SUPPLEMENTARY MATERIAL

TITLE: Biomarkers in neurodegeneration: A beginner's guide into curated analyses using publicly available datasets

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SUPPLEMENTARY FILES:

- FIGURES, S1-4
- TABLES, S1-S3
- SUPPLEMNATRY EXCEL FILES, 1-3

Supplementary Figure Legends

Figure S1. Pictoral overview of the method for curated analyses within GEO2R

Figure S2. Curated gene expression analyses of glutathione biogenesis related factors within GEO microarray dataset GSE26927 across common neurodegenerative diseases (and Multiple sclerosis, a demyelinating disease). (A) Glutathione synthetase (gene symbol, *GSS*), gamma-Glutamylcyclotransferase (gene symbol, *GGCT),* gamma-glutamylcysteine synthetase (gene symbol, *GCLC),* gamma-glutamyltransferase/transpeptidase 1 (gene symbol, *GGT1),* glucose-6-phosphate dehydrogenase (gene symbol, *G6PD)* and superoxide dismutase (gene symbol *SOD1)***.** The values across the dataset are expressed relative to the controls in each disease condition, i.e., mean value of control samples=1 (a.u., arbitrary units). Error bars represent standard deviation of the mean, s.d. Pair-wise comparisons were assessed by Mann-Whitney test- only significant differences (*=p≤0.05, **=p≤0.01, ***=p≤0.005) are highlighted. The number of controls and cases, microarray platforms and original studies are included in Table S1. Unique probe IDs within each dataset are included in Table 2. Legend: Ctrl (controls); Alzheimer disease (AD); Motor neurone disease (ALS); Huntington disease (HD), and Multiple sclerosis (MS).

Figure S3. Curated gene expression analyses of neuronal excitability/calcium signaling related factors within GEO microarray dataset GSE26927 across common neurodegenerative diseases (and Multiple sclerosis, a demyelinating disease). (A) Sodium-potassium ATPase, catalytic subunit alpha-1 (*ATP1A1*), sarcoplasmic/endoplasmic reticulum (ER) Ca^{2+} transporting ATPase 2, alias SERCA2 (*ATP2A2*), ryanodine receptor 1 (*RYR1*), voltage dependent anion channel 1 (*VDAC1*), glutamate metabotropic receptor 5 (*GRM5*), and phospholipase c gamma 1 (*PLGC1*). The values across the dataset are expressed relative to the controls in each disease condition, i.e., mean value of control samples=1 (a.u.,

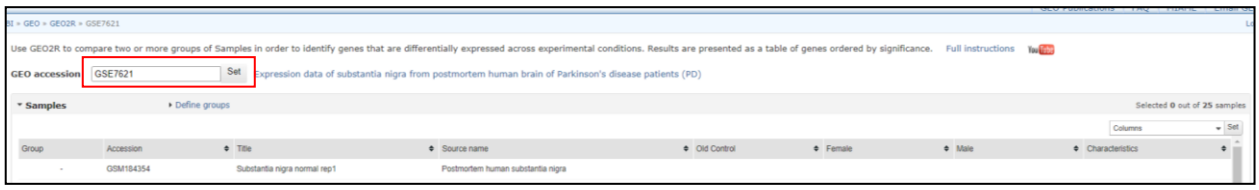
arbitrary units). Error bars represent standard deviation of the mean, s.d. Pair-wise comparisons were assessed by Mann-Whitney test- only significant differences (*=p≤0.05, **=p≤0.01, ***=p≤0.005) are highlighted. The number of controls and cases, microarray platforms and original studies are included in Table S1. Unique probe IDs within each dataset are included in Table 2. Legend: Ctrl (controls); Alzheimer disease (AD); Motor neurone disease (ALS); Huntington disease (HD), and Multiple sclerosis (MS).

