Supplemental Table 1: KEGG pathways containing mitochondrial proteins differentially regulated *in vivo* following APAP treatment compared to control.

KEGG pathway	%[a]	p value[b]	Upregulated proteins
Parkinson's disease	21	2.95E-08	NDUFA4, UQCRC2, ATP5D, UQCRC1, SLC25A5, ATP5B, SDHA, UQCRH, LOC674583, COX6B1, COX6A1, ATP5O, ATP5A1, ATP5H, LOC100047429, ATP5J
Huntington's disease	22	1.27E-07	NDUFA4, UQCRC2, ATP5D, UQCRC1, SLC25A5, ATP5B, SOD2, SDHA, UQCRH, LOC674583, COX6B1, COX6A1, ATP5O, ATP5A1, ATP5H, LOC100047429, ATP5J
Oxidative phosphorylation	19	3.78E-07	NDUFA4, UQCRC2, ATP5D, UQCRC1, ATP5B, SDHA, UQCRH, LOC674583, COX6B1, COX6A1, ATP5O, ATP5A1, ATP5H, LOC100047429, ATP5J
Valine, leucine and isoleucine degradation	13	2.65E-06	ACAA2, ACADM, HMGCS2, IVD, DLD, ALDH2, ABAT, HADH, PCCA
Alzheimer's disease	19	1.83E-05	NDUFA4, UQCRC2, ATP5D, UQCRC1, ATP5B, SDHA, UQCRH, LOC674583, COX6B1, COX6A1, ATP5O, ATP5A1, ATP5H, LOC100047429, ATP5J
Fatty acid metabolism	9	3.11E-02	ACAA2, ACOX1, ACADM, ALDH2, ACADL, HADH

[a] Indicates the percentage of genes identified experimentally from the total number of genes related to that KEGG term (only KEGG pathways with % > 1 were considered).
[b] p value < 0.05; includes FDR correction.

Supplemental Table 2: ETC proteins identified by DAVID to be differentially regulated *in vivo* following APAP treatment compared to control.

Complex	Protein	Description	APAP/CON Ratio[a]
I	Ndufa4	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 4	1.79
II	Sdha	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial	2.21
III	Uqcrc1	Cytochrome b-c1 complex subunit 1, mitochondrial	5.00
III	Uqcrc2	Cytochrome b-c1 complex subunit 2, mitochondrial	2.75
III	Uqcrh	Cytochrome b-c1 complex subunit 6, mitochondrial	N.D.[b]
IV	Cox6a1	Cytochrome c oxidase polypeptide VIa	1.87
IV	Cox6b1	Cytochrome c oxidase subunit VIb isoform 1	4.32
V	Atp5a1	ATP synthase subunit alpha, mitochondrial	1.36
V	Atp5b	ATP synthase subunit beta, mitochondrial	1.40
V	Atp5d	ATP synthase subunit delta, mitochondrial	1.93
V	Atp5h	ATP synthase subunit d, mitochondrial	N.D.[b]
V	Atp5j	ATP synthase-coupling factor 6, mitochondrial (LOC674583)	N.D.[b]
V	Atp5o	ATP synthase subunit O, mitochondrial (LOC100047429)	6.00
mPTP	Slc25a5	ADP/ATP translocase 2	1.64
ROS defense	Sod2	Superoxide dismutase [Mn], mitochondrial	2.15

[a] Ratio of APAP-induced spectral counts over control spectral counts as described in reference 56; ratios greater than 1 represent upregulation, whereas ratios less than 1 represent downregulation

[b] Spectral count ratio could not be determined because no spectra were identified in control treatment.

Supplemental Table 3: KEGG pathways containing mitochondrial proteins differentially regulated *in vitro* following APAP treatment compared to control.

KEGG pathway	%[a]	p value[b]	Proteins
Parkinson's disease	14	5.86E-06	UQCRC2, ATP5E, SLC25A4, NDUFA8, SLC25A5, NDUFA9, NDUFA6, COX8A, VDAC1, NDUFV3, UBC, ATP5O, UBB, RPS27A, LOC100047429
Huntington's disease	13	1.58E-03	NDUFV3, UQCRC2, ATP5E, NDUFA8, SLC25A4, NDUFA9, SLC25A5, NDUFA6, COX8A, ATP5O, LOC100047429, VDAC1
Oxidative phosphorylation	11	8.36E-03	NDUFV3, UQCRC2, ATP5E, NDUFA8, NDUFA9, NDUFA6, COX8A, ATP5O, COX17, LOC100047429

[a] Indicates the percentage of genes identified experimentally from the total number of genes related to that KEGG term (only KEGG pathways with % > 1 were considered).
[b] p value < 0.05; includes FDR correction.

Supplemental Table 4: ETC proteins identified by DAVID to be differentially regulated *in vitro* following APAP treatment compared to control.

Complex	Protein	Description	APAP/CON Ratio[a]
I	Ndufa6	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 6	N.D.[b]
I	Ndufa8	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 8	1.07
I	Ndufa9	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 9, mitochondrial	5.00
I	Ndufv3	NADH dehydrogenase [ubiquinone] flavoprotein 3, mitochondrial	N.D.[b]
III	Uqcrc2	Cytochrome b-c1 complex subunit 2, mitochondrial	1.61
IV	Cox8a	Cytochrome c oxidase polypeptide 8A, mitochondrial	1.09
V	Atp5o	ATP synthase subunit O, mitochondrial (LOC100047429)	1.17
mPTP	Slc25a4	ADP/ATP translocase 1	1.51
mPTP	Slc25a5	ADP/ATP translocase 2	1.33
mPTP	Vdac1	Isoform Pl-VDAC1 of Voltage-dependent anion-selective channel protein 1	1.65

[a] Ratio of APAP-induced spectral counts over control spectral counts as described in reference 56; ratios greater than 1 represent upregulation, whereas ratios less than 1 represent downregulation

[b] Spectral count ratio could not be determined because no spectra were identified in control treatment.

Supplemental Table 5: Peptide detection and sequence coverage for P450 isoforms and Mgst1 identified experimentally as differentially regulated in the drug metabolism KEGG pathway following 6 h APAP treatment compared to control *in vivo.*

Murine protein	Sequence coverage	Unique peptides	Unique peptide sequences
Cyp1a2	22.4	7	FKTFNDNFVLFLQK IGSTPVVVLSGLNTIK IHEELDTVVGR KIHEELDTVVGR KSEEMLNIVNNSKDFVENVTSGNAVDFFPVLR LSDRPQLPYLEAFILEIYR SFSIASDPTSASSCYLEEHVSK
Cyp2a5	2.8	1	IQEEAGFLIDSFRK
Cyp2c54	9.8	5	GTTVITSLSSVLR KPTVVLHGYEAVK SIEDRVQEEAR VQEEIEHVIGK YAILLLLK
Cyp2e1	32.3	11	DIDLSPVTIGFGSIPR DVTDCLLIEMEKEK EAHFLVEELKK FGPVFTLHLGQR FSLSILR GQPFDPTFLIGCAPCNVIADILFNKR GTVVIPTLDSLLFDNYEFPDPETFKPEHFLNENGK SLDINCPR SLVDPKDIDLSPVTIGFGSIPR TKGQPFDPTFLIGCAPCNVIADILFNK YGLLILMKYPEIEEKLHEEIDR
Cyp3a11	33.1	9	AISISKDDEWKR GSIDPYVYLPFGNGPR GSTVMIPSYALHHDPQHWSEPEEFQPER LKEMFPVIEQYGDILVK LQDEIDEALPNKAPPTYDTVMEMEYLDMVLNETLR QGILQPEKPIVLK QGIPGPKPLPFLGTVLNYYK QGLLQPEKPIVLK TWGLFDGQTPLLAVTDPETIKNVLVK
Cyp2d9	18.1	7	DIEVQDFLIPK FGDIVPVNLPR FHPEHFLDAQGHFVKPEAFMPFSAGR ITSHDIEVQDFLIPK NLTDAFLAEIEK SFIAILDNLLTENR STCNVIASLIFAR
Mgst1	54.9	7	ITNKVFANPEDCAGFGK ITNKVFANPEDCAGFGKGENAK MMFMSSATAFQR QLMDNEVLMAFTSYATIILTK VFANPEDCAGFGK VFANPEDCAGFGKGENAK VFANPEDCAGFGKGENAKK