Longitudinal Analysis of Intermediate CAG_n Repeat Length Expansion in the Prospective Huntington Disease At-Risk Observational Study (PHAROS)

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Background

Recent reports suggest that some individuals at risk for Huntington disease (HD) who carry an intermediate CAGn repeat expansion in the huntingtin gene may develop manifest HD (Mov Disord 2007;22:127). There is limited population data regarding the clinical features and longitudinal course of individuals with intermediate repeat expansions. It remains unclear how to counsel individuals with intermediate repeat expansions about their risk of manifesting HD. PHAROS (*Arch Neurol* 2006; 63:991) aims to identify the earliest and most specific features associated with motor diagnosis of HD in individuals at-risk for HD but unaware of their gene status. PHAROS therefore represents a unique cohort to explore, in an unbiased manner, the clinical phenotