Huntington's Disease Society of America

Cognitive, Behavioral and Motor Issues: Early Motor Symptoms

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Presenter Disclosures

Juan Sanchez-Ramos

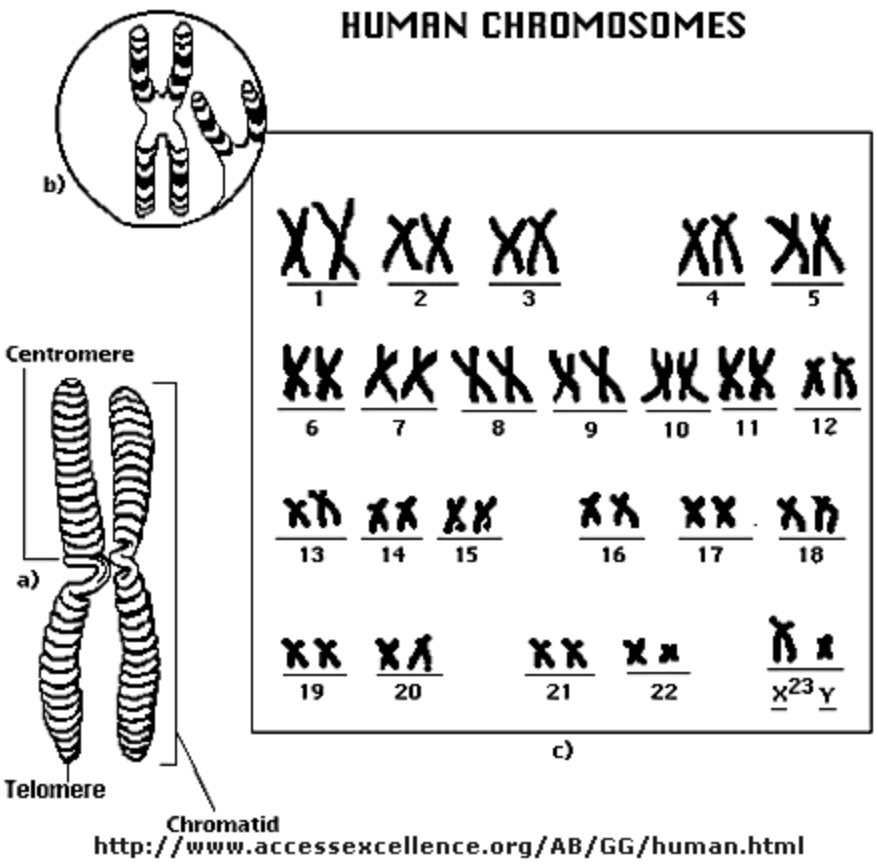
The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

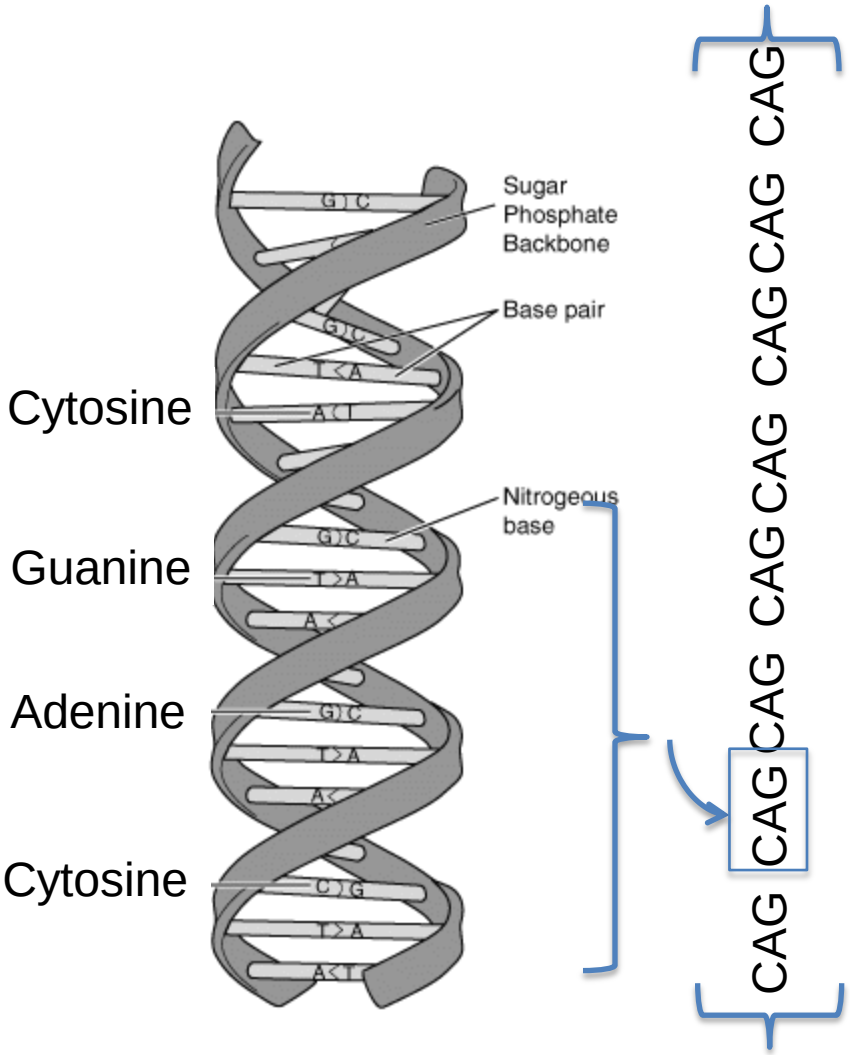
No relationships to disclose or list

Huntington's Disease

- Progressive, hereditary, neurological disease known for its prominent clinical feature of chorea
- Behavioral and cognitive changes are also prominent
- Genetics: Autosomal dominant pattern of inheritance
  - Affects males and females equally
  - Each child of an affected parent has a 50% chance of inheriting the HD gene

HD Gene





N≥39 CAG= HD

Characteristics of the Movement Disorder

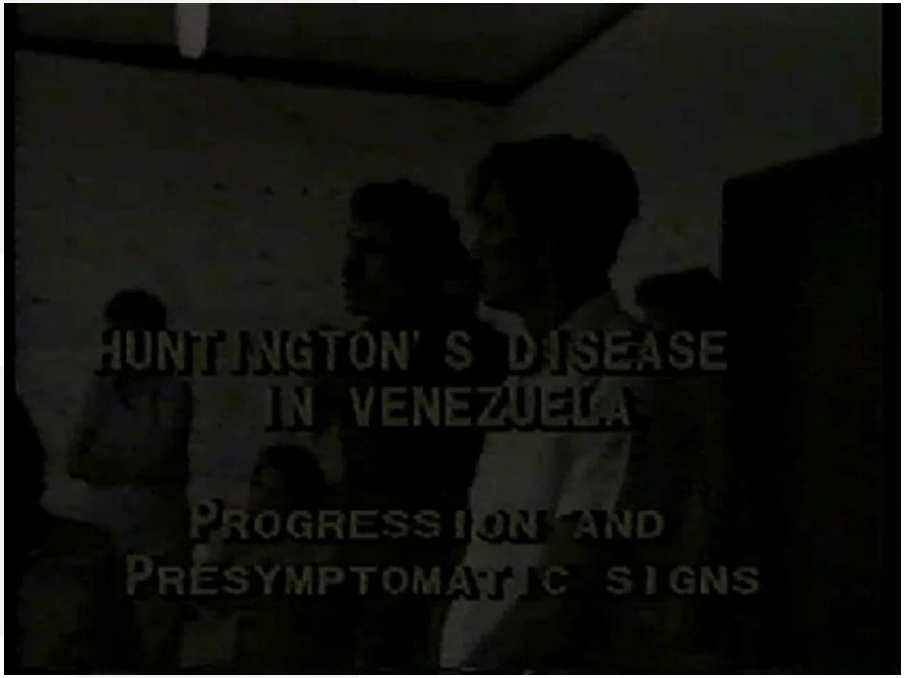
- Most often hyperkinetic, choreiform (dance-like movements of limbs, face, body)
- Dystonia (abnormal postures of limbs, trunk or slow twisting movements), rigidity, akinesia (inability to move) supervene later in course
- Rigidity, bradykinesia (slowness of move-ment) , tremor can be prominent in juvenile onset HD (<20 yrs age)

