Supplemental Table 1. Demographic information

	Huntington's Disease Carriers[A]				Healthy Controls			
	HD1[B]	**HD2**		**HD3**	**HC1**	**HC2**	**HC3**	**HC4**
	Premanifest	Premanifest	Symptomatic	Premanifest				
N	12	9	5	21	12	20	12	18
Age	46.8(11.0)[C]	38.5(12.3)	53.8(6.3)	40.3(6.8)	40.8(14.7)	47.7(13.5)	42.5(15.6)	39.8(15.1)
CAG repeat length	41.6(1.7)	41.4(1.4)	N/A	42.9(2.3)	-	-	-	-
Predicted YTO	10.3(8.6)	13.8(5.9)	N/A	11.7(6.5)	-	-	-	-
Imaging	FDG PET RAC PET MRI	FDG PET	FDG PET	FDG PET MRI	FDG PET	FDG PET	RAC PET	MRI

[A]See text for definitions of the Huntington's disease (HD1-HD3) and healthy control (HC1-HC4) groups.

[B]Baseline data.

[C]Values are presented as mean (SD).

HD=Huntington's Disease Carrier Groups, HC=Healthy Control Groups, YTO=Years-to-onset.

Supplemental Table 2. UHDRS motor ratings and measurements of caudate/putamen D_2 binding and tissue volume

	HD1 (longitudinal cohort)				HD2	HC
UHDRS (motor)	**Baseline (n=12)**	**1.5 years (n=12)**	**4 years (n=10)**	**7 years (n=9)**	**(symptomatic) (n=5)**	
Phenoconverters	23.8 (9.8)[A]	22.7 (11.0)	27.0 (10.9)	33.3 (9.2)	42.8 (4.4)	N/A
Non-phenoconverters	2.5 (2.5)	5.5 (6.7)	2.2 (1.0)	2.0 (1.6)		
Total	9.6 (11.8)	10.2 (10.9)	12.1 (14.3)	15.9 (17.4)		
Striatal D_2 Binding						
Caudate						
Phenoconverters	0.92 (0.42)	0.95 (0.22)	0.79 (0.28)	0.71 (0.19)	0.72 (0.20)	2.09 (0.43)
Non-phenoconverters	1.50 (0.27)	1.39 (0.30)	1.31 (0.38)	1.28 (0.04)		
Total	1.34 (0.40)	1.23 (0.34)	1.10 (0.43)	1.06 (0.32)		
Putamen						
Phenoconverters	1.01 (0.25)	1.02 (0.11)	0.87 (0.13)	0.79 (0.11)	0.80 (0.22)	2.07(0.39)
Non-phenoconverters	1.50 (0.29)	1.36 (0.28)	1.29 (0.27)	1.26 (0.08)		
Total	1.37 (0.35)	1.24 (0.28)	1.12 (0.30)	1.08 (0.26)		
Striatal Tissue Volume						
Caudate						
Phenoconverters	0.64 (0.29)[B]	0.59 (0.29)	0.57 (0.30)	0.45 (0.16)	0.56 (0.12)	1.00(0.05)
Non-phenoconverters	0.86 (0.18)	0.82 (0.19)	0.84 (0.20)	0.78 (0.12)		

Total	0.79 (0.24)	0.74 (0.24)	0.74 (0.26)	0.63 (0.22)		
Putamen						
Phenoconverters	0.68 (0.17)	0.68 (0.19)	0.64 (0.18)	0.56 (0.17)	0.60 (0.14)	1.00 (0.05)
Non-phenoconverters	0.98 (0.22)	0.90 (0.22)	0.87 (0.20)	0.87 (0.11)		
Total	0.88 (0.24)	0.82 (0.23)	0.78 (0.22)	0.73 (0.21)		

[A]Mean (SD).
[B]Percent of the normal mean
UHDRS=Unified Huntington's Disease Rating Scale; HD=Huntington's disease; HC=healthy control.

Supplemental Table 3. Regions with significant loadings on the HD volume-loss progression pattern

Brain region	Coordinates[A] x	y	z	Zmax[B]
Declining Activity				
Putamen, right	24	8	0	4.53***
left	–22	6	6	4.03***
Caudate, right	14	4	18	3.47***
left	–10	12	10	2.92**
Posterior occipital (BA 18)	2	–92	–14	3.35***
Supplementary motor area (BA 6)	4	28	54	3.14**
Premotor cortex (BA 6)	–24	–8	62	2.96**
Superior temporal (BA 38), right	36	14	–18	2.46*
left	–42	12	–10	2.93**
Insula	–44	–4	0	2.52*
Prefrontal cortex (BA 9), right	2	50	34	2.65**
(BA 10)	0	54	6	2.58*
Prefrontal cortex (BA 9), left	–50	12	36	2.88**
Precuneus (BA 7)	6	–80	38	2.51*

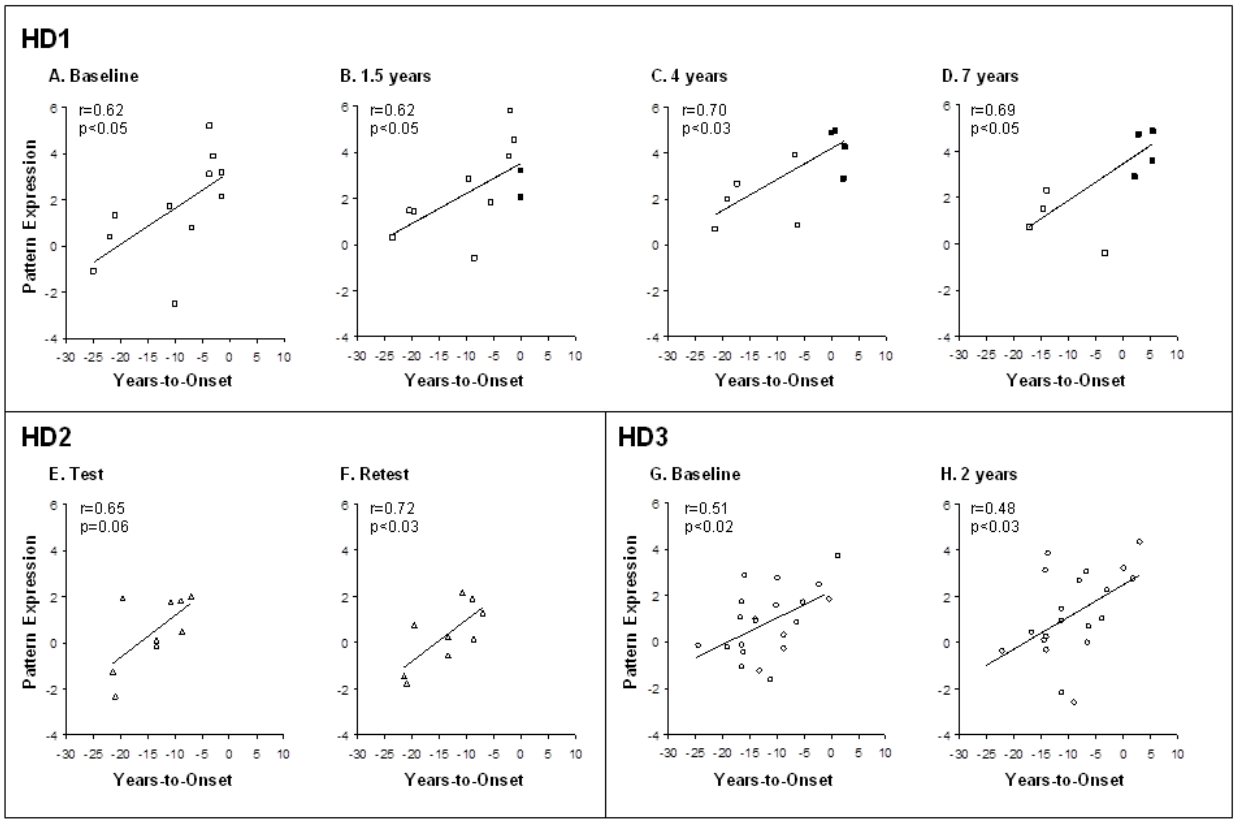
[A]Montreal Neurological Institute (MNI) standard space (1).

[B]Regions with significant loadings on the metabolic progression pattern (see text). *Z*-values at peak voxel are given for each region (*p<0.05, **p<0.01, ***p<0.001). Additionally, the weights on each of the regions were found to be reliable on bootstrap estimation (p<0.001; 1,000 iterations).

BA=Brodmann Area.

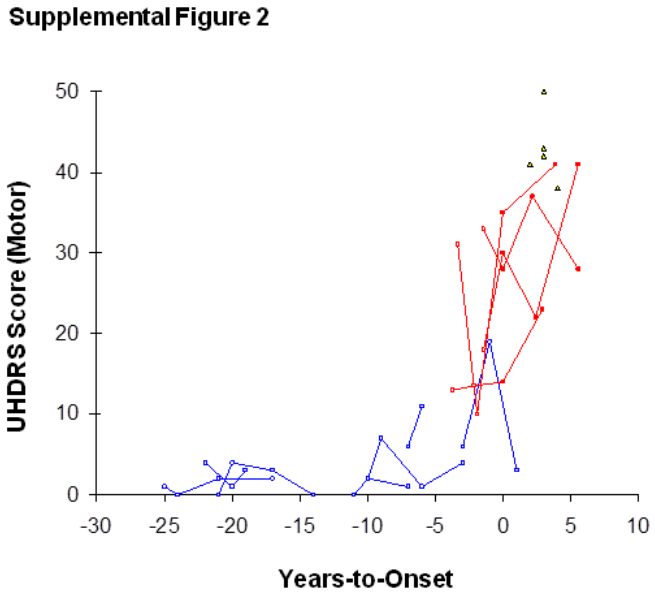
Supplemental Figures

Supplemental Figure 1



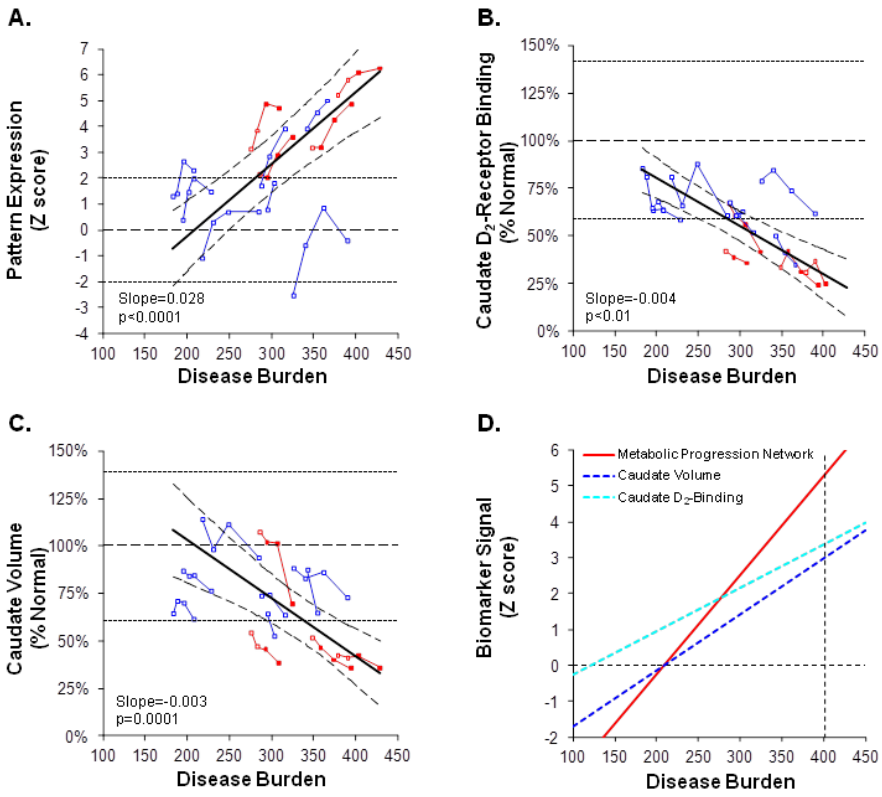
Supplemental Figure 1. Cross-sectional correlations of metabolic progression pattern expression with the predicted years-to-onset

In the premanifest HD1 cohort, the expression of the metabolic progression pattern correlated with the predicted years-to-onset ($p<0.05$; Pearson's correlations) at baseline (**A**) and at the three follow-up time points (**B-D**). Correlations of similar magnitude between these variables were evident in the test ($p=0.06$) and retest ($p<0.03$) scans of the premanifest HD2 subjects (**E**, **F**), and in the baseline ($p<0.02$) and follow-up ($p<0.03$) scans of the premanifest HD3 cohort (**G**, **H**). [Post-phenoconversion values are represented by filled symbols].



Supplemental Figure 2. Changes in UHDRS motor ratings vs. years-to-onset
Unified Huntington's disease rating scale (UHDRS) motor ratings plotted against years-to-onset values for the members of the initially premanifest HD1 cohort (see text). Predicted years-to-onset values (2) were used for the non-phenoconverters (*blue*). The time until actual clinical diagnosis was used for the four members of this cohort who subsequently phenoconverted (*red*), and for the five early symptomatic members (*yellow*) of the HD2 prospective testing cohort (see text).

Supplemental Figure 3



Supplemental Figure 3. Changes in the expression of the HD metabolic progression pattern, caudate D_2-receptor binding and tissue volume as a function of the disease burden index

As an alternative to using an empirically predicted years-to-onset measure (2), we repeated the IGM analyses using the disease burden index (3). The results were very similar to those reported using the former measure.

(**A**) Pattern expression in the longitudinal HD1 cohort increased linearly with increasing disease burden index ($p<0.0001$; IGM).

(**B**) Caudate D_2-receptor binding values measured using [^{11}C]-raclopride PET exhibited a linear decline with increasing disease burden index ($p<0.01$; IGM).

(**C**) Caudate tissue volume measurements acquired with volumetric MRI also exhibited a linear decrease with disease burden ($p<0.0001$; IGM).

[Disease burden=(CAG length – 35.5)×age. Red and blue lines denote the phenoconverters and non-phenoconverters. Solid line and broken curves depict the best fitted line and the 95% CI. Dotted lines represent 2 SD above and below the normal mean. In (**B**) and (**C**), individual values represented percent of the normal mean (*broken line*)].

(**D**) The rate of increase in the HD metabolic pattern expression (*red*) was greater ($p<0.0001$, IGM) than the rates of decline measured for caudate D_2-receptor binding (*light blue*) and tissue volume (*dark blue*). [Values for caudate D_2-receptor binding and tissue volume were flipped and analyzed as increasing mirror lines (*dotted lines*). Y-axis represents the standard z-scale. Horizontal dotted line represents the normal mean (zero) for each parameter. Vertical dotted line represents the time of phenoconversion (i.e., years-to-onset was zero)].

Supplemental References

1. Collins, DL, Neelin, P, Peters, TM, and Evans, AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr*. 1994;18:192-205.
2. Langbehn, DR, Brinkman, RR, Falush, D, Paulsen, JS, and Hayden, MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin Genet.* 2004;65:267-277.
3. Tabrizi, SJ, Reilmann, R, Roos, RA, Durr, A, Leavitt, B, Owen, G, Jones, R, Johnson, H, Craufurd, D, Hicks, SL, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. *Lancet Neurol.* 2012;11:42-53.