PREQUEL Multicenter Phase II Therapeutic Trial in Pre-symptomatic ("pre-manifest") HD

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HDSA Convention

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--Many slices adapted from Kevin Biglan

Huntington's Disease Society of America

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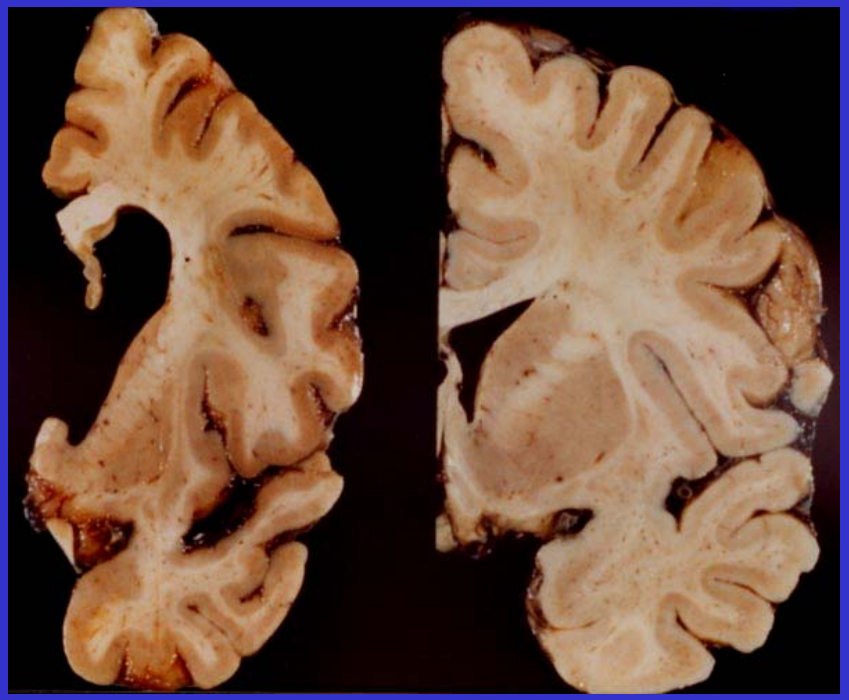
Huntington's Disease

- Selective neuronal degeneration in Basal Ganglia--Caudate and putamen, but also cerebral cortex and other regions
- CAG expansion mutation: longer CAG repeats have earlier onset and more widespead degeneration



CAG-CAG-CAG (DNA)

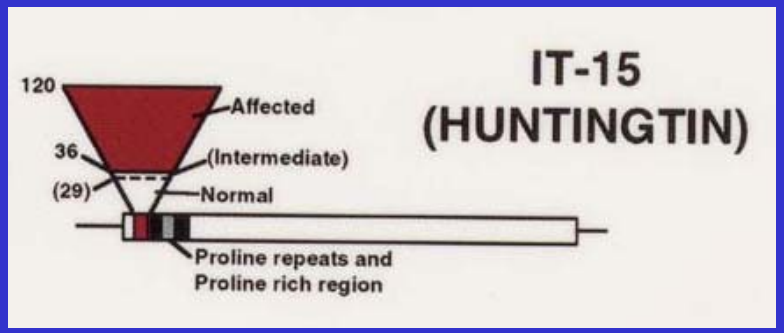
↓

CAG-CAG-CAG (RNA)

↓

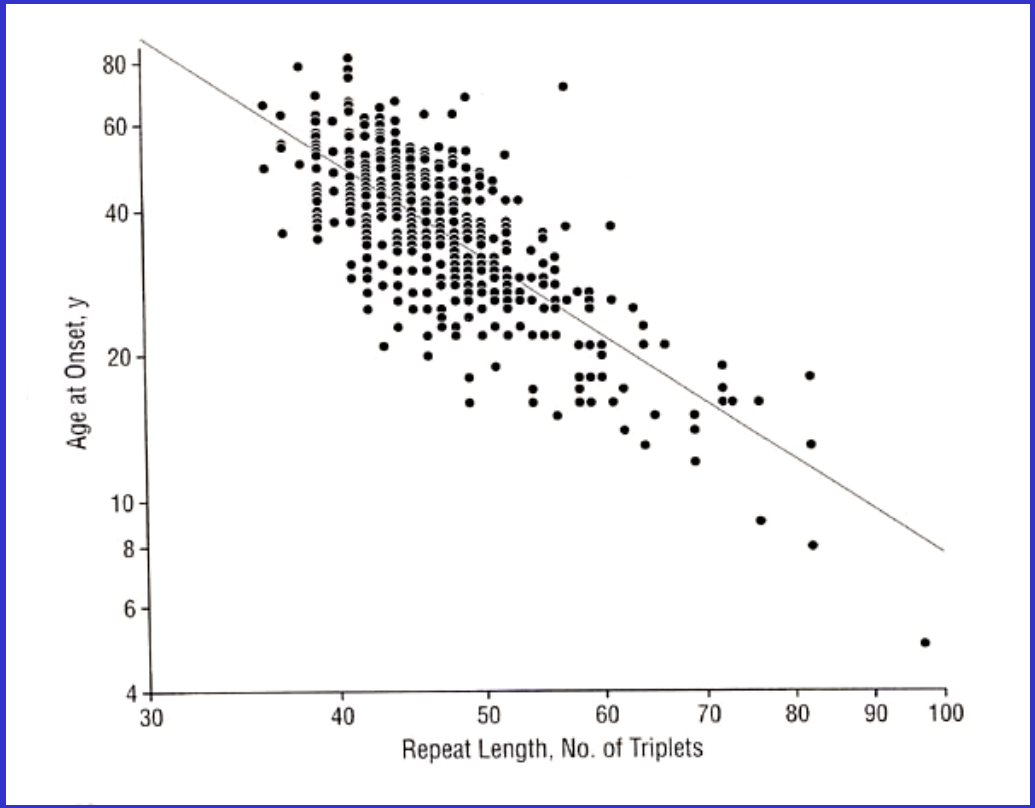
Gln---Gln---Gln (Protein)

(Q) (Q) (Q)



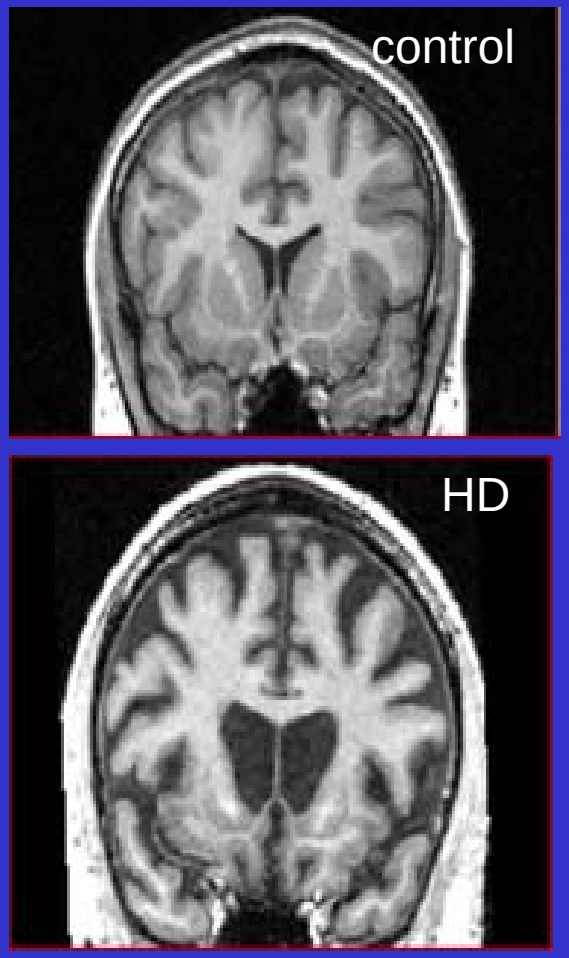
CAG Repeat length and Age of Onset of HD

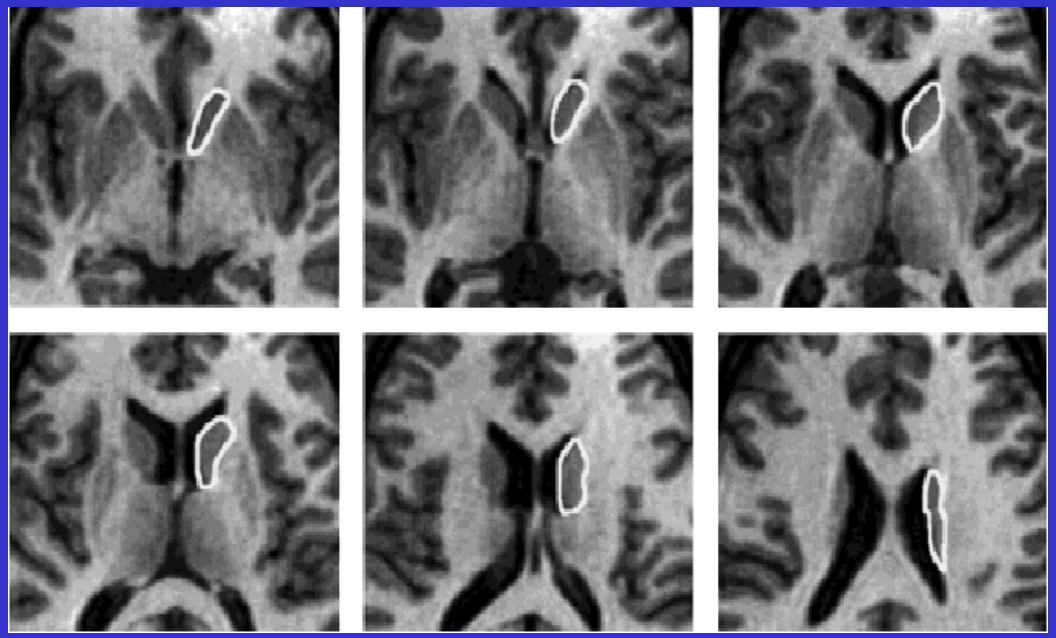
- CAG repeats of 35 or less do not cause HD
- Incomplete penetrance (delayed onset) for CAG 36 to 40
- Longer expansions result in earlier onset ages—thus can roughly predict onset age
- Determinants of the rate of progression are still unknown



--Ranen et al Am. J. Hum. Genet. 1995, and Margolis et al Arch. Gen. Psychiat. 1999

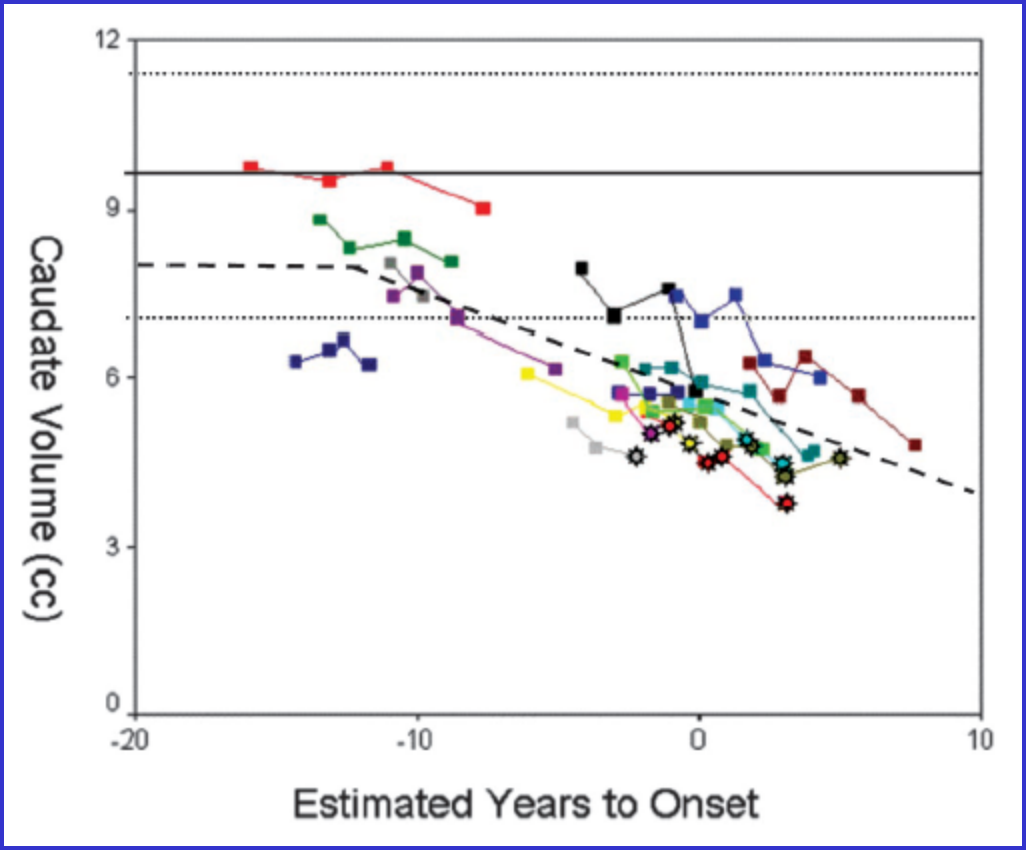
Quantification of Caudate Volumes: Regions of Interest





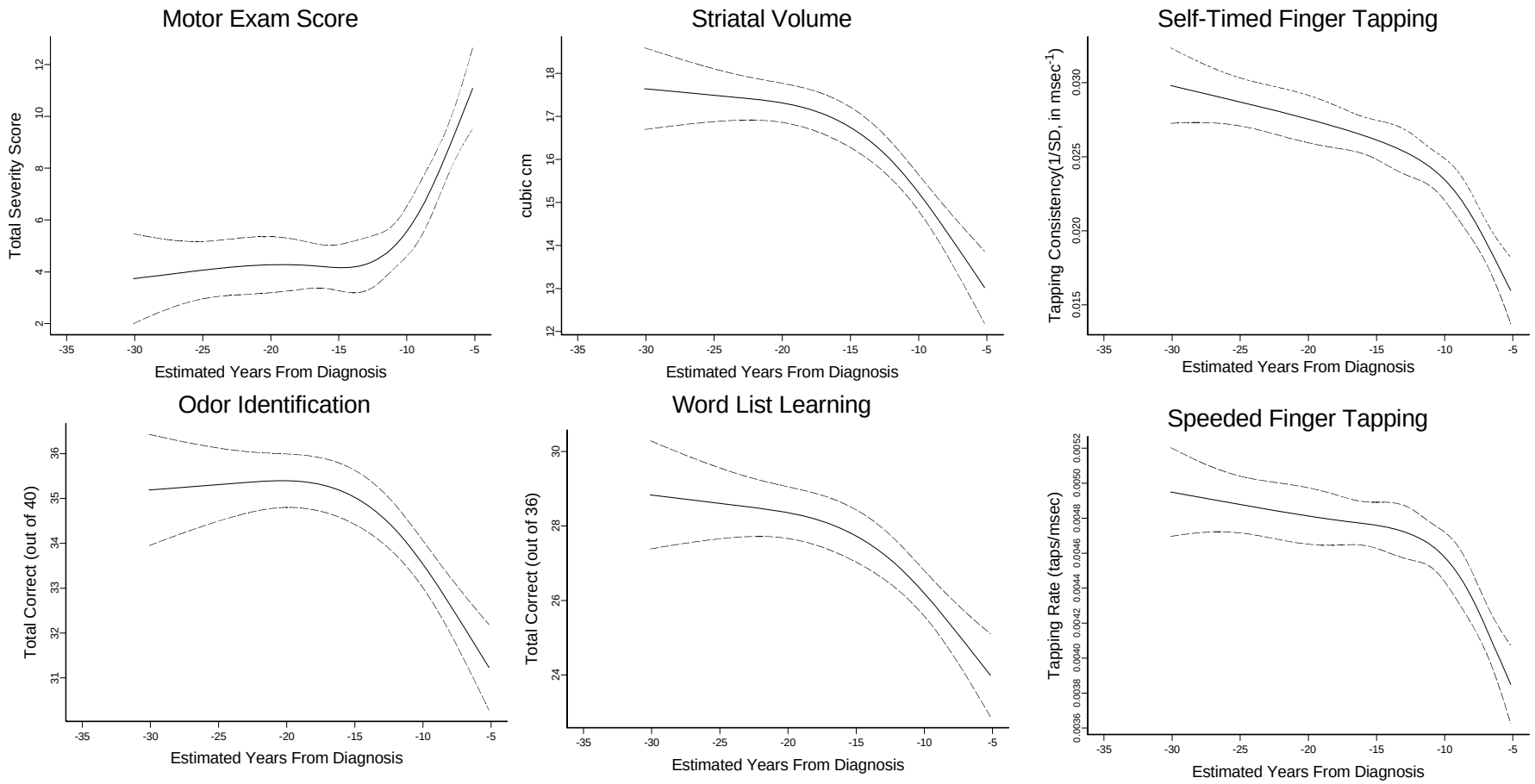
--Aylward et al Neurology 2004

Caudate Atrophy in Pre-Symptomatic HD: Longitudinal Study in Hopkins Cohort



--Aylward et al, Neurology 2004

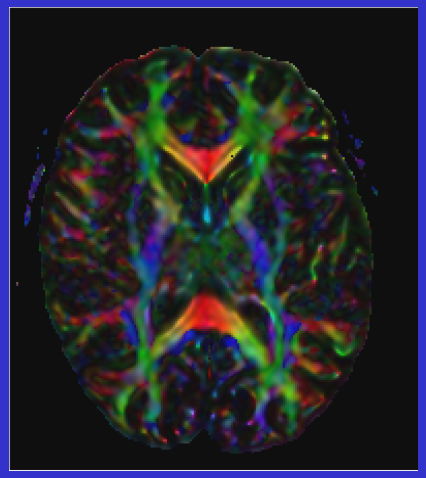
Predict-HD Multicenter
HD Presymptomatic Study

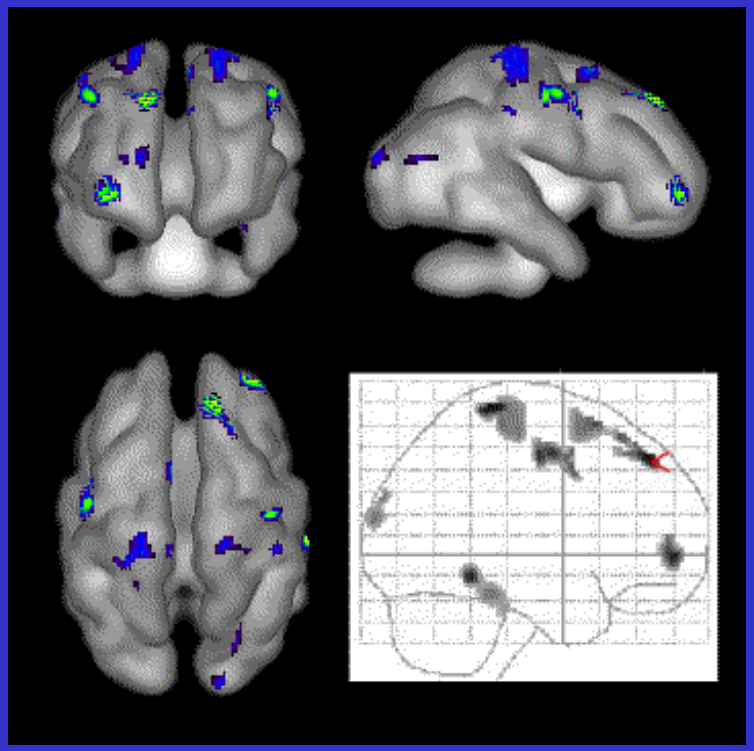


--Paulsen and REDICT-HD 2007

White Matter Alterations in HD Mutation-Positive Pre-Symptomatic Individuals

- DTI: Water diiffusion for fiber tract directionality



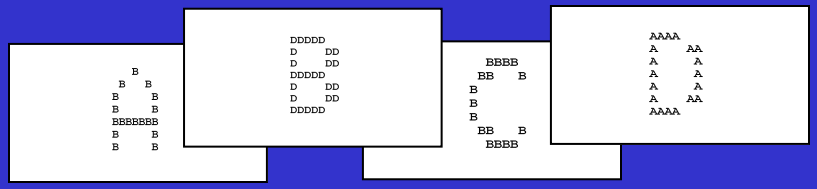


  - Fractional anisotropy measure of white matter integrity
  - SPM map of significant differences—blue and green represent HD Pre-Sx less than control

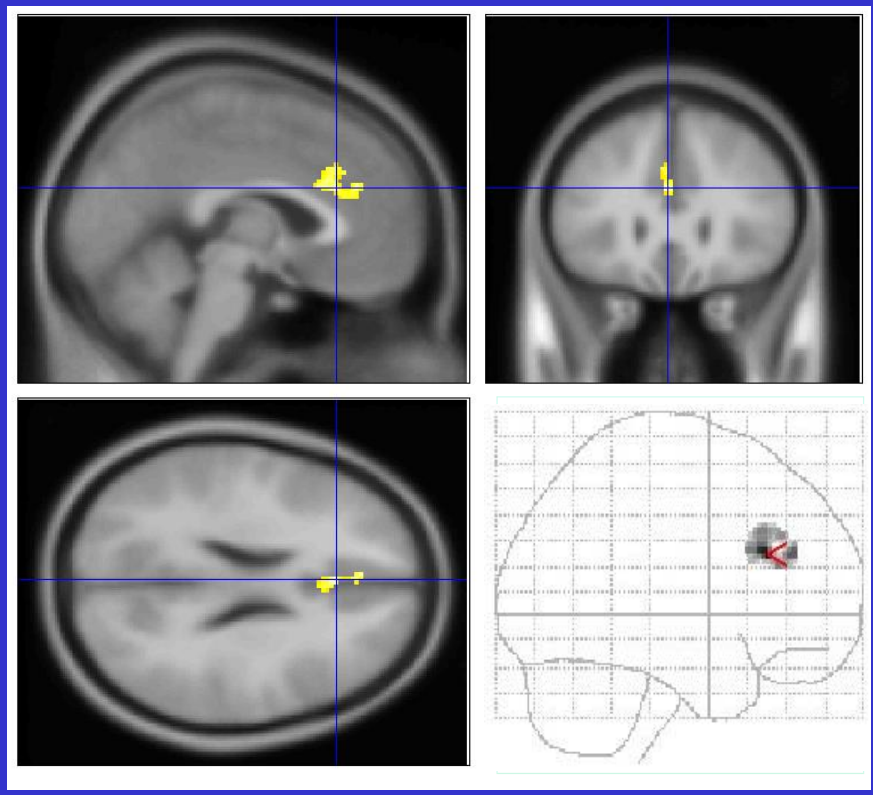
--Reading, Mori et al 2005

fMRI Alterations in HD Mutation-Positive Pre-Symptomatic Individuals

- 7 Pre-Symptomatic HD
- 7 controls
- Stroop interference type task



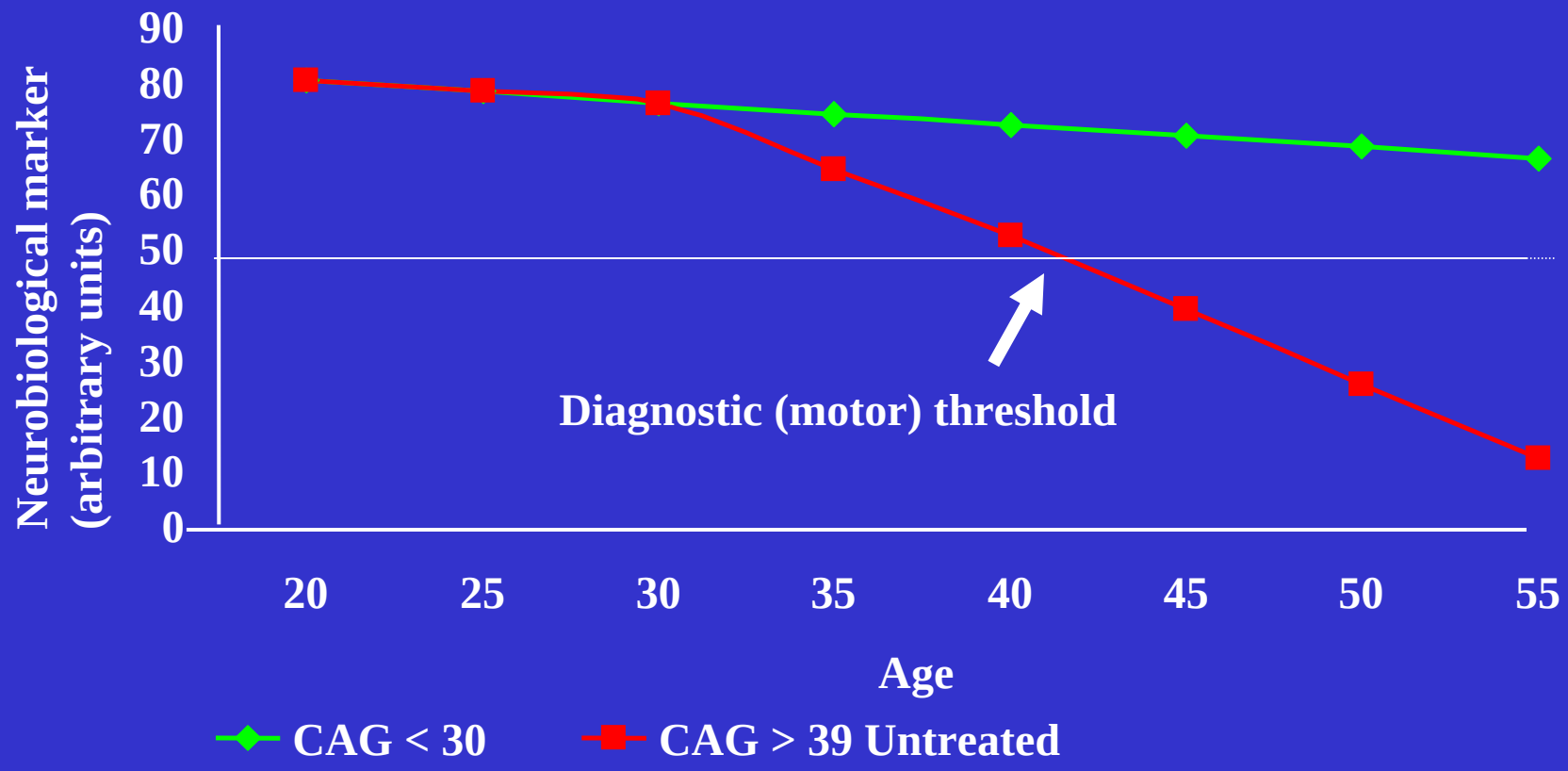
- SPM subtractive analysis
  - Baseline from active (by group)
  - Pre-Sx from controls



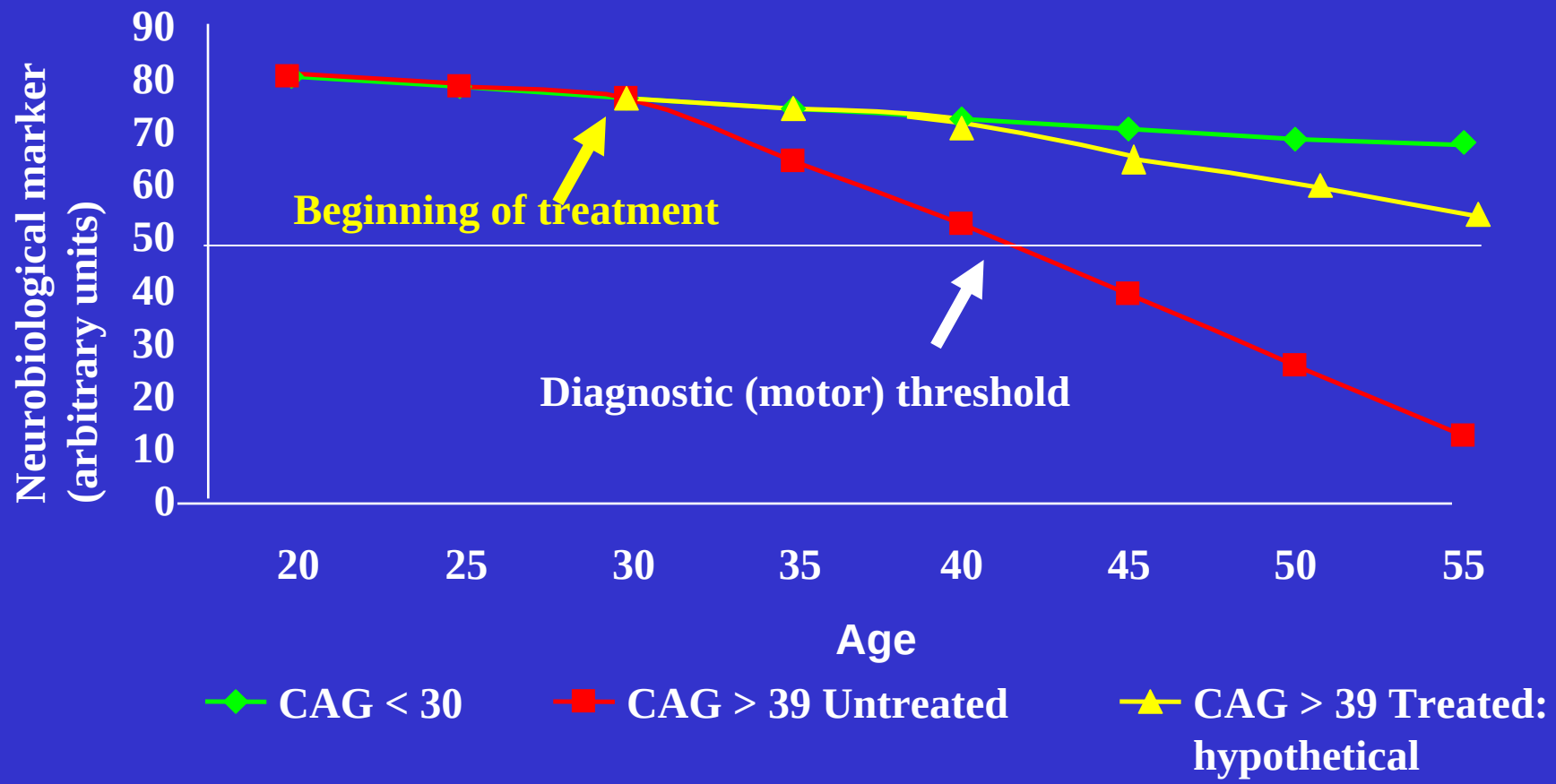
Between-group differences of BOLD response with the “active” condition of the task

--Reading et al Ann Neurol 2004

HD Over the Lifetime



Design of Therapeutic Trials for Pre-Symptomatic HD



Study in **Pre**-manifest HD of Coenzyme **Q**10 (**U**biquinon**e**) **L**eading to preventive trials (**PREQUEL**)

DEFINITION: “A literary, dramatic, or cinematic work whose narrative takes place before that of a preexisting work or a sequel”[1]

ORIGIN: George Lucas[2]

First known use: Press materials for the Godfather II[2]

Popularized in American culture by the Star Wars trilogy prequel (episodes 1-3)[2]

1http://dictionary.reference.com
[2]http://en.wikipedia.org/wiki/Prequel

Long Term Objective

- Development of future preventive therapeutic trials in pre-manifest expansion positive individuals (with Coenzyme Q10 and/or other compounds?)

Primary Aim

- To determine the highest dosage of Co-Enzyme Q10 (amongst 600 mg/day, 1200 mg/day, 2400 mg/day) that is well tolerated in a pre-manifest mutation positive cohort in the context of a randomized, double-blind, parallel group trial.

Secondary Aim

- To establish the biological activity of CoQ10 in this population by assessing changes in serum levels of CoQ10, 8OHdG/8OHrG

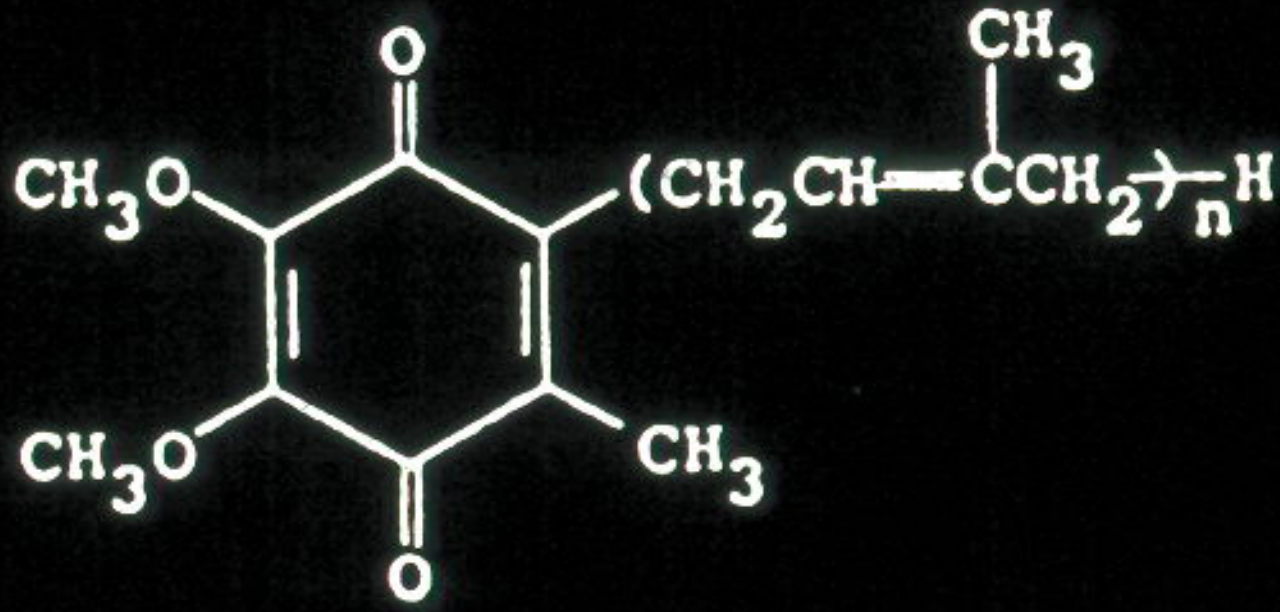
Additional Objectives

- To assess the feasibility of designing and implementing a therapeutic trial in a pre-manifest population
- To assess the relationship between serum levels of CoQ, measures of oxidative stress (8OHdG/8OHrG), DNA repair mechanisms (OGG1)
- To further validate functional measures of disease in a pre-manifest population

Significance

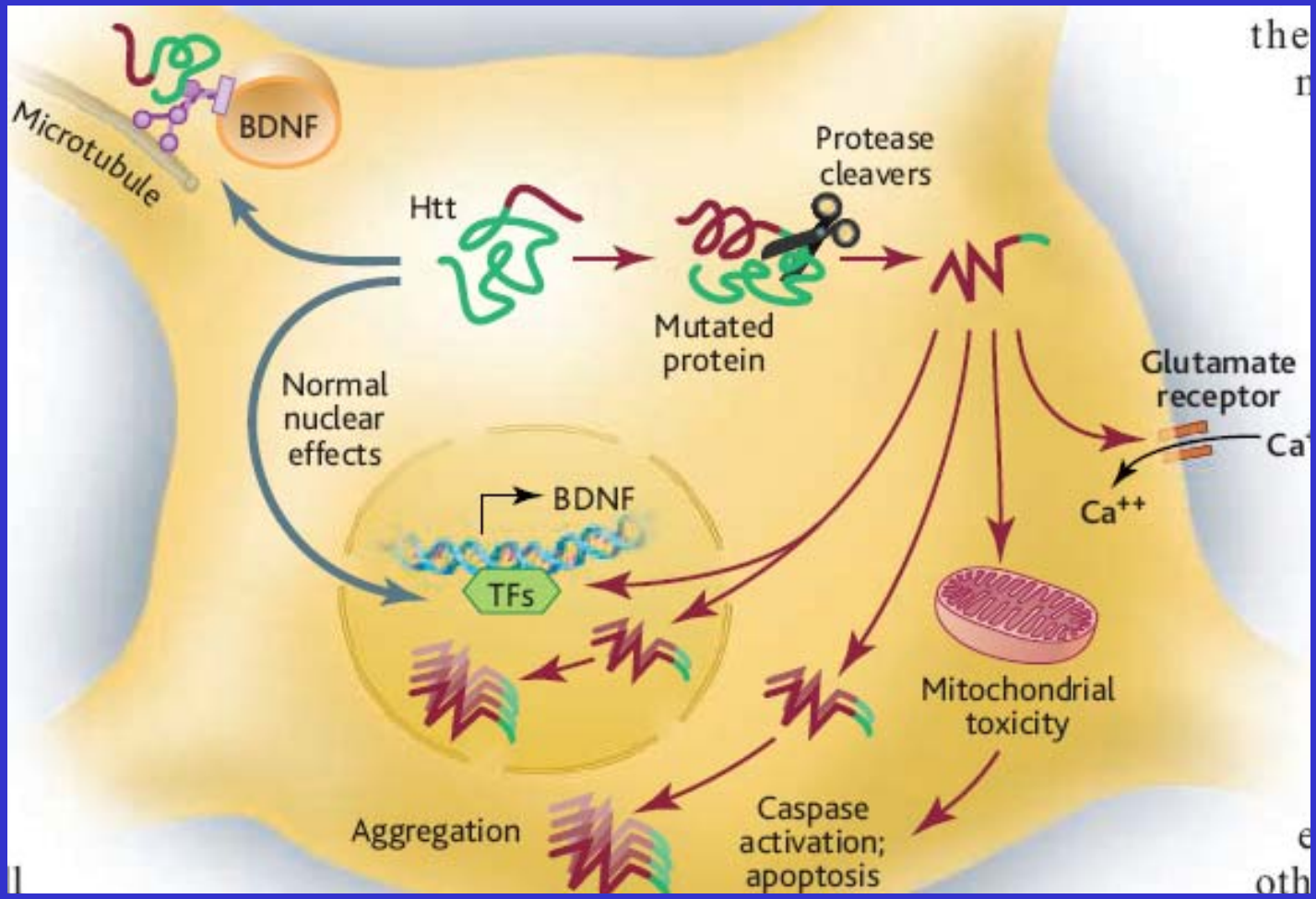
- First trial to evaluate potential therapy in participants 100% at-risk for HD
- Allow selection of dosage that is tolerable (and biologically active?)
- Provide insight into process and feasibility of trials in pre-symptomatic participants

Why Coenzyme Q10?



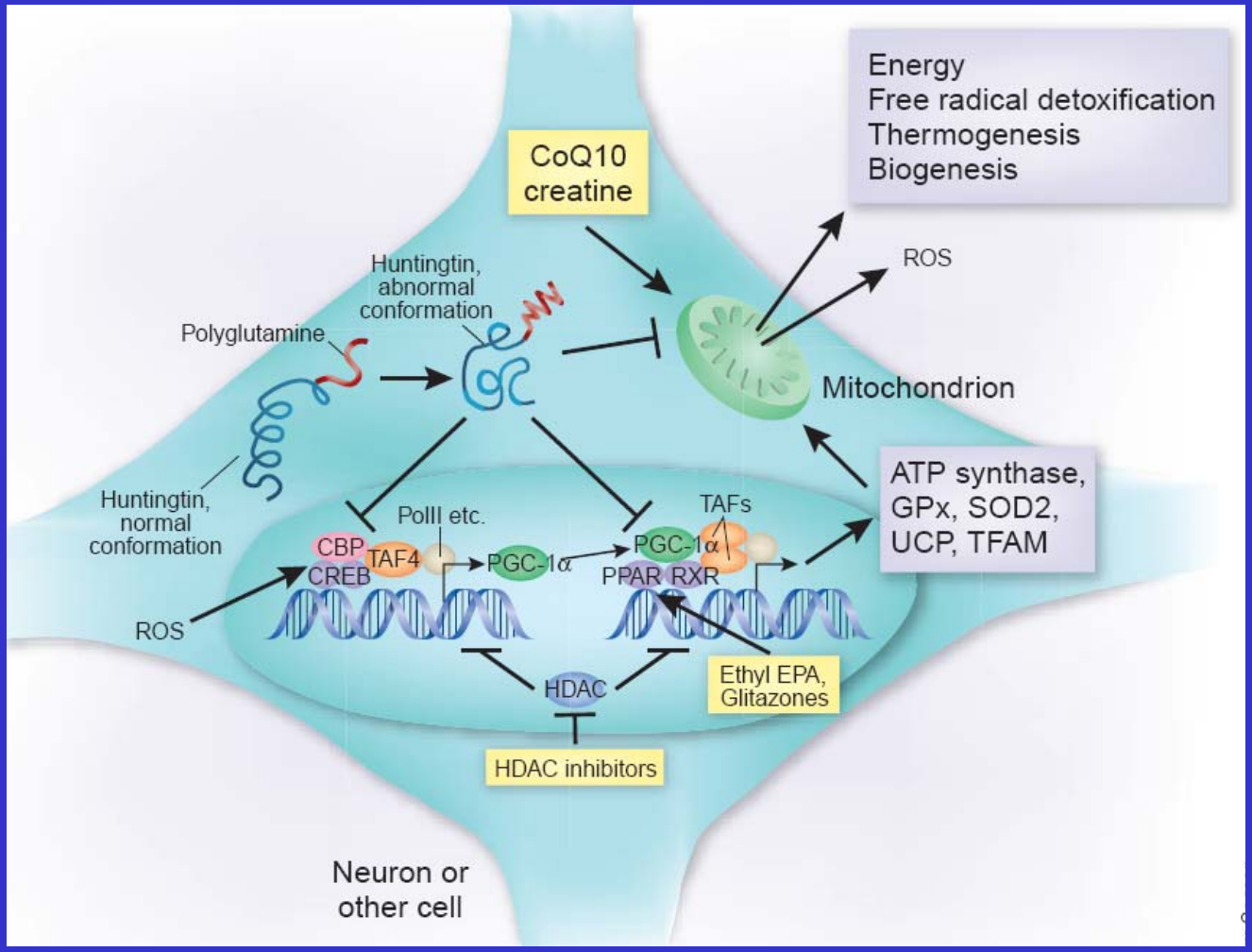
Ubiquinone, coenzyme Q_{10}

HD Cell Biology



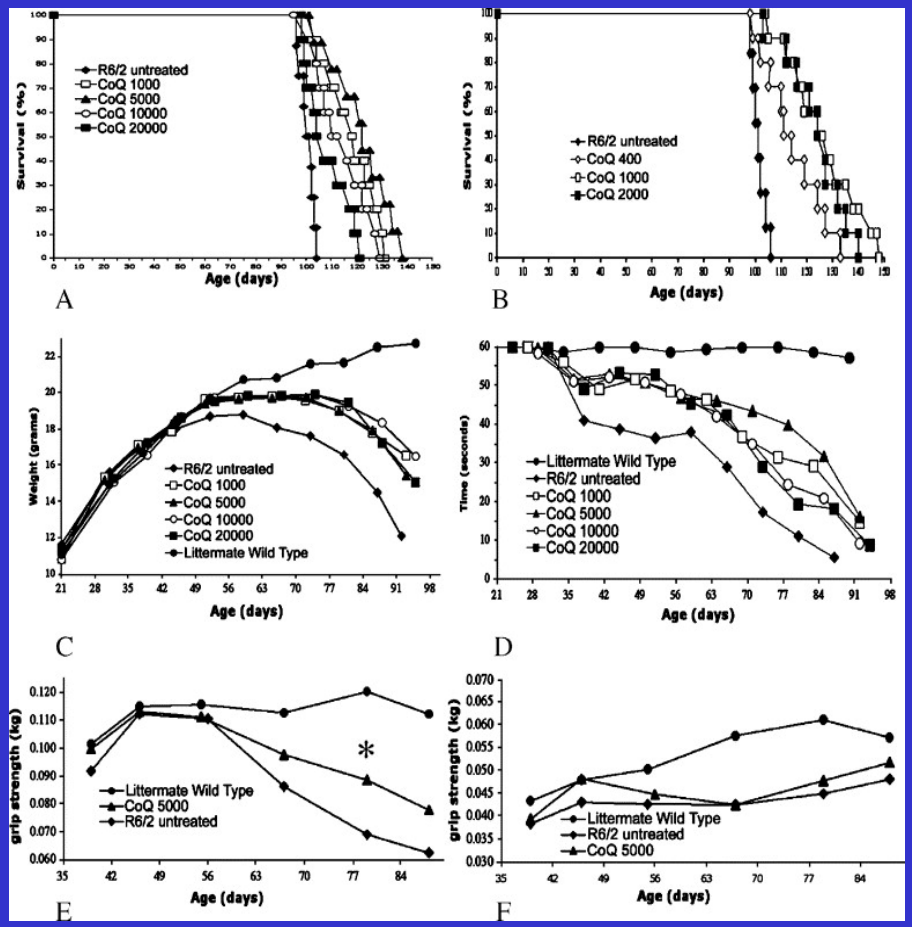
Jean Marx, Science 2005

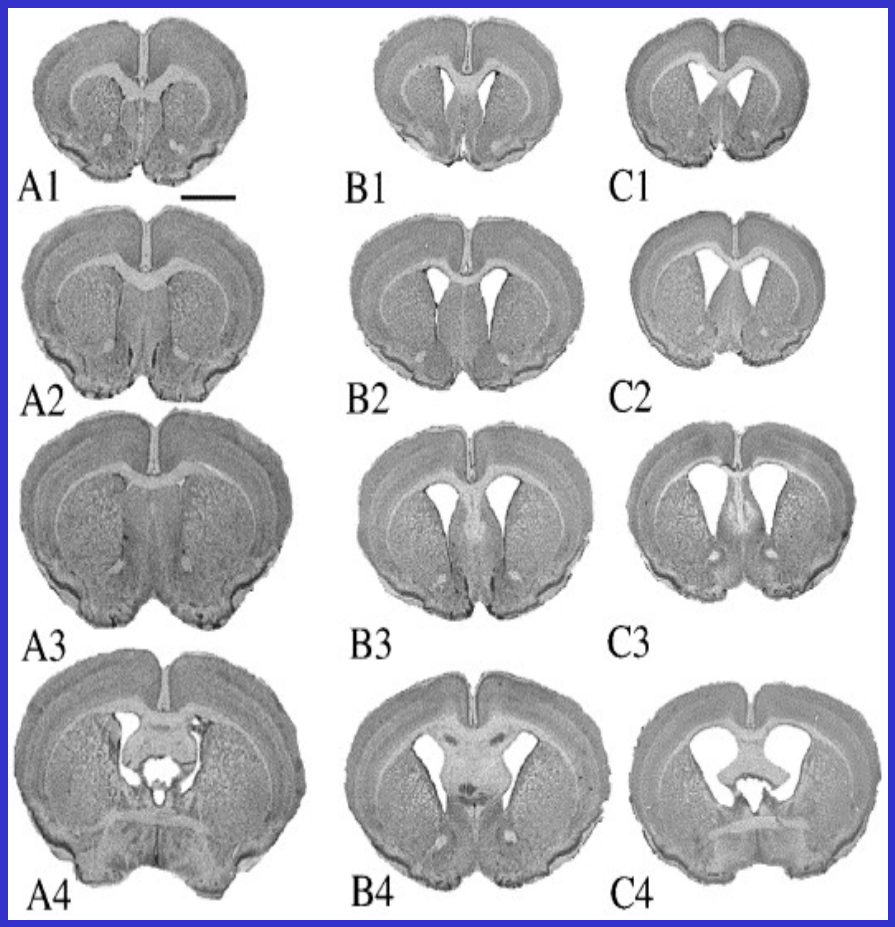
Intersection of Transcription and Metabolism



--Ross and Thompson Nature Medicine 2006

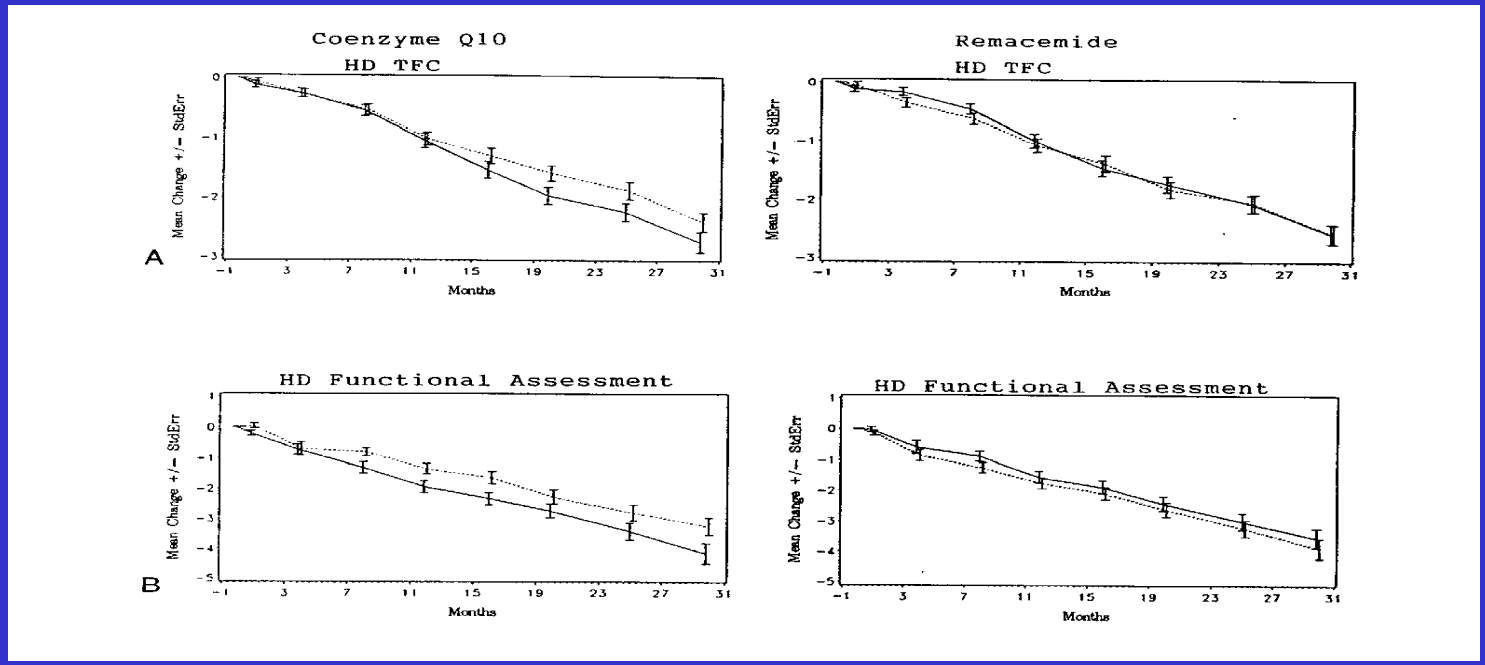
Preclinical Efficacy in R6/2 HD Mouse Model





K.M. Smith et al. BBA. 2006;

CARE-HD: Suggestive Evidence in Manifest HD
Dose of 600 mg/day for 30 Months



HSG. Neurology. 2001;57:397-404

CoQ in PD (-Schults 2002)

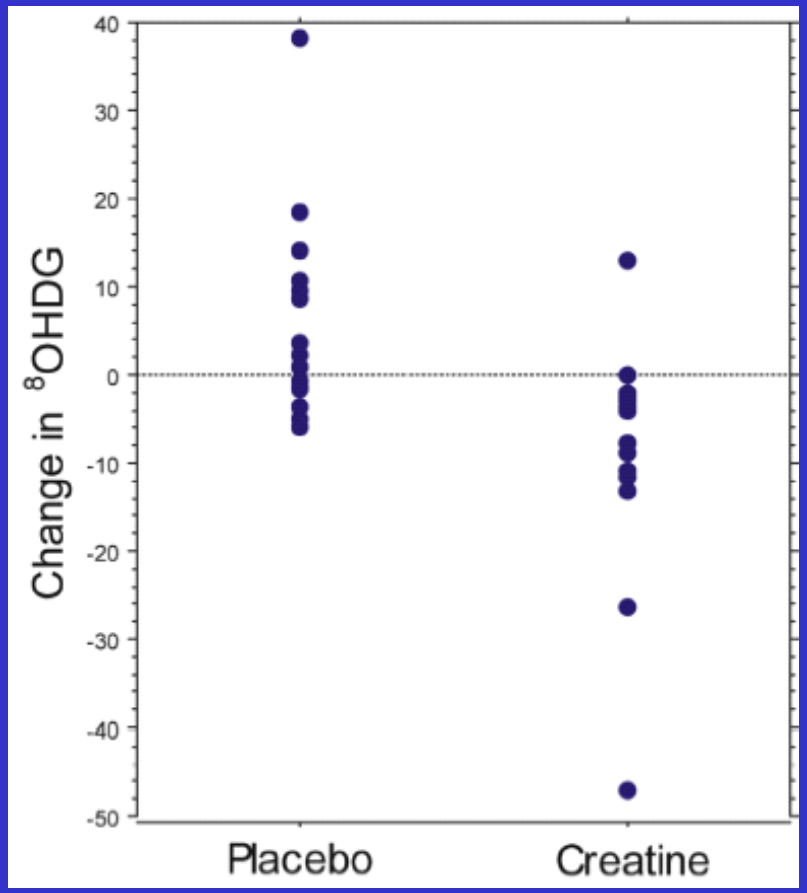
- 80 PD patients, randomized, double blind, 16 months
- Placebo, 300, 600, 1200 mg/ day
- 300 or 600 mg/ day modestly beneficial
- 1200 mg/ day –more benefit
- --suggestive, not conclusive

Rationale for Safety and Tolerability

- Healthy subjects
- Long exposures
- Lower tolerability threshold in non-ill participants?
  - Suggestion of differential tolerability of CoQ in healthy vs. manifest HD (Pre2care)

8OHDG: A biomarker of DNA oxidative damage

- Stable in serum and may be useful biomarker of oxidative damage
- Increased in caudate, parietal cortex in HD post-mortem brains
- Increased in R6/2 mouse model
- Increased in ALS and Friedreich's Ataxia



Hersch et al. *Neurology.* 2006;66:250-252

Trial Population

- 90 Pre-manifest participants (Diagnostic confidence ≤ 3)
- Previously tested expansion (HD mutation) positive through standard pre-manifest testing programs
- No concomitant medication restrictions
- No unstable medical/psychiatric illness

Design

- 1:1:1 Randomized to 600 mg/day, 1200 mg/day, or 2400 mg/day
- Double-blind parallel group trial
- Titrated over 4 weeks to assigned dosage
- Followed for 20 weeks after randomization
- Primary outcome is tolerability

Outcomes

- Primary Outcome
  - Tolerability: ability to complete study on randomized treatment assignment
- Secondary Outcomes
  - Additional tolerability: ability to complete study on active drug, AEs, # of dosage reductions
  - Safety: serum chemistries, UA, CBC, EKG
  - Serum CoQ levels
  - Serum 8OHdG/8OHrG levels and OGG1 levels
  - HD clinical and functional scales

Power Analysis

- Sample Size of 30 per group
- Observed tolerability compare to a tolerability that would be unacceptably low (<75%)
- 90% power to correctly detect dosage as tolerable
- 20% probability of incorrectly identifying dosage as tolerable if dosage is actually intolerable

Sites

Site #	Site Name	Investigator	Coordinator
1	University of Rochester	Peter Como, PhD	Amy M. Chesire, LCSW-R, MSG
7	Baylor College of Medicine	Joseph Jankovic, MD	Christine Hunter, RN
24	University of Iowa	Leigh J. Beglinger, PhD	William H. Adams, BA
27	Washington University	Joel S. Perlmutter, MD	Stacey K. Barton, MSW, LCSW
28	Johns Hopkins University	Russell Margolis, MD	Claire Welsh
32	Emory	Claudia Testa, MD, PhD	Joan M. Harrison, MN
45	Indiana University	Joanne M. Wojcieszek, MD	Jo Belden, LPN, CCRC
52	Colorado Neurological Institute	Rajeev Kumar, MD	Dawn Miracle, BS, MS
61	University of California Davis Medical Center	Vicki L. Wheelock, MD	Margaret Sanders, BS
71	Hennepin County Medical Center	Martha Nance, MD	Dawn Radtke, RN, CCRC
73	UC San Francisco	Michael Geschwind, MD, PhD	Mira Guzijan, MA

Study Sites

- University of Rochester
- Baylor College of Medicine
- University of Iowa
- Washington University
- Johns Hopkins University
- Indiana University
- Colorado Neurological Institute
- University of California—Davis
- Hennepin County Medical Center
- University of California—San Francisco

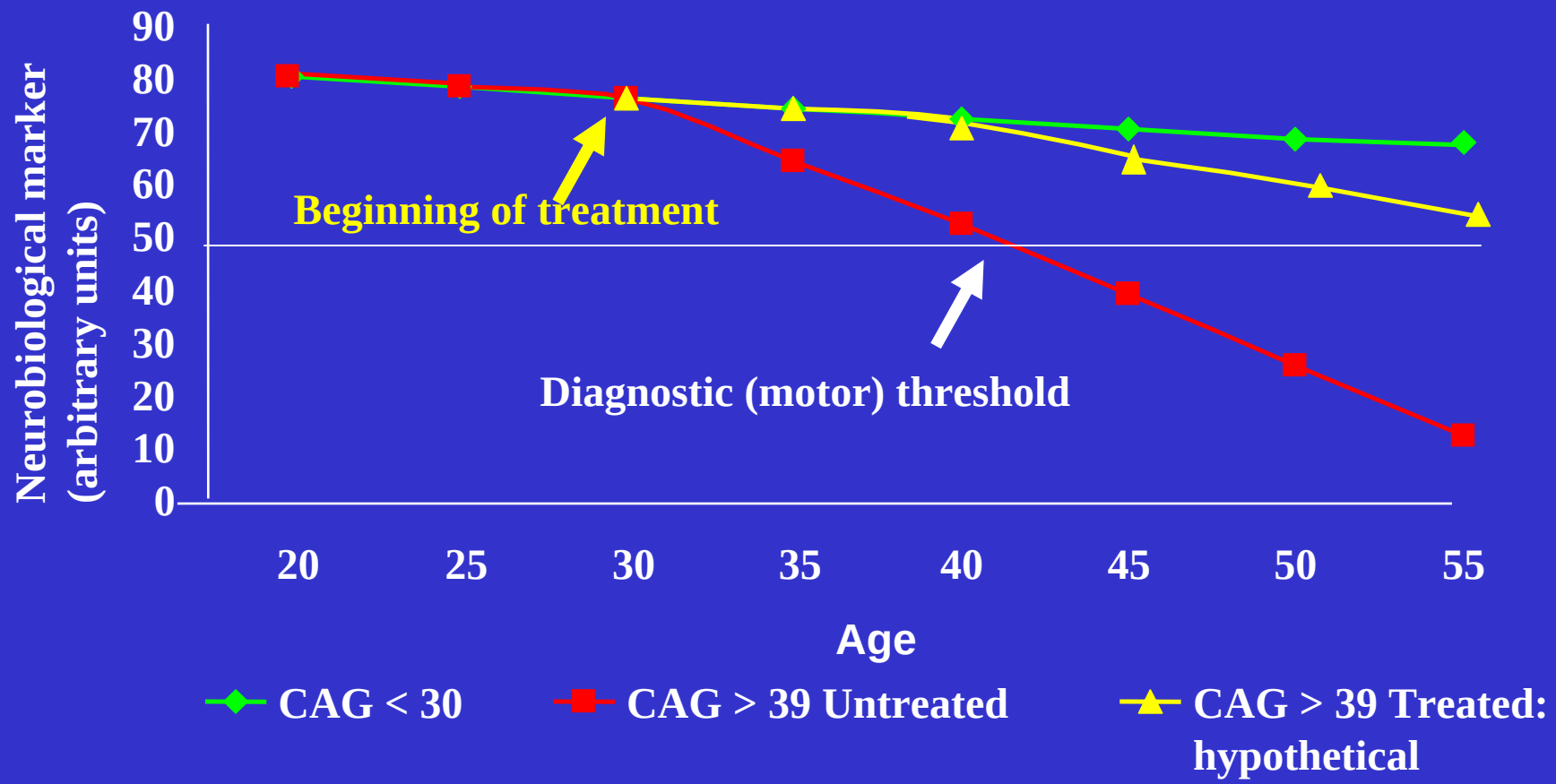
HD Drugs in the "Pipeline"

Some Potential Huntington's Drugs

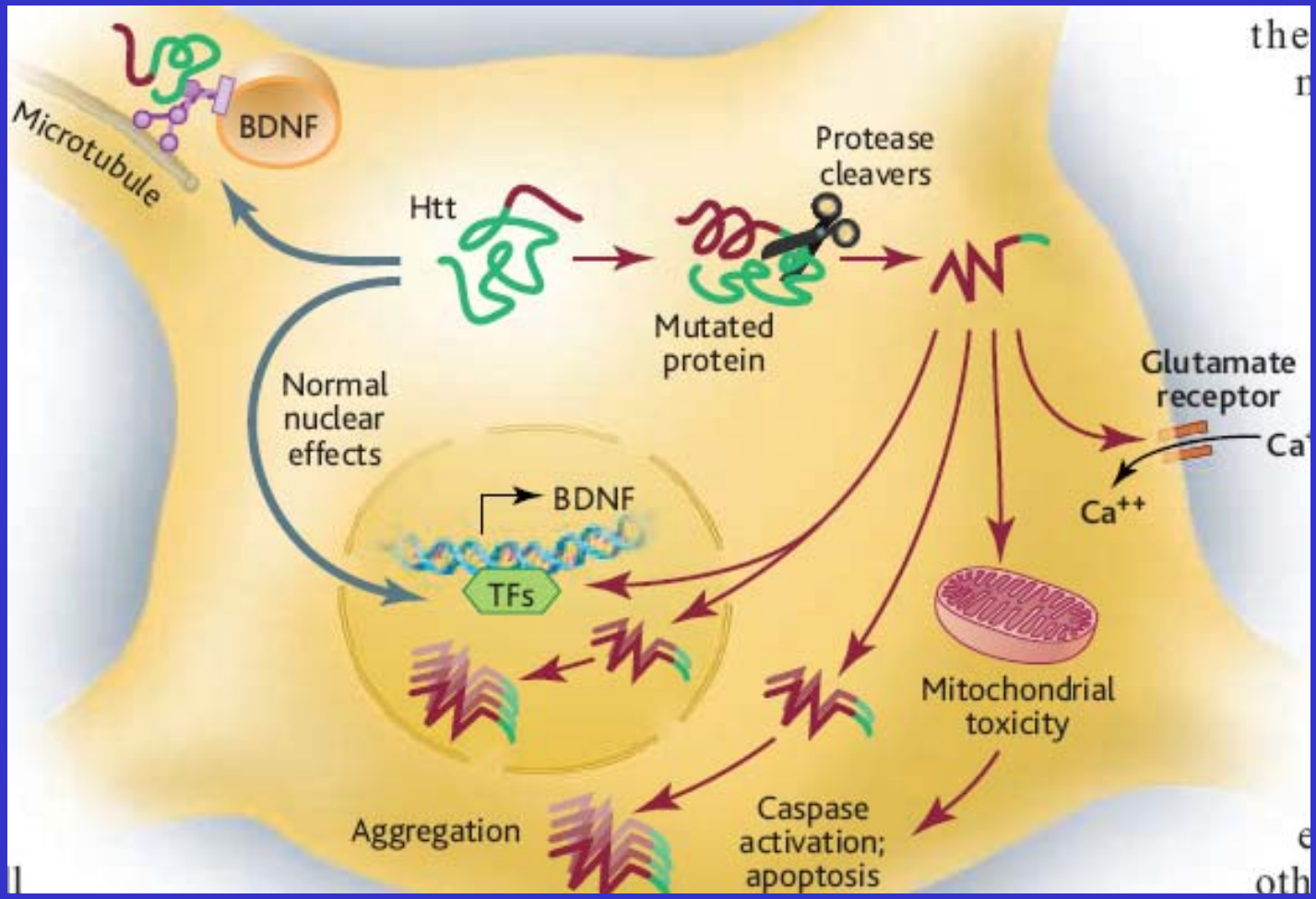
DRUG	ACTIONS	STATUS IN HUNTINGTON'S
Coenzyme Q10	Antioxidant; protects mitochondria	Late clinical trials
Creatine	Stabilizes mitochondria	Early clinical trials
Cystamine	Decreases Htt aggregation?	Early clinical trials
Geldanamycin	Decreases Htt aggregation	Preclinical
HDAC inhibitors (butyrates, SAHA)	Counters Htt's transcription effects	Early clinical trials
Memantine	Neurotransmission	Early clinical trials
Minocycline	Decreases cell death, Htt aggregation	Early clinical trials
Paroxetine	Protects neurons by increasing BDNF	Preclinical
Rapamycin	Decreases Htt aggregation by stimulating autophagy	Preclinical

--Jean Marx Science 2005

Design of Therapeutic Trials for Pre-Symptomatic HD

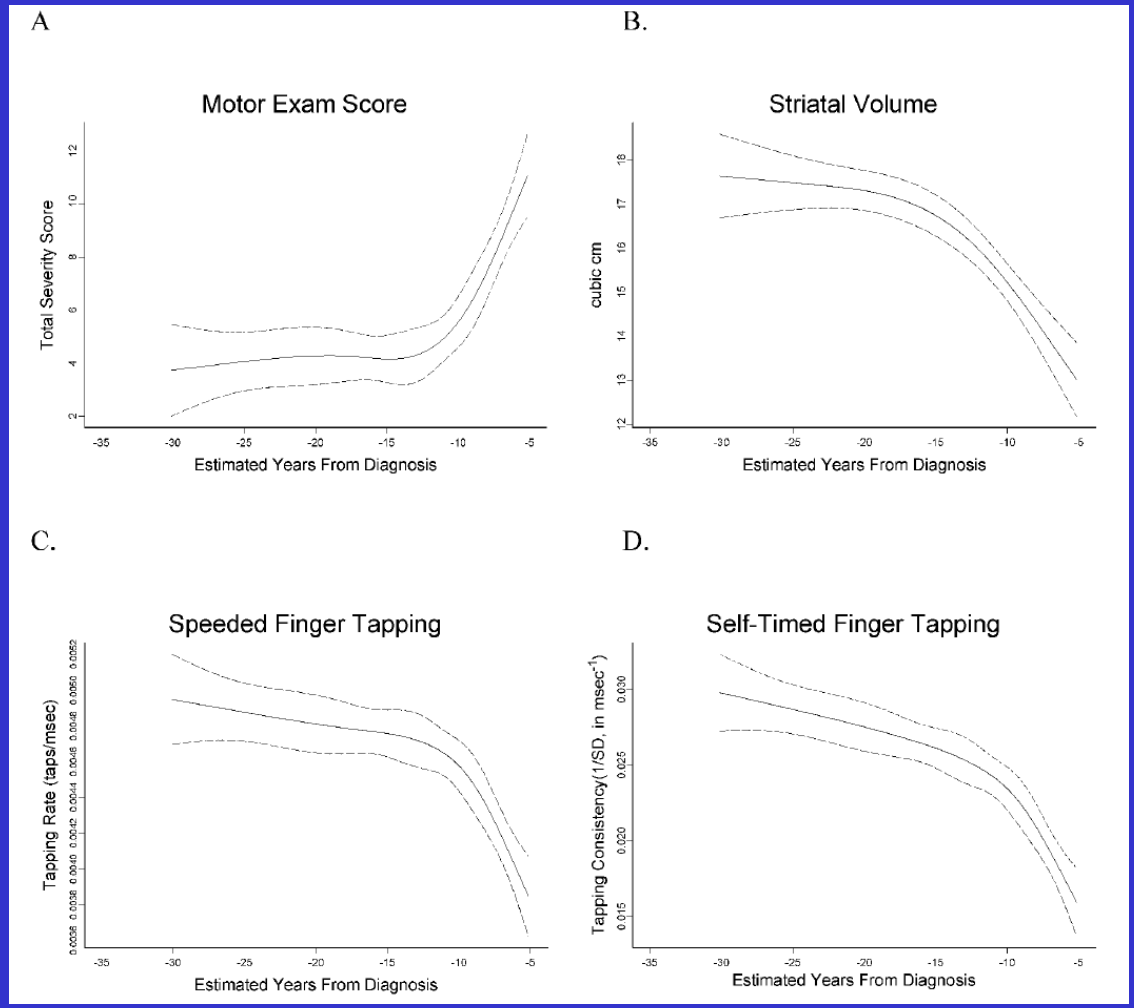


HD Cell Biology



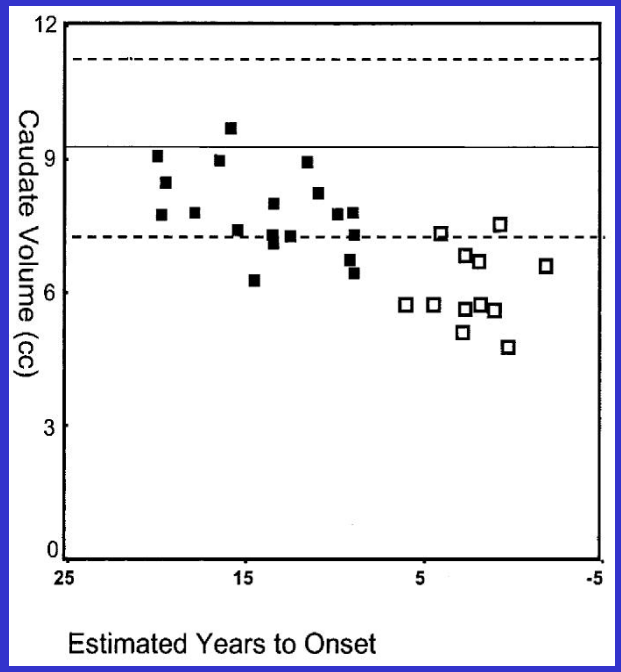
Jean Marx, Science 2005

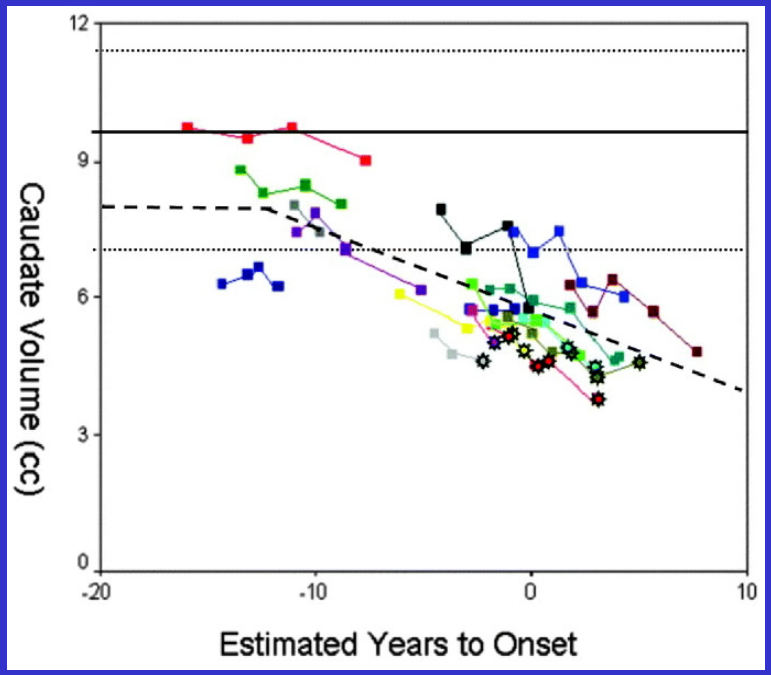
Predict-HD Multicenter HD Presymptomatic Study



--Paulsen and Predict-HD in preparation

Caudate Atrophy Predates Disease Onset





E.H. Aylward, et al. Neurology. 2004;63:66-72