Figure S4. Curated gene expression analyses of factors involved in the regulation of autophagy within GEO microarray dataset GSE26927 across common neurodegenerative diseases (and Multiple sclerosis, a demyelinating disease). (A) Autophagy Related 3 (*ATG3)*, lysosomal associated membrane protein 2 (*LAMP2)*, microtubule associated protein 1 Light Chain 3, alias LC3 alpha (*MAP1LC3*,) PTEN Induced Kinase 1 (*PINK1)*, Unc-51 like autophagy activating kinase 1 (*ULK1*) and TANK binding kinase 1 (*TBK1).* The values across the dataset are expressed relative to the controls in each disease condition, i.e., mean value of control samples=1 (a.u., arbitrary units). Error bars represent standard deviation of the mean, s.d. Pair-wise comparisons were assessed by Mann-Whitney test- only significant differences (*=p≤0.05, **=p≤0.01, ***=p≤0.005; ns= not significant) are highlighted. The number of controls and cases, microarray platforms and original studies are included in Table S1. Unique probe IDs within each dataset are included in Table 2. Legend: Ctrl (controls); Alzheimer disease (AD); Motor neurone disease (ALS); Huntington disease (HD), and Multiple sclerosis (MS).

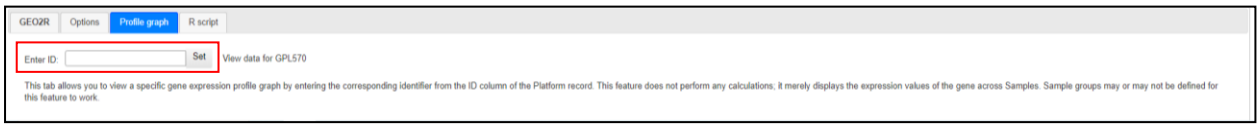
FIGURE S1. PICTORAL OVERVIEW

1) Search the datasets on https://www.ncbi.nlm.nih.gov/geo/, by entering the dataset ID (e.g., GSE7621)

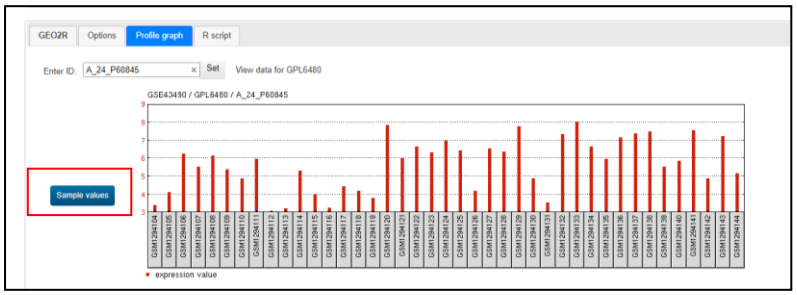
2) On the next page, scroll to the bottom and click: "Analyze with GEO2R", it will load the GEO2R interface



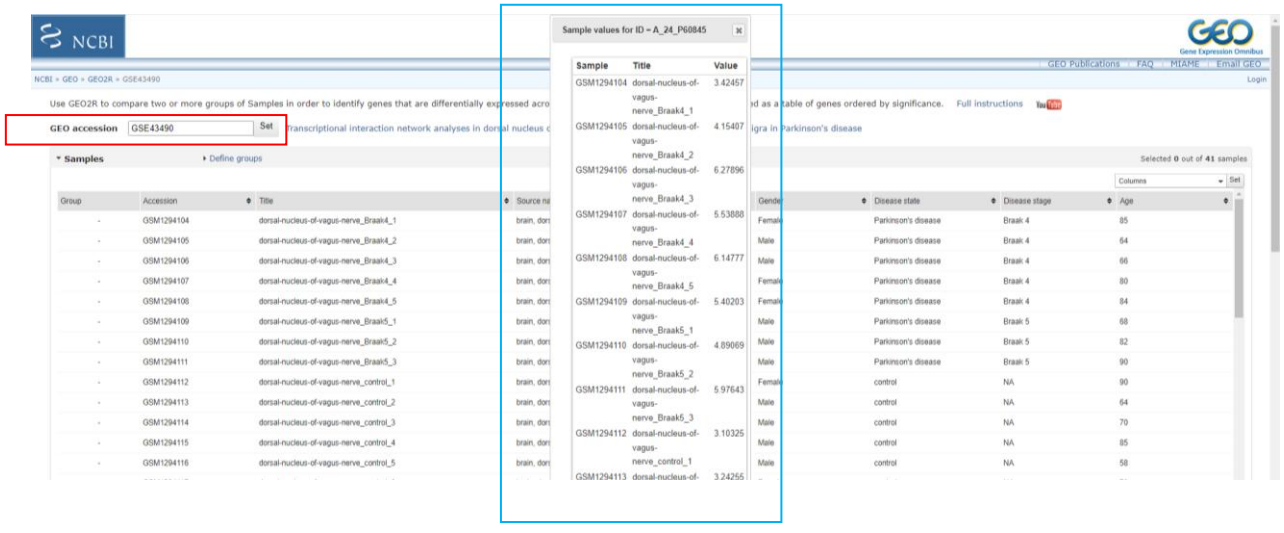
3) Then, Click on "Profile Graph"



4) In the box "Enter ID", enter the unique probe ID for a marker of interest and click "Set". It will load a plot as shown below. Next to the plot, click "Sample values"



5) A pop-up table (highlighted by blue box below) will be displayed



6) Copy the table and transfer as text into a data processing software.

NOTE: A quicker way to navigate all datasets in the same window is the following: Scroll to the top of the page and enter dataset accession (e.g. GSE20146, as shown in the red box above), followed by Set. This action will load the new dataset. Then, enter the unique probe ID for the gene(s) of interest and repeat the process.

Fig. S2

A)

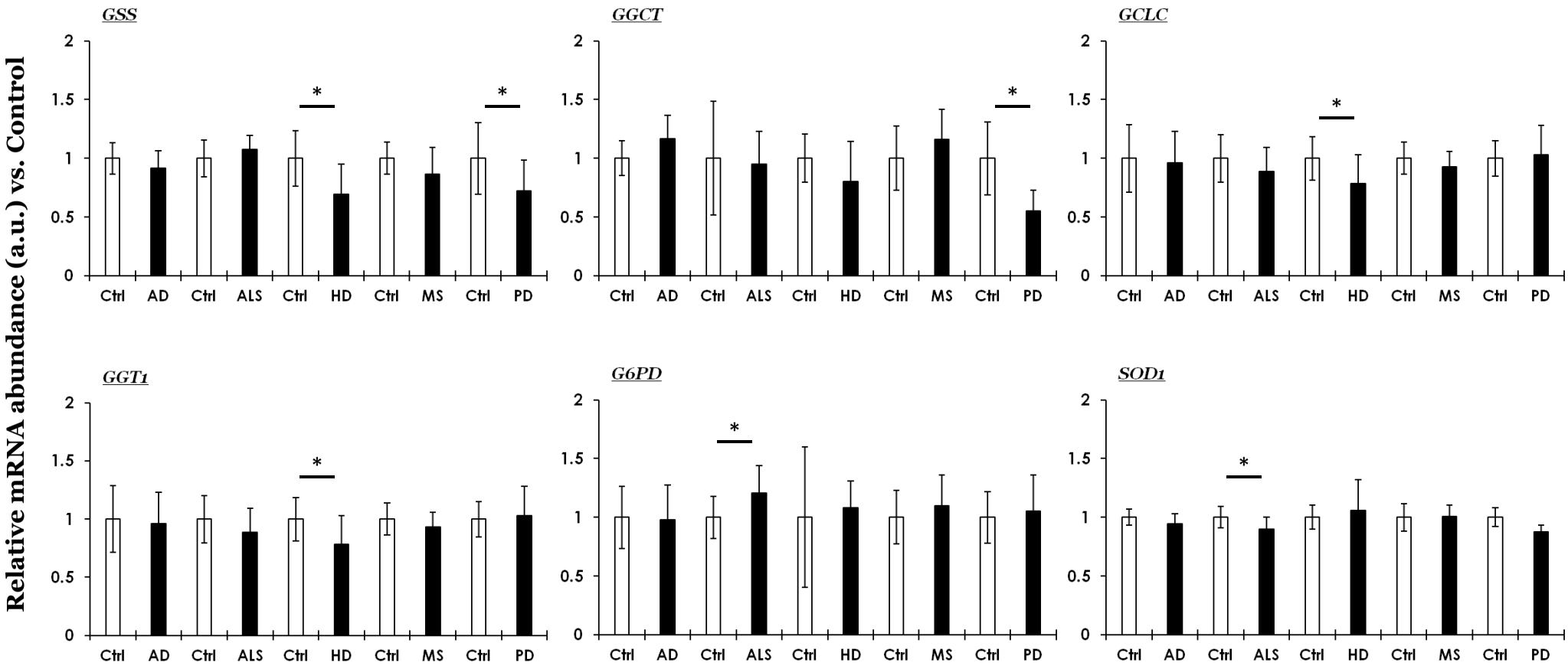
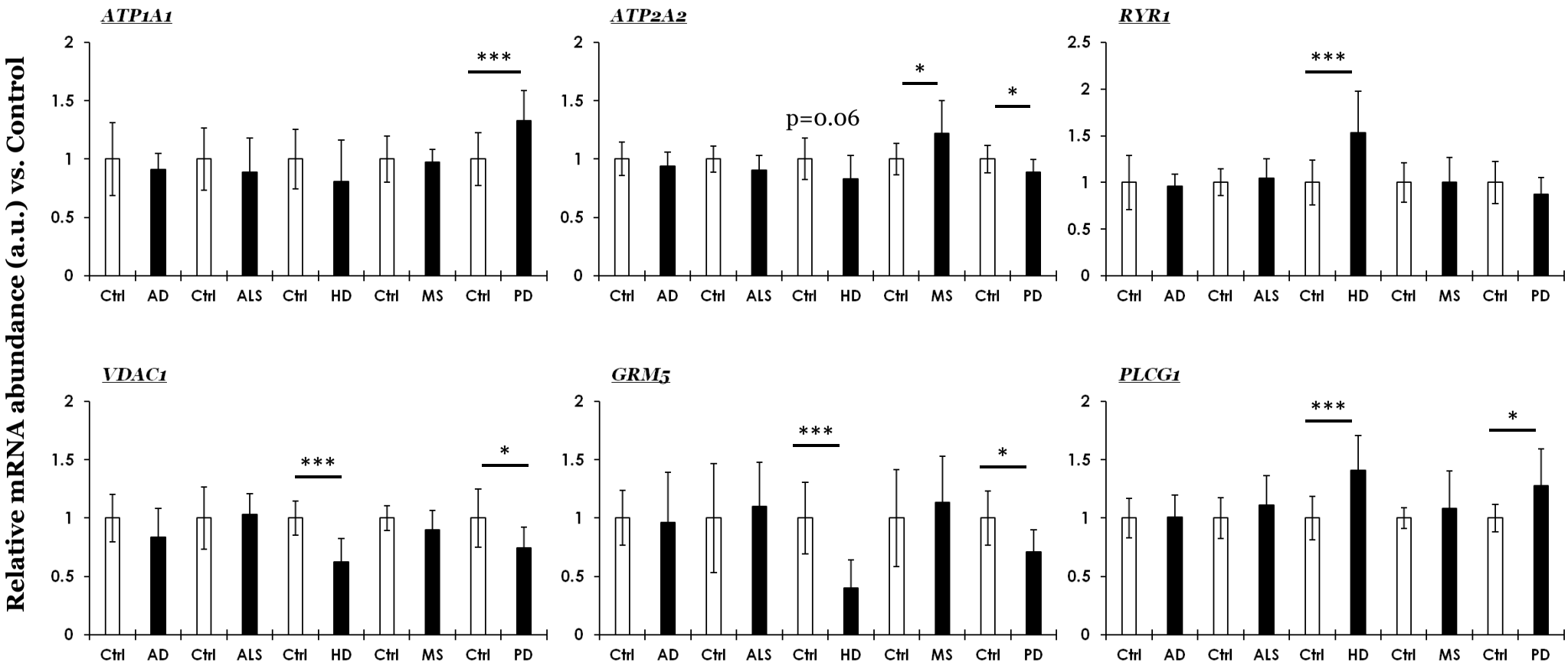

Relative mRNA abundance (a.u.) vs. Control
GSS
GGCT
GCLC
GGT1
G6PD
SOD1
0
0.5
1
1.5
2
*
Ctrl
AD
Ctrl
ALS
Ctrl
HD
Ctrl
MS
Ctrl
PD

Fig. S3

A)


Relative mRNA abundance (a.u.) vs. Control
ATP1A1
ATP2A2
RYR1
VDAC1
GRM5
PLCG1
p=0.06
Ctrl
AD
ALS
HD
MS
PD

A)

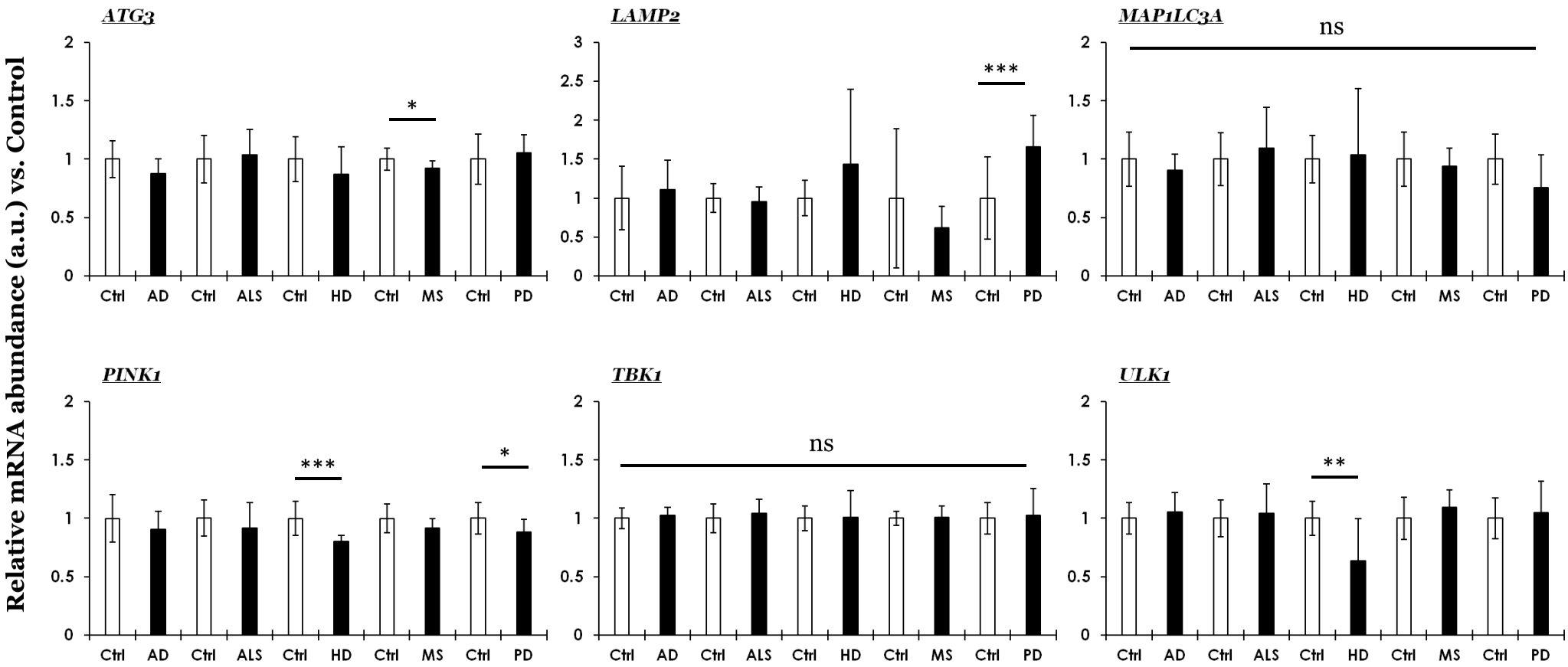

Relative mRNA abundance (a.u.) vs. Control
ATG3
LAMP2
MAP1LC3A
PINK1
TBK1
ULK1
ns
*
***
**
Ctrl
AD
ALS
HD
MS
PD

Table S1. Study details				
GEO accession	**GSE7621**	**GSE43490**	**GSE20146**	**GSE26927**
Samples	SN: Ctrl (n=9), PD (n=16)	SN: Ctrl (n=6), PD (n=8) DMX: Ctrl (n=5), PD (n=8) LC: Ctrl (n=7), PD (n=8)	GPi : Ctrl (n=10), PD (n=10)	SN : Ctrl (n=7), PD (n=12) Ent. Ctx: Ctrl (n=6), AD (n=12) Cerv. SC: Ctrl (n=7), ALS (n=9) Caudate: Ctrl (n=10), HD (n=10) Front. gyri: Ctrl (n=10), MS (n=10) Temp. lobe: Ctrl (n=10), SZ (n=10)
Platform	GPL570 Affymetrix Human Genome U133	GPL6480 Agilent-014850 Whole Human Genome	GPL570 Affymetrix Human Genome U133 Plus	GPL6255 Illumina humanRef-8 v2.0
Reference	*Lesnick, T.G. et al.,*	*Corradini, B.R. et al.,*	*Zheng, B. et al.,*	*Durrenberger, P.F. et al.,*

Abbreviations: **GSE7621**- Ctrl (control), PD (Parkinson Disease), SN (*substantia nigra*). **GSE43490-** Ctrl (control), PD (Parkinson Disease), SN (*substantia nigra*), DMX (*dorsal motor nucleus CN. X*), LC (*locus coeruleus*). **GSE20146-** Ctrl (control), PD (Parkinson Disease), GPi (*globus pallidus, interna*). **GSE26927-** Ctrl (control), PD (Parkinson Disease), AD (Alzheimer Disease), HD (Huntington Disease), ALS (Amyotrophic Lateral Sclerosis), MS (Multiple Sclerosis), SZ (Schizophrenia), SN (*substantia nigra*), Ent. Ctx (*entorhinal cortex*), Cerv. SC (*cervical spinal cord*), Front. Gyri (grey matter lesions in *frontal gyri*), Temp. lobe (*temporal lobe*, left area BA22).

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3. Zheng, B. et al., Sci Transl Med 2010 Oct 6;2(52):52ra73. PMID: 20926834.

4. Durrenberger, P.F. et al., . J Neural Transm (Vienna) 2015 Jul;122(7):1055-68. PMID: 25119539

5. NCBI Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/)

Table S2. Microarray datasets in the GEO repository with expression profile in brain				
DISEASE	**DATASETS**	**SAMPLES**	**PLATFORM**	**REFERENCE**
PD	GSE7621	SN: Ctrl (n=9), PD (n=16)	GPL570 Affymetrix Human Genome U133	Lesnick, T.G. et al., (1)
	GSE49036	SN: Ctrl: (n=8), PD (n=20)	GPL570 Affymetrix Human Genome U133	Dijkstra, A. A. et al., (2)
	GSE8397	SN: Ctrl: (n=15), PD (n=32)	GPL96 Affymetrix Human Genome U133A	Moran, L. B. et al., (3)
	GSE20168	A9: Ctrl (n=15), PD (n=15)	GPL96 Affymetrix Human Genome U133A	Zhang, Y. et al., (4)
	GSE20291	PT: Ctrl (n=15), PD (n=15)	GPL96 Affymetrix Human Genome U133A	Zhang, Y. et al., (4)
	GSE20292	SN: Ctrl (n=15), PD (n=15)	GPL96 Affymetrix Human Genome U133A	Zhang, Y. et al., (4)
	GSE77667	PT: Ctrl (n=12), PD (n=12)	GPL21437 NanoString nCounter human miRNA	Nair, V. et al., (5)
	GSE26927	SN: Ctrl (n=7), PD (n=12)	GPL6255 Illumina humanRef-8	Durrenberger, P. F. et al., (6)
	GSE20146	GPi: Ctrl (n=10), PD (n=10)	GPL570 Affymetrix Human Genome U133	Zheng, B. et al., (7)
	GSE20163	SN: Ctrl (n=9), PD (n=8)	GPL96 Affymetrix Human Genome U133A	Zheng B. et al., (7)
	GSE54282	SN: Ctrl (n=3), PD (n=3)	GPL17047 Affymetrix Human Gene 1.0 ST Array	Riley, B. E. et al., (8)
		St: Ctrl (n=6), PD (n=6)		
		Cx: Ctrl (n=5), PD (n=5)		
	GSE20333	SN: Ctrl (n=6), PD (n=6)	GPL201Affymetrix Human HG-Focus Target Array	No ref
	GSE26927	SN: Ctrl (n=8), HD (n=12)	GPL6255 Illumina humanRef-8	Durrenberger, P. F. et al., (6)
AD/MCI	GSE26927	EC: Ctrl (n=7), AD (n=11)	GPL6255 Illumina humanRef-8	Durrenberger, P. F. et al., (6)
	GSE6777	TC: Ctrl (n=31), AD (n=32)	GPL4757 Ion Channel Splice Array	Heinzen, E. L. et al., (9)
	GSE29378	HC, FC: Ctrl (n=16), AD (n=17)	GPL6947 Illumina HumanHT-12 V3.0 expression beadchip	Miller, J. A. et al., (10)
	GSE37264	STG: Ctrl (n=8), AD (n=8)	GPL5188 Affymetrix Human Exon 1.0 ST Array	Lai, M. K. P. et al., (11)
	GSE80970	STG: Ctrl (n=60), AD (n=82)	GPL13534 Illumina HumanMethylation450 BeadChip	Smith, R. G. et al., (12)
		PFC: Ctrl (n=60), AD (n=84)		
	GSE39420	PC: Ctrl (n=7), AD (n=14)	GPL11532 Affymetrix Human Gene 1.1 ST Array	Antonell, A. et al., (13)
	GSE16759	PL: Ctrl (n=4), AD (n=4)	GPL570 Affymetrix Human Genome U133 Plus 2.0 Array	Nunez-Iglesias, J. et al., (14)
				Blalock, E. M. et al., (15)

	GSE28146 GSE76105 GSE33000 GSE12685	CA1: Ctrl (n=8), AD (n=22) STG: Ctrl (n=34), AD (n=34) DLPFC: Ctrl (n=157), AD (n=310) PFC: Ctrl (n=2), AD (n=2)	GPL570 Affymetrix Human Genome U133 GPL13534 Illumina HumanMethylation450 BeadChip GPL4372 Rosetta/Merck Human 44k 1.1 microarray GPL96 Affymetrix Human Genome U133A Array	Watson, C. T. et al., (16) Narayanan, M. et al., (17) Williams, C. et al., (18)
HD	GSE26927 GSE33000	CN: Ctrl (n=10), HD (n=9) DLPFC: Ctrl (n=157), AD (n=157)	GPL6255 Illumina humanRef-8 GPL4372 Rosetta/Merck Human 44k 1.1 microarray	Durrenberger, P. F. et al., (6) Narayanan, M. et al., (17)
ALS	GSE40438 GSE26927	MB: Ctrl (n=4) SC: Ctrl (n=10), ALS (n=10)	GPL570 Affymetrix Human Genome U133 Plus 2.0 Array GPL6255 Illumina humanRef-8	Brockington, A. et al., (19) Durrenberger, P. F. et al., (6)
MS	GSE26927 GSE5839 GSE52139 GSE37670 GSE32645	SFG: Ctrl (n=10), MS (n=10) BT: Ctrl (n=3), MS (n=7) SC: Ctrl (n=?), MS (n=6) CSF: Ctrl (n=26), MS (n=33) Cx: Ctrl (n=17), MS (n=21)	GPL6255 Illumina humanRef-8 GPL96 Affymetrix Human Genome U133A Array GPL570 Affymetrix Human Genome U133 Plus 2.0 Array GPL15506 SUWHR Lipids 104 v2.0 GPL4133Agilent-014850 Whole Human Genome Microarray 4x44K G4112F	Durrenberger, P. F. et al., (6) No ref Lieury, A. et al., (20) Ho, P. P. et al., (21) Fischer, M. T. et al., (22)
Abbreviations: Ctrl (control), PD (Parkinson Disease), SN (*substantia nigra;* DMX (*dorsal motor nucleus CN. X*), LC (*locus coeruleus*).AD (Alzheimer Disease), HD (Huntington Disease), ALS (Amyotrophic Lateral Sclerosis), MS (Multiple Sclerosis), HC (Hippocamus), EC (entorhinal cortex), SFG (superior frontal gyrus), PCG (postcentral gyrus), MTG (medial temporal gyrus), PC (posterior cingulate), PVC (primary visual cortex), MTG (middle temporal gyrus), PT (putamen), A9 (Area 9), MB (midbrain), CN (caudate nucleus), GPi (Globus Pallidus interna), St (striatum), Cx (cortex), TC (temporal cortex), FC (frontal cortex), STG (superior temporal gyrus), PFC (prefrontal cortex), PC (posterior cingulate), PL (parietal lobe), SC (spinal cord). CA1 (CA1 hippocampal gray matter), STG (superior temporal gyrus), DLPFC (dorsolateral prefrontal cortex), PFC (prefrontal cortex), BT (brain tissue), CSF (cerebrospinal fluid)			

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TABLE S3. Summary of the reports on the detection of selected markers in human CSF					
Marker	**Uniprot ID**	**AD**	**PD**	**ALS**	**MS**
GSS	P48637	Increased Higginbotham et al., (2020) (1)			Equal Kroksveen et al., (2017) (2)
GGCT	O75223	Increased Higginbotham et al., (2020) (1)			Equal Kroksveen et al., (2017) (2)
GCLC	P48506	Decreased Higginbotham et al., (2020) (1)			
GGT1	P19440	Decreased Higginbotham et al., (2020) (1)			Equal Kroksveen et al., (2017) (2)
SOD1	P00441	Increased Higginbotham et al., (2020) (1) Decreased Barucker et al (2015) (3)		Equal Bereman et al., (2018) (4)	Equal Kroksveen et al., (2017) (2) Decreased Liu et al., (2022) (5) Decreased Timirci-Kahraman et al., (2019) (6) Decreased Stoop et al.,

					(2017) (7) Equal Jia et al., (2012) (8) Equal Hinsinger et al., (2015) (9) Equal Kroksveen et al., (2012) (10) Equal Stoop et al., (2013) (11) Equal Kroksveen et al., (2013) Increased Stoop et al., (2017) (7)
ATP1A1	P05023	Decreased Higginbotham et al., (2020) (1)		Equal Hayashi et al., (2020) (12)	Equal Kroksveen et al., (2017) (2) Equal

					Stoop et al., (2017) (7)
ATP2A2	P16615	Decreased Higginbotham et al., (2020) (1)			Equal Opsahl et al., (2016) (13)
RYR1	P21817				Equal Kroksveen et al., (2015) (3) Equal Kroksveen et al., (2017) (2)
VDAC1	P21796	Decreased Higginbotham et al., (2020) (1)			
GRM5	P41594				Decreased Kroksveen et al., (2017) (2)
LAMP2	P13473	Equal Higginbotham et al., (2020) (1)	Equal Rotunno et al., (2020) (14)		Increased Kroksveen et al., (2017) (2) Equal Kroksveen et al., (2015) (3) Equal Opsahl et al.,

					(2016) (13) Equal Stoop et al., (2013) (11) Equal Kroksveen et al., (2013)

NOTE: The empty boxes indicate that a study was not found on the portal for a particular marker in the disease

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