Other Motor Manifestions

- Motor sequencing- coordination of movements is poor
- Bradykinesia- slow movements
- Dysarthria/Dysphagia- speech/swallow
- Awkward gait, poor balance and falls
  - Leading cause of nursing home placement
  - More difficult to treat

Evolution of the abnormal movements in clinically manifest HD

- Tic-like (sudden jerking) movements of fingers, hands, toes, feet, face may be the first involuntary movements noticed
- These early movements may be small and subtle and initially observed as repetitive movements of the toes, fingers, feet, hands
- Gradually movements flow into each other giving the appearance of a dance-like movements (chorea); they can be of larger amplitude
- As the illness advances, the chorea slows down and dystonia may appear (slow twisting movements that result in abnormal postures of the limbs, trunk, head)
- At later stages, slowness of all movements and rigidity supervene


HUNTINGTON'S DISEASE
IN VENEZUELA
PROGRESSION AND
PRESYMPTOMATIC SIGNS

Profile of Motor Features as a Function of Stage of Disease

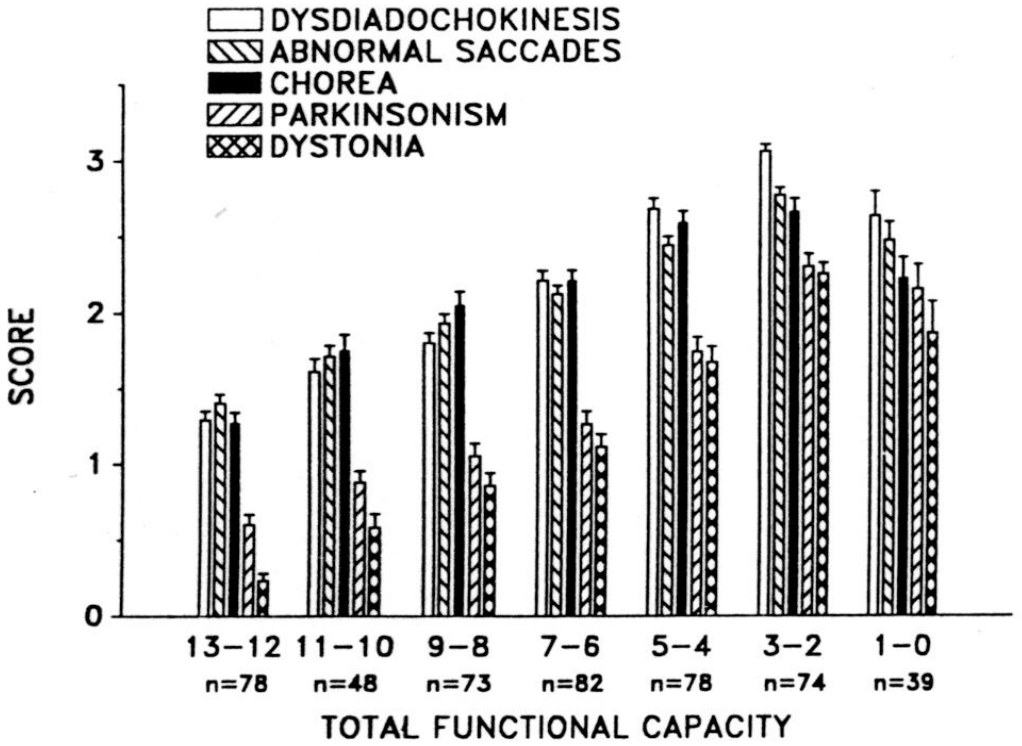


FIG. 2. Profile of motor features according to total functional capacity. Normal ability is 0; severely impaired is 3. The scores for each category of disability were averaged (error bars = SEM). Juvenile cases were excluded from the analysis. The examination of each adult patient from every year they were examined is included in the analysis. The number of patients examined at each functional capacity is indicated below each set of bars.

HD in Venezuela… Movement Disroders v2: pp 93-99, 1990

Earliest motor symptoms in HD Gene Carriers (pre-HD)

- Individuals who carry the gene sometimes will sometimes notice and tell the doctor the following:
  - Dropping objects more often
  - Fine hand coordination is not quite right
  - Decreased dexterity while playing a musical instrument
  - Decreased sense of rhythm
  - Tripping more easily on uneven surfaces
- When the doctor examines them he may notice
  - subtle irregularity (speed and amplitude) in the rhythm of finger taps
  - Irregularity (in speed, timing and amplitude) in the rapid alternating movement task
  - Subtle gait awkwardness

Measurement of motor function in Pre-HD

- Need for objective measurements: Increased subjective complaints of incoordination, tripping or awkwardness in an HD-gene carrier may be simply the tendency for an HD-gene carrier to see every little bit of clumsiness as the first indication of disease appearance.
- In the search for the earliest clinical manifestations of HD, several large observational studies were conducted in HD gene carriers who were near or far from clinical diagnosis
- PREDICT-HD and TRACK-HD were multinational prospective observational studies of HD that examined clinical and biological findings of disease progression in individuals with premanifest HD (preHD) and early-stage HD.

Motor Abnormalities in Pre-manifest HD (PREDICT-HD Study)

- Study was designed to identify clinical and biological markers in premanifest individuals who have undergone predictive genetic testing.
- baseline motor data between gene-expansion carriers (cases) and non gene-expansion carriers (controls) were compared.
- Cases were categorized as near (<9 yrs), mid (9-15yrs) or far (>15 yrs) from diagnosis using a CAG-based formula (far from estimated Dx
- Participants were recruited from 30 sites in the United States, Canada, Australia and Europe

Mov Disord. 2009 September 15; 24(12): 1763–1772.

Results from PREDICT-HD (Motor Function)

- Pre-HD Cases with closer estimated proximity to diagnosis had worse **total motor scores** and **worse scores on the motor domains** than individuals further from estimated diagnosis.
- This was most apparent for total motor scores, the **chorea domain, the bradykinesia domain and the oculomotor domain**.
- These findings are consistent with other reports that suggest chorea and quantitative measures of eye movements may be sensitive in pre-HD.
- finger tapping and tandem gait performance, saccade (quick eye movement) velocity and chorea scores were inversely associated with striatal volume (the greater shrinkage of the striatum, the worse the performance on those items)

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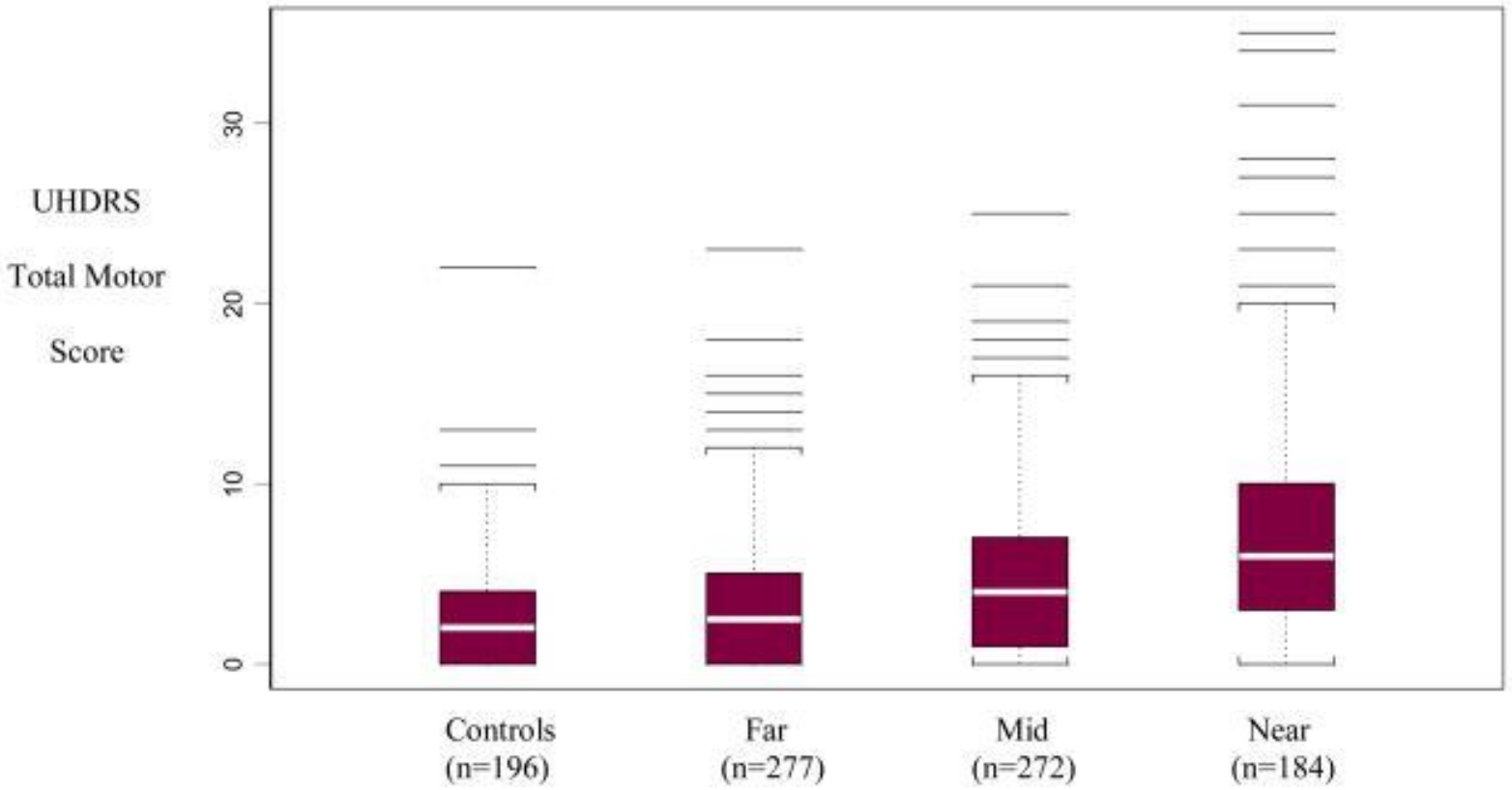
PREDICT-HD Study: Motor Scores organized by Proximity to Diagnosis



Total Motor Scores for Controls and Cases by Proximity to Diagnosis*
*p<0.0001 for trend by proximity to diagnosis; Multiple horizontal lines are outlying individual values. The box represent the 25–75 percentile (“inter-quartile”) range. The white stripe in the middle of each box is the median.

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Relationship of UHDRS Motor Domains* and Probability of Diagnosis and Striatal Volumes in Cases.‡

Variable	Probability of diagnosis		Striatal Volume†	
	Partial R2Ψ (n=732)	p-value	Partial R2Ψ (n=490)	p-value
Oculomotor	0.07	<0.0001	0.09	<0.0001
Bradykinesia	0.14	<0.0001	0.11	<0.0001
Rigidity	0.01	0.05	0.01	0.02
Dystonia	0.02	0.0001	0.02	0.002
Chorea	0.06	<0.0001	0.07	<0.0001

*Groupings based on factors by Marder et al. (2000).(19)

‡Controlling for age and gender in the model.

†Percent of total of intracranial volume.

ΨConsidering variables one at a time controlling for age and gender.

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PREDICT-HD Motor Summary

- Subtle motor abnormalities were present in pre-HD
- These motor abnormalities distinguished were associated with closer proximity to estimated disease diagnosis and greater striatal atrophy.
- These findings suggest that the UHDRS motor examination may be a useful outcome measure in clinical trials aimed at delaying diagnosis

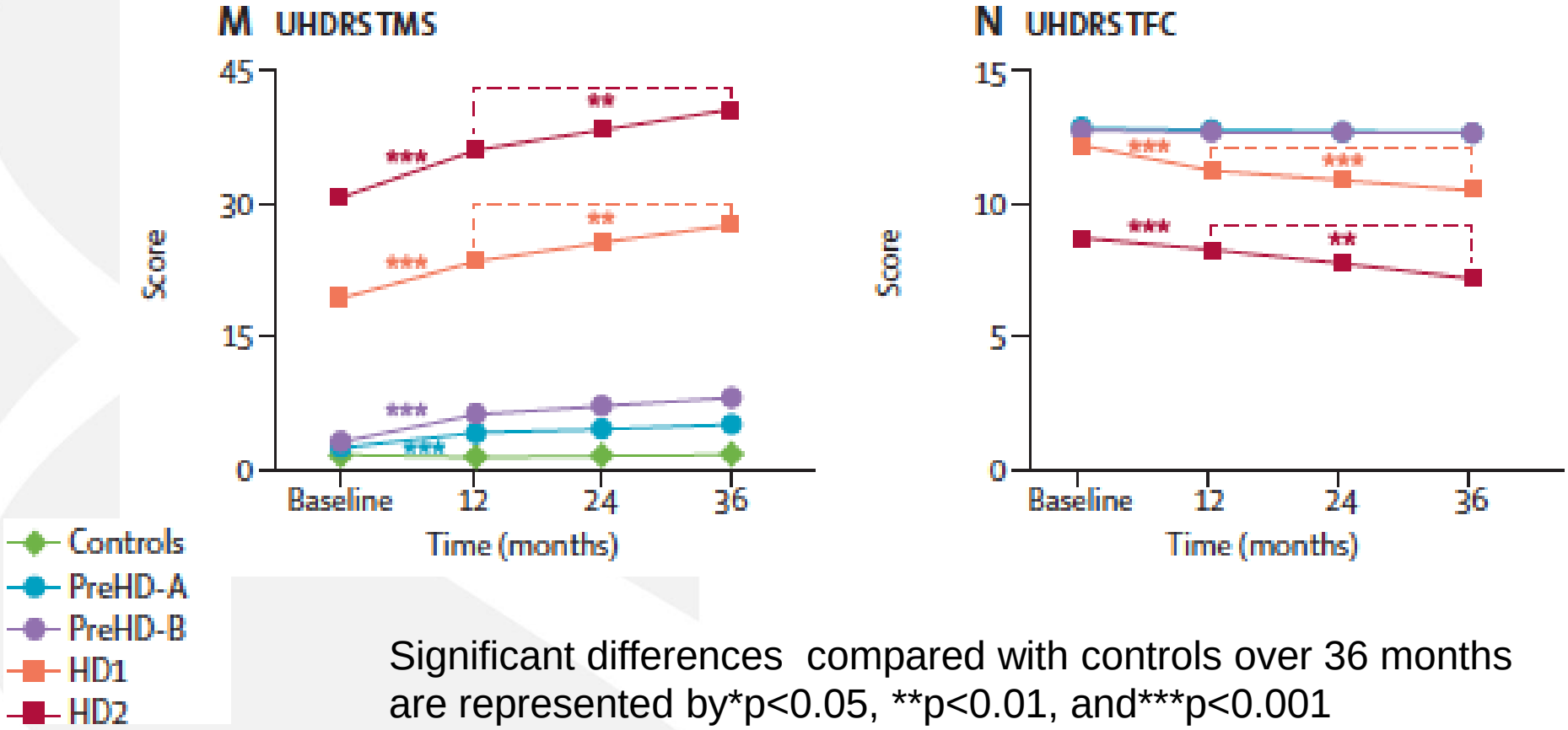
TRACK-HD Study

- Purpose of this observational study was to answer the critical question:
  - ***When should drugs that will delay onset of HD be started?***
- Subjects were recruited from Canada, France, UK, Netherlands
- Participants were thoroughly examined every year for 3 years
- Dozens of measurements were made on each subject that included:
  - Neuroimaging (MRI of brain)
  - Motor symptoms (including high tech eye movement tracking
  - Intellectual (cognitive) function
  - Emotional well being

TRACK-HD Study

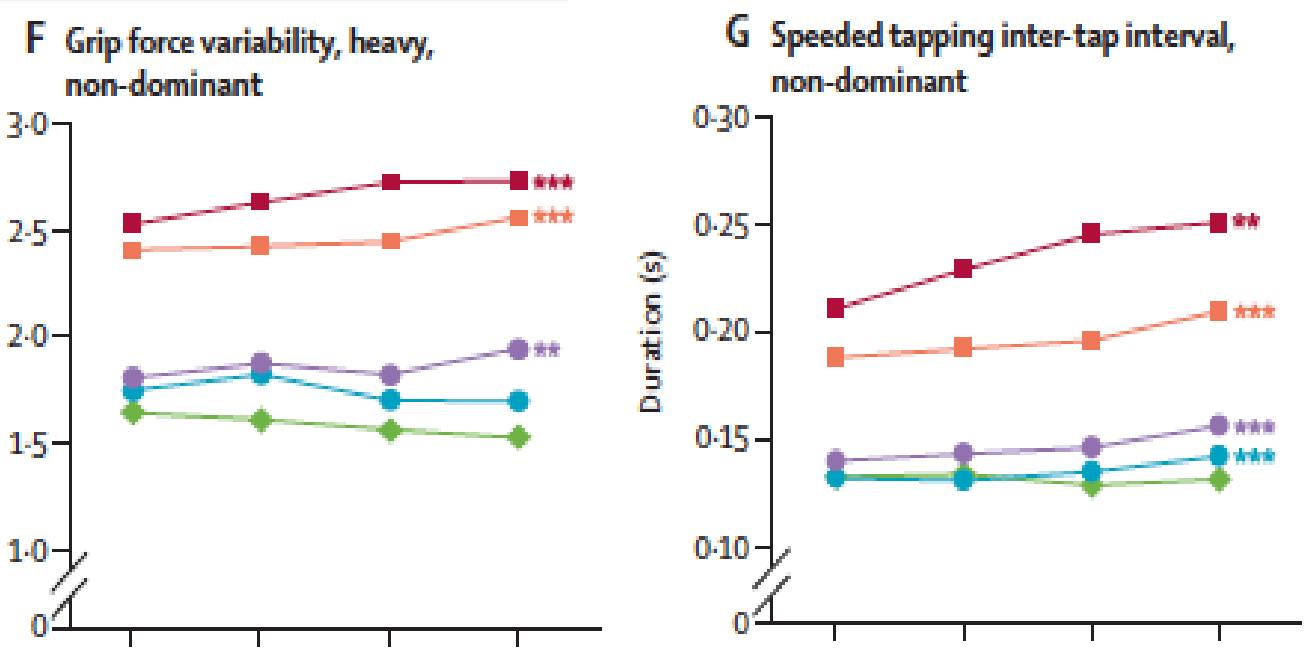
- Subjects without symptoms of HD (but gene carriers) were divided into two groups: those who are estimated to be close to or far from disease onset:
  - Predicting how close subjects were to onset was based on a mathematical calculation
- A group of subjects in the early stages of HD and a control population that didn't carry the gene were also studied
- 366 subjects were enrolled and 298 were able to complete the 36 month followup (those that dropped out of the study were in the more advanced stages of disease)

Changes in Total Motor Score and Total Functional Capacity over 3 years in Pre-HD and Diagnosed HD



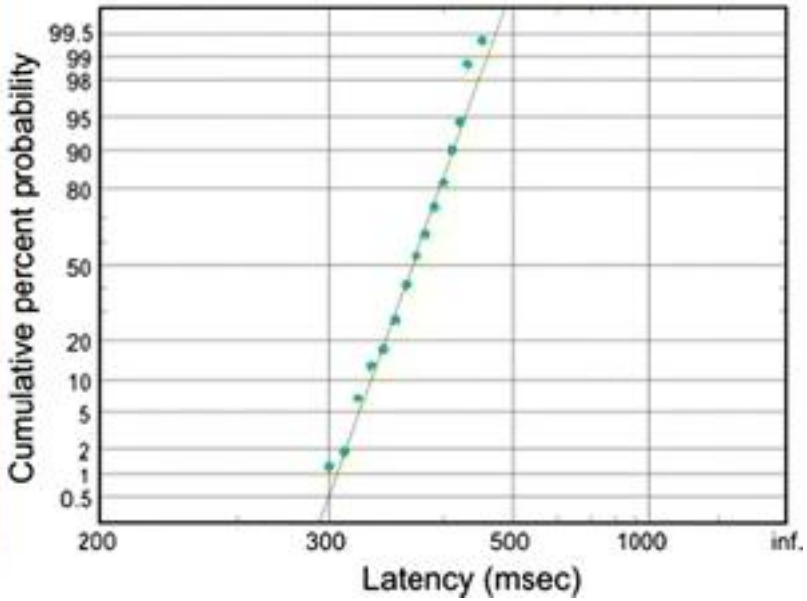
Significant differences compared with controls over 36 months are represented by*p<0.05, **p<0.01, and***p<0.001

TRACK-HD: Quantitative early motor manifestations in pre-HD



The mean length of the speeded tapping inter-tap interval seemed to be a robust measure of progression HD1 and HD2 subjects. This measure was also among the few that showed significant 36-month change, even in pre HD.

Finger tapping (example of device and single case output)



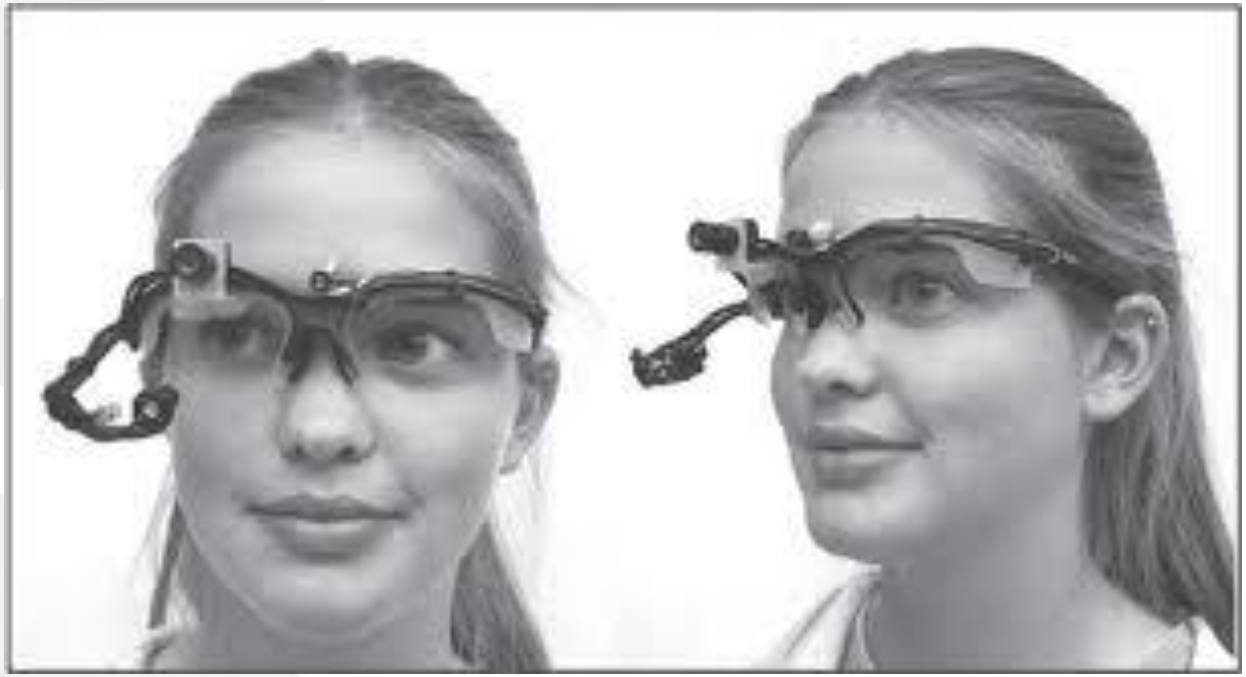
In the TRACK-HD study, the mean inter-tap interval becomes longer over 3 yrs in pre-HD

Eye Movements in Pre-HD and early HD

- Pre-HD (asymptomatic HD gene carriers) and individuals with early HD demonstrated three types of significant abnormalities while performing memory guided and anti-saccade tasks:
  - increased error rate,
  - increased saccade latency and
  - increased variability of saccade latency.
- The eye movement abnormalities increased with advancing motor signs of HD
- Conclusion: Abnormalities in eye movement measures are a sensitive biomarker in pre-HD and early stages of Huntington disease

Blekher et al., Neurology 67: 2006

Apparatus for Quantitative Measurement of Eye Movements



Summary

- Early changes in motor control can be observed and measured in pre-manifest HD in carriers of the HD gene.
- Total motor scores measured in the clinical examination (UHDRS) are increased in pre-HD persons who are estimated to be near diagnosis
- Quantitative measurements are much more sensitive than a clinical diagnosis
  - In a prospective longitudinal study (TRACK-HD), finger tapping (inter-tap interval duration and variability) was one of the best motor indicators of progression along the trajectory from pre-HD to clinically manifest HD.

Thank You for Your Attention

Key Staff at the HDSA Center of Excellence at University of South Florida

Huntington's Disease Society of America

Resources

- HDSA Website: www.hdsa.org
- HD Buzz: www.hdbuzz.net
- HD in Venezuela
  - *Movement Disorders v2: pp 93-99, 1990*
- PREDICT-HD: early motor changes
  - *Mov Disord. 2009 September 15; 24(12): 1763–1772*