Defining Clinical Progression of Juvenile-Onset Huntington's Disease

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Background

Huntington's Disease (HD) is a hereditary neurodegenerative disease caused by elongated trinucleotide (CAG) repeats in the HTT gene. The longer one's CAG repeat, the earlier one manifests the affiliated motor and cognitive dysfunction.

There is no cure to this disease and still very little is known about the exact biological functions of the mutant Huntington protein.

Aim/Objective

At motor-onset diagnosis, an Adult-Onset HD (AOHD) patient presents differently than a Juvenile-Onset (JOHD) individual. This analysis set out to characterize the motor symptom trajectories across groups with HD.

Materials and Methods

- Retrospective analysis utilizing the Enroll-HD database only looking at HD patients with motor manifestation
- Split cohort into 3 groups based on CAG and age of motor-onset to model CAG repeat spectrum
- Followed 0-20 years disease duration, time=0 defined as motor-onset
- Evaluated trajectories of Unified Huntington's Disease Rating Scale (UHDRS) measures
  - **TMS** – sum of all motor scores
  - **Hyperkinesis** – average chorea scores
  - **Hypokinesis** – average dystonia + rigidity + bradykinesia + finger-tapping scores
- Performed non-linear mixed effect regression models to compare motor trajectories between groups
  - Controlled for sex, age, CAG, age*cag interaction, tetrabenazine/antipsychotics medications (affect motor symptoms)

Results

- JOHD has fastest rate of total motor score progression
- Our models suggest the motor trajectories between AOHD, EOHD, and JOHD are statistically significant

The transition point where hypokinetic symptoms predominate is manifested earlier in disease course the higher the CAG expansion

	AOHD (N=5588)	EOHD (N=581)	JOHD (N=66)
Age (years)			
Mean (SD)	55.9 (10.0)	31.9 (4.91)	23.5 (3.98)
Median [Min, Max]	55.0 [31.0, 91.0]	31.0 [22.0, 50.0]	23.0 [18.0, 33.0]
Age of Motor-Onset (years)			
Mean (SD)	50.6 (9.60)	26.9 (2.53)	15.8 (3.62)
Median [Min, Max]	50.0 [31.0, 86.0]	27.0 [22.0, 30.0]	16.0 [5.00, 21.0]
Sex			
Female	2848 (51.0%)	317 (54.6%)	29 (43.9%)
Male	2740 (49.0%)	264 (45.4%)	37 (56.1%)
CAG Repeats			
Mean (SD)	42.3 (1.66)	50.5 (3.41)	64.1 (2.72)
Median [Min, Max]	42.0 [36.0, 45.0]	50.0 [46.0, 65.0]	64.0 [60.0, 70.0]
Antipsychotics Use			
Mean (SD)	0.263 (0.440)	0.265 (0.442)	0.242 (0.432)
Tetrabenazine Use			
Mean (SD)	0.124 (0.330)	0.117 (0.322)	0.106 (0.310)

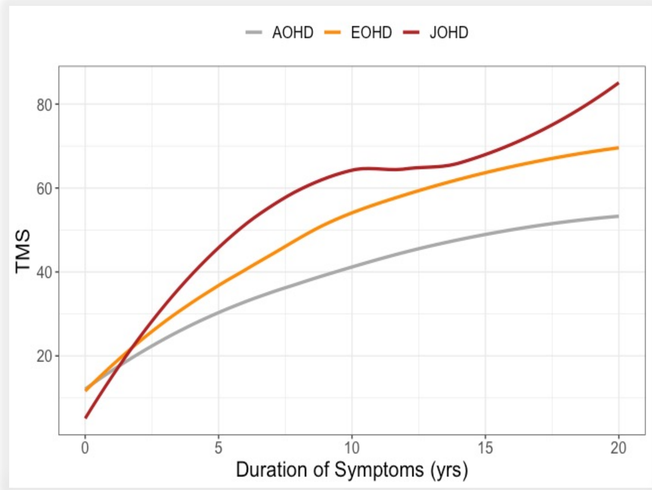
Variable Between Groups	DF, Mean Square	F-value	P-value
TMS	4, 1659	33.9135	< 2.2e-16
Hypokinesis	4, 1.29	15.369	1.616e-12
Hyperkinesis	4, 0.98	5.5432	0.0001875

All HD patients follow a similar progressive motor pattern

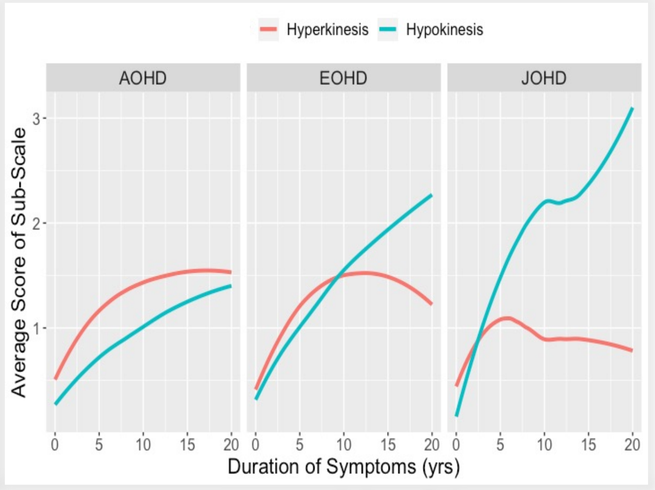
Pre-symptomatic → Hyperkinetic → Hypokinetic

The rate of progression through these stages recapitulates the CAG repeat spectrum which explains the unique motor presentations between groups at motor-onset diagnosis.

Total Motor Score Trajectory Across Groups



Hyper/Hypokinesis Trajectory Within and Across Groups



SCAN ME

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