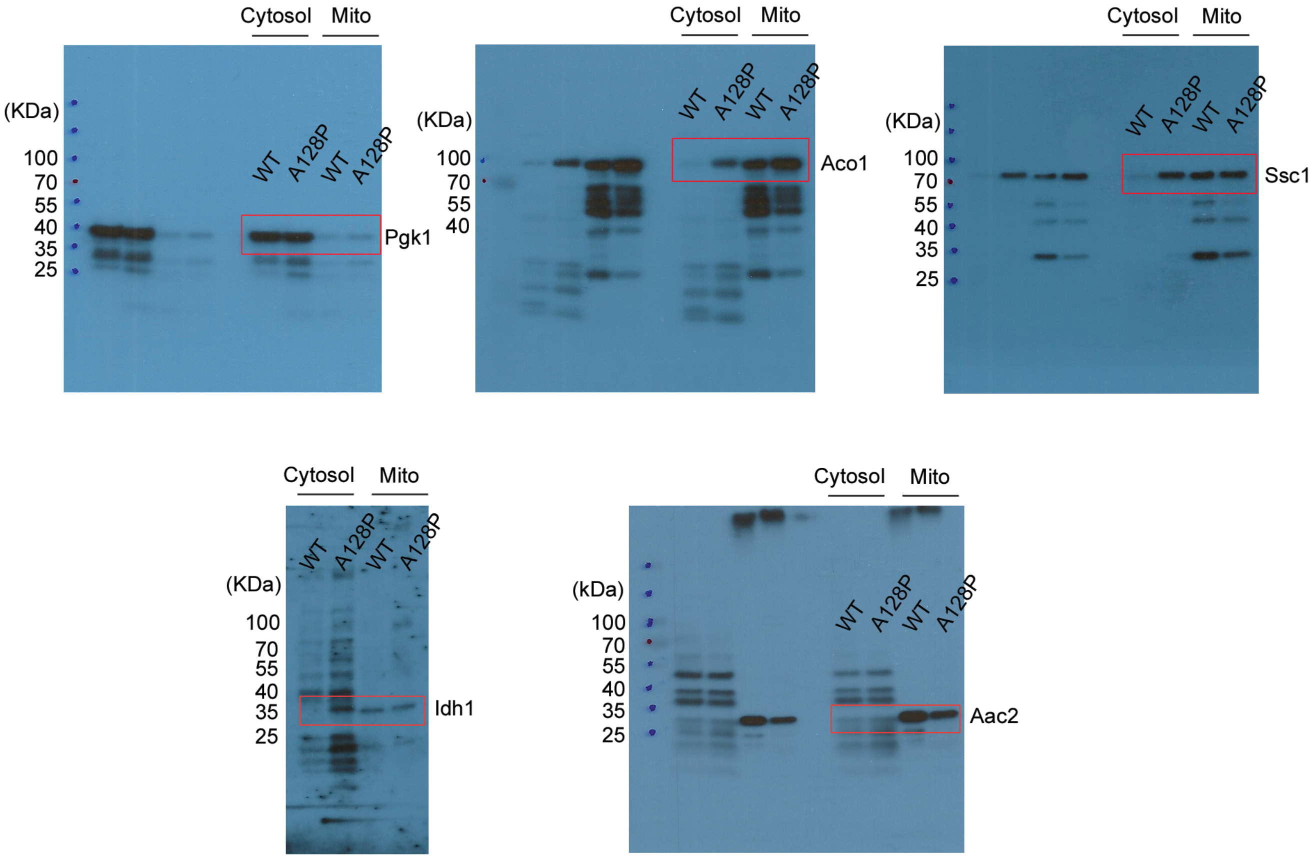
References:

35. Senapin, S., Clark-Walker, G.D., Chen, X.J., Seraphin, B. & Daugeron, M.C. RRP20, a component of the 90S preribosome, is required for pre-18S rRNA processing in *Saccharomyces cerevisiae*. *Nucleic Acids Res* **31**, 2524-2533 (2003).
36. Pulst, S.M. *et al.* Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. *Nat Genet* **14**, 269-276 (1996).
37. Imbert, G. *et al.* Cloning of the gene for spinocerebellar ataxia 2 reveals a locus with high sensitivity to expanded CAG/glutamine repeats. *Nat Genet* **14**, 285-291 (1996).
38. Sanpei, K. *et al.* Identification of the spinocerebellar ataxia type 2 gene using a direct identification of repeat expansion and cloning technique, DIRECT. *Nat Genet* **14**, 277-284 (1996).
39. Elden, A.C. *et al.* Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. *Nature* **466**, 1069-1075 (2010).
40. Chartier-Harlin, M.C. *et al.* Translation initiator EIF4G1 mutations in familial Parkinson disease. *Am J Hum Genet* **89**, 398-406 (2011).
41. Zeggini, E. *et al.* Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. *Lancet* **380**, 815-823 (2012).
42. Houlden, H. *et al.* Mutations in *TTBK2*, encoding a kinase implicated in tau phosphorylation, segregate with spinocerebellar ataxia type 11. *Nat Genet* **39**, 1434-1436 (2007).
43. Noben-Trauth, K. & Latoche, J.R. Ectopic mineralization in the middle ear and chronic otitis media with effusion caused by RPL38 deficiency in the Tail-short (Ts) mouse. *J Biol Chem* **286**, 3079-3093 (2010).
44. Tarpey, P.S. *et al.* Mutations in UPF3B, a member of the nonsense-mediated mRNA decay complex, cause syndromic and nonsyndromic mental retardation. *Nat Genet* **39**, 1127-1133 (2007).
45. Sammons, M.A., Samir, P. & Link, A.J. *Saccharomyces cerevisiae* Gis2 interacts with the translation machinery and is orthogonal to myotonic dystrophy type 2 protein ZNF9. *Biochem Biophys Res Commun* **406**, 13-19 (2011).
46. Furujo, M., Kinoshita, M., Nagao, M. & Kubo, T. Methionine adenosyltransferase I/III deficiency: neurological manifestations and relevance of *S*-adenosylmethionine. *Mol Genet Metab* **107**, 253-256 (2012).

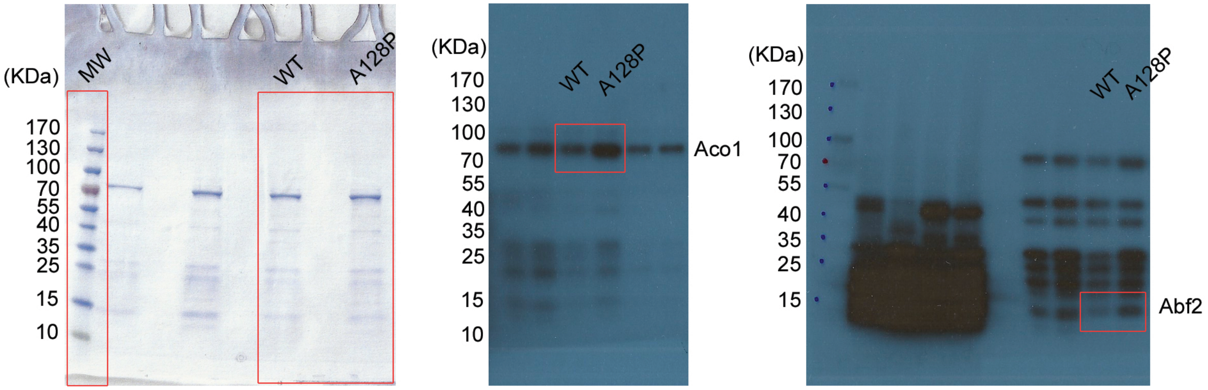
Full scans of Figure 3c



Full scans for Extended Data Figure 5a



Full scans for Extended Data Figure 5b



SDS PAGE

Western blot

Full scans for Extended Data Figure 7