Supporting Information for:

Probing the metabolic aberrations underlying mutant huntingtin toxicity in yeast and assessing their degree of preservation in humans and mice.

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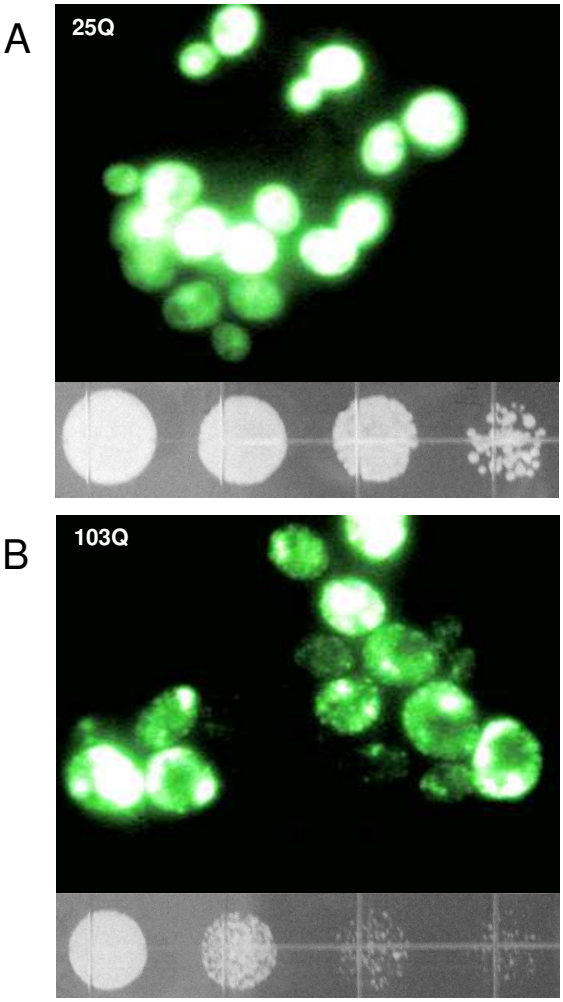
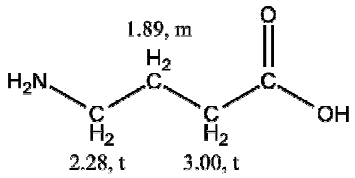
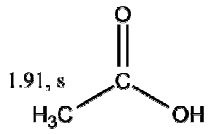
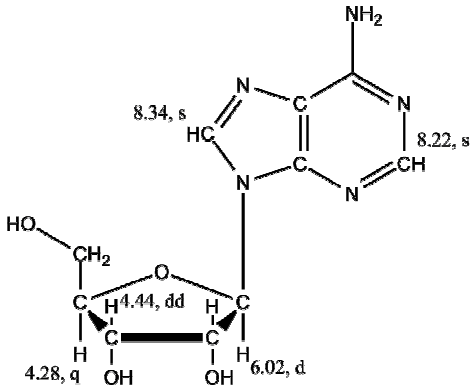
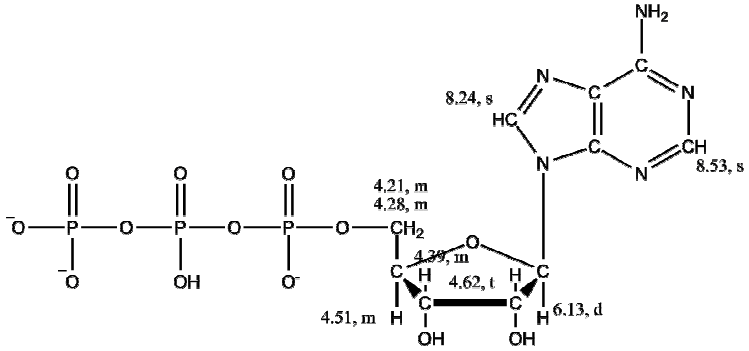
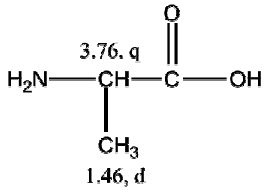
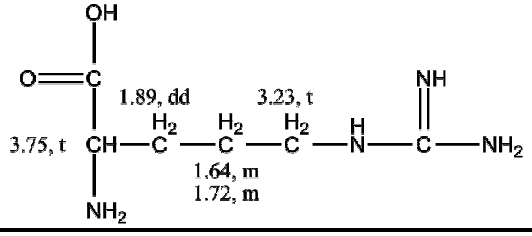
INDEX FOR SUPPORTING INFORMATION

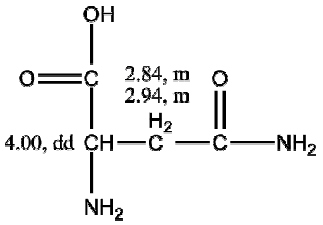
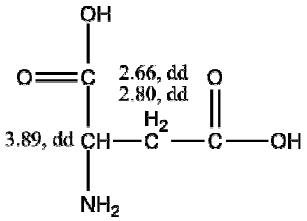
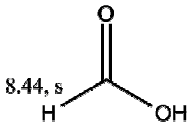
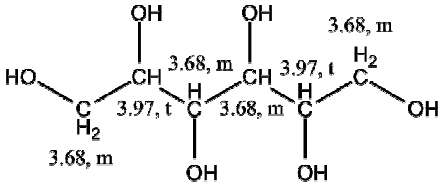
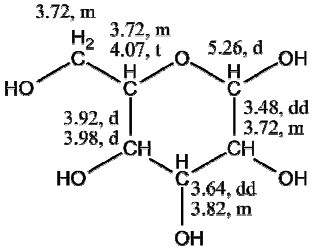
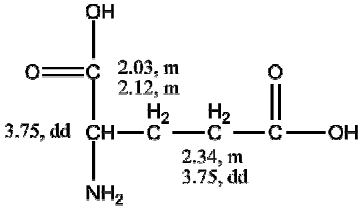
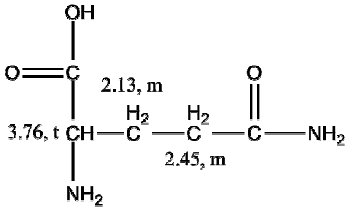
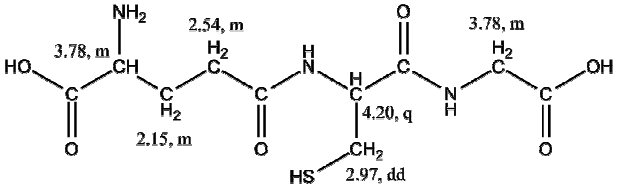


Supporting Information Figure 1 False-color fluorescent microscopy images of yeast cells expressing human *Htt* fragments. A) Yeast expressing *Htt* fragment with 25 glutamine repeats. B) Yeast expressing m*Htt* fragment with 103 glutamine repeats. Spot cultures (A, lower panel; B, lower panel) show a significant decrease in cell viability due to mutant huntingtin toxicity.

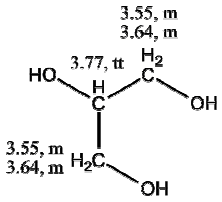
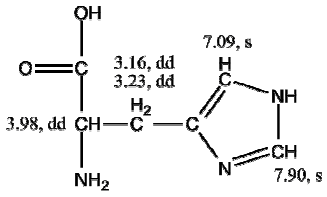
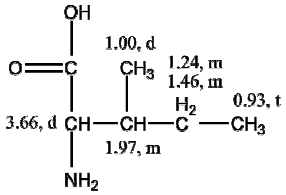
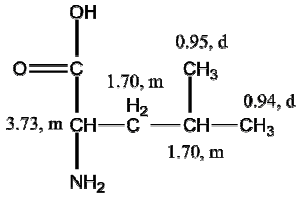
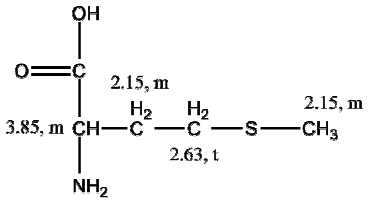
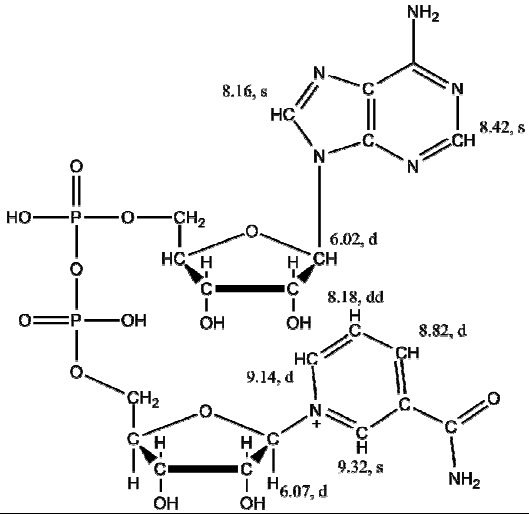
Supporting Information, Table 1 Structures of Metabolites with ^{1}H NMR Chemical Shifts and Multiplicities

Metabolite	Structure with ^{1}H NMR Chemical Shifts and Multiplicities
4-aminobutyrate	
acetate	
adenosine	
adenosine triphosphate	
alanine	
arginine	

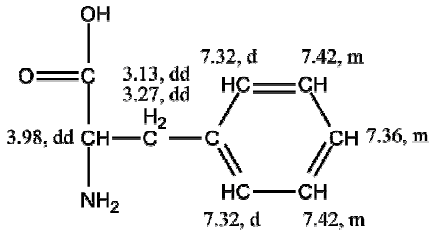
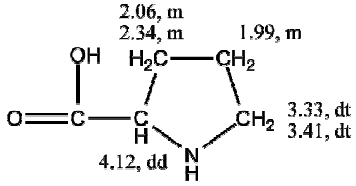
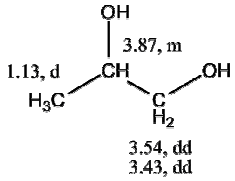
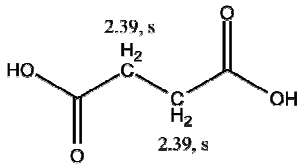
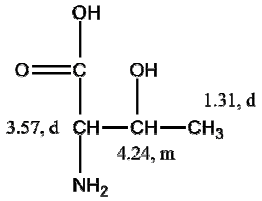
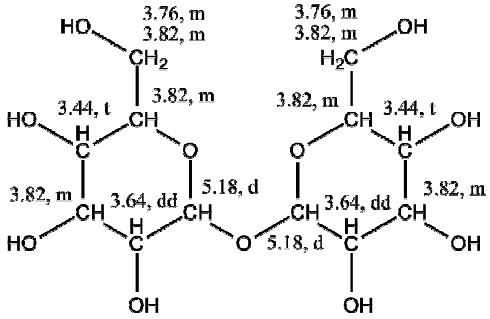
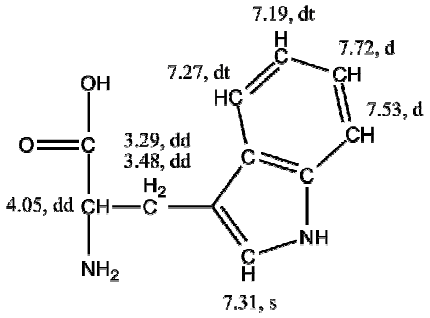
Supporting Information, Table 1 Structures of Metabolites with ^{1}H NMR Chemical Shifts and Multiplicities (continued from page 3)

Metabolite	Structure with ^{1}H NMR Chemical Shifts and Multiplicities
asparagine	
aspartate	
formate	
galactitol	
galactose	
glutamate	
glutamine	
glutathione	

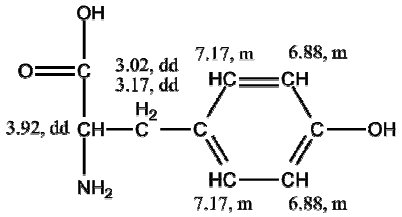
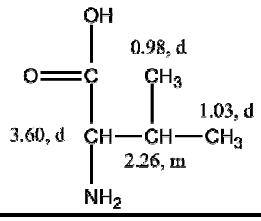
Supporting Information, Table 1 Structures of Metabolites with ^{1}H NMR Chemical Shifts and Multiplicities (continued from page 4)

Metabolite	Structure with ^{1}H NMR Chemical Shifts and Multiplicities
glycerol	
histidine	
isoleucine	
leucine	
methionine	
Nicotinamide adenine dinucleotide (oxidized)	

Supporting Information, Table 1 Structures of Metabolites with ^{1}H NMR Chemical Shifts and Multiplicities (continued from page 5)

Metabolite	Structure with ^{1}H NMR Chemical Shifts and Multiplicities
phenylalanine	
proline	
propylene glycol	
succinate	
threonine	
trehalose	
tryptophan	

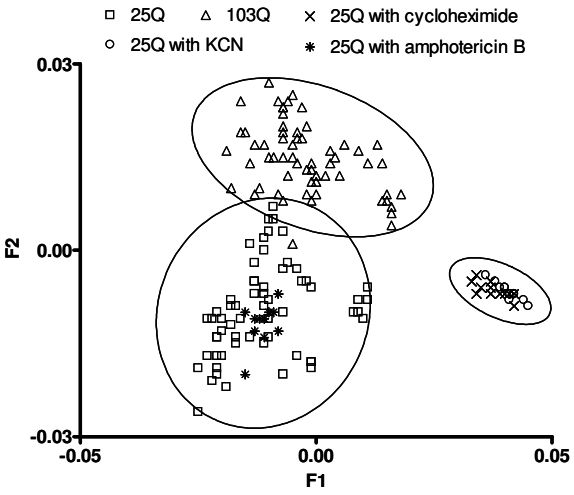
Supporting Information, Table 1 Structures of Metabolites with ^{1}H NMR Chemical Shifts and Multiplicities (continued from page 6)

Metabolite	**Structure with ^{1}H NMR Chemical Shifts and Multiplicities**
tyrosine	
valine	

Supporting Information, Methods

Metabolomic analysis of potassium cyanide, amphotericin B, and cycloheximide treated 103Q and 25Q yeast

Stage I and stage II were prepared as described in the experimental procedures, with the exception that stage II cultures were treated with either potassium cyanide[1], amphotericin B[2], or cycloheximide[3] at concentrations of 46 µM, 38 nM, and 98 nM, respectively. Concentrations of toxins were chosen that inhibited 25Q yeast growth to 30% of the growth of untreated controls. Data was collected and analyzed as described above.



Supporting Information, Figure 2 Comparison of metabolic changes in response to various toxins. Potassium cyanide (KCN) and cycloheximide treatment cause distinct metabolic changes in 25Q yeast that are different from the changes caused by *mHtt* toxicity.

Supporting Information, Table 2 Metabolic Profiling Data for Selected Key Metabolites Identified in Studies of Huntington's Disease Model Systems and Humans

	This study	Nicoli et al. (1993)[4]	Taylor-Robinson et al. (1996)[5]	Reynolds et al. (2005)[6]	Underwood et al. (2006)[7]	Jenkins et al. (2000)[8]	Jenkins et al. (2005)[9]	Tsang et al. (2006)[10]	Tkac et al. (2007)[11]
Organism	yeast	human [a, b]	human [c, d]	human [d]	human [b], mouse [b]	mouse [c, d, e]	mouse [c, d]	mouse [b, c, e, f]	mouse [c, d]
Data collection technique	^{1}H NMR	^{1}H NMR, HPLC	^{1}H MRS	^{1}H MRS	GC-TOF-MS	^{1}H-NMR	^{1}H MRS	^{1}H NMR, HR-MAS ^{1}H NMR	*in vivo* ^{1}H NMR
2-amino-*n*-butyrate	ND	ND	ND	ND	significant [g, h]	ND	ND	ND	ND
2-oxoglutarate	ND	ND	ND	ND	ND	ND	ND	increase	ND
4-aminobutyrate	ns	ns	ND	ND	ND	ns	ND	decrease	ns
acetate	decrease	ns	ND	ND	ND	ND	ND	decrease	ND
adenosine	ns	ND	ND	ND	ND	ND	ND	ND	ND
alanine	decrease	ns	ND	ND	significant [g, h]	ns	ND	decrease	ND
arginine	ns	ND	ND	ND	ND	ND	ND	ND	ND
ascorbate	ND	ND	ND	ND	ND	ND	ND	ND	increase
asparagine	ns	ND	ND	ND	ND	ND	ND	ND	ND
aspartate	ns	ns	ND	ND	ND	ns	ND	decrease	ND
ATP	ns	ND	ND	ND	ND	ND	ND	ND	ND
choline	ND	ND	ns	ND	ND	increase	increase	decrease	ND
citrate	ND	ns	ND	ND	ND	ND	ND	ND	ND
creatine	ND	ns	ns	decrease	ND	ns	ns	increase	increase
dimethylglycine	ND	ND	ND	ND	ND	ND	ND	decrease	ND
ethylene glycol	ND	ND	ND	ND	significant [g, h]	ND	ND	ND	ND
formate	ns	ND	ND	ND	ND	ND	ND	ND	ND
galactitol	ns	ND	ND	ND	ND	ND	ND	ND	ND
galactose	increase	ND	ND	ND	ND	ND	ND	ND	ND
glucose	ND	ND	ND	ND	significant [g, i]	increase	ND	ND	ns
glutamate	ns	ns	increase	increase	ND	decrease	ns	decrease	increase
glutamine	increase	ns	increase	increase	ND	increase	ns	increase	increase
glutathione	ns	ND	ND	ND	ND	ND	ND	ND	increase
glycerol	increase	ND	ND	ND	significant [g]	ND	ND	ND	ND
glycerophosphocholine	ND	ND	ND	ND	ND	ND	ND	increase	increase
glycine	ND	increase	ND	ND	ND	ns	ND	ns	ND
histidine	decrease	ND	ND	ND	ND	ND	ND	ND	ND
isoleucine	ns	ns	ND	ND	ND	ND	ND	ND	ND
lactate	ND	ns	ns	increase	significant [g]	decrease	ND	increase	ns
leucine	ns	ns	ND	ND	ND	ND	ND	ND	ND
lysine	ND	ns	ND	ND	ND	ND	ND	ND	ND
malonate	ND	ND	ND	ND	significant [g]	ND	ND	ND	ND
methionine	ns	ND	ND	ND	ND	ND	ND	ND	ND

Supporting Information, Table 2 Metabolic Profiling Data for Selected Key Metabolites Identified in Studies of Huntington's Disease Model Systems and Humans (continued from page 9)

	This study	Nicoli et al. (1993)[4]	Taylor-Robinson et al. (1996)[5]	Reynolds et al. (2005)[6]	Underwood et al. (2006)[7]	Jenkins et al. (2000)[8]	Jenkins et al. (2005)[9]	Tsang et al. (2006)[10]	Tkac et al. (2007)[11]
Organism	yeast	human [a, b]	human [c, d]	human [d]	human [b], mouse [b]	mouse [c, d, e]	mouse [c, d]	mouse [b, c, e, f]	mouse [c, d]
Data collection technique	^{1}H NMR	^{1}H NMR, HPLC	^{1}H MRS	^{1}H MRS	GC-TOF-MS	^{1}H-NMR	^{1}H MRS	^{1}H NMR, HR-MAS ^{1}H NMR	*in vivo* ^{1}H NMR
myo-inositol	ND	ND	ND	ns	ND	ns	ND	increase	increase
N-acetylaspartate	ND	ND	ns	decrease	ND	decrease	decrease	decrease	decrease
N-acetylaspartate glutamate	ND	ND	ND	ND	ND	ND	ND	increase/ decrease	ns
NAD^+	ns	ND	ND	ND	ND	ND	ND	ND	ND
phenylalanine	ns	ND	ND	ND	ND	ND	ND	ND	ND
phosphocholine	ND	ND	ND	ND	ND	ND	ND	decrease	ns
phosphocreatine	ND	ND	ND	ND	ND	ND	ND	ND	increase
phosphorylethanolamine	ND	ND	ND	ND	ND	ND	ND	ND	decrease
proline	decrease	ns	ND	ND	ND	ND	ND	ND	ND
propylene glycol	ns	ND	ND	ND	ND	ND	ND	ND	ND
pyroglutamate	ND	ND	ND	ND	significant [g, i]	ND	ND	ND	ND
pyruvate	ND	increase	ND	ND	ND	ND	ND	ND	ND
scyllo-inositol	ND	ND	ND	ND	ND	increase	ND	increase	ND
spermine	ND	ND	ND	ND	ND	ND	ND	decrease	ND
succinate	decrease	ND	ND	ND	ND	decrease	ND	decrease	ND
taurine	ND	ND	ND	ND	ND	increase	increase	increase	increase
threonine	increase	ND	ND	ND	ND	ND	ND	ND	ND
trehalose	decrease	ND	ND	ND	ND	ND	ND	ND	ND
trimethylamine	ND	ND	ND	ND	ND	ND	ND	decrease	ND
trimethylamine *N*-oxide	ND	ND	ND	ND	ND	ND	ND	increase	ND
tryptophan	ns	ND	ND	ND	ND	ND	ND	ND	ND
tyrosine	ns	ND	ND	ND	ND	ND	ND	ND	ND
urea	ND	ND	ND	ND	significant [g]	ND	ND	ND	ND
valine	increase	ND	ND	ND	significant [g]	ND	ND	ND	ND
α-hydroxybutyric acid	ND	ND	ND	ND	significant [g, h]	ND	ND	ND	ND
α-ketoisocaproate	ND	ND	ND	ND	ND	ND	ND	decrease	ND

Abbreviations: ND = Not detected or not reported, ns = not significant, MRS = magnetic resonance spectroscopy, HR-MAS = high-resolution magic angle spinning, HPLC = high performance liquid chromatography. [a] Cerebrospinal fluid. [b] Serum. [c] Results from multiple tissue types summarized in this table. [d] *In vivo* brain. [e] *In vitro* brain. [f] Urine. [g] Direction of change (increase/decrease) not reported. [h] Detected only in human serum.

Supporting Information, Table 3 Contingency Table of Metabolic Studies of Mutant Huntingtin Toxicity

Metabolite	Yeast	Human	Mouse	TOTALS
2-amino-n-butyrate	0	1	0	1
2-oxoglutarate	0	0	1	1
4-aminobutyrate	0	0	1	1
acetate	1	0	1	2
alanine	1	1	1	3
ascorbate	0	0	1	1
aspartate	0	0	1	1
choline	0	0	3	3
creatine	0	1	2	3
dimethylglycine	0	0	1	1
ethylene glycol	0	1	0	1
galactitol	1	0	0	1
glucose	0	0	2	2
glutamate	0	2	3	5
glutamine	1	2	3	6
glutathione	0	0	1	1
glycerol	1	1	1	3
glycerophosphocholine	0	0	2	2
glycine	0	1	0	1
histidine	1	0	0	1
lactate	0	2	3	5
malonate	0	1	1	2
myo-inositol	0	0	2	2
N-acetylaspartate	0	1	4	5
phosphocholine	0	0	1	1
phosphocreatine	0	0	1	1
phosphorylethanolamine	0	0	1	1
proline	1	0	0	1
pyroglutamate	0	0	1	1
pyruvate	0	1	0	1
scyllo-inositol	0	0	2	2
spermine	0	0	1	1
succinate	1	0	2	3
taurine	0	0	4	4
threonine	1	0	0	1
trehalose	1	0	0	1
trimethylamine	0	0	1	1
trimethylamine N-oxide	0	0	1	1
urea	0	1	1	2
valine	1	1	1	3
alpha-hydroxybutyric acid	0	1	0	1
alpha-ketoisocaproate	0	0	1	1
TOTALS	11	18	52	81

REFERENCES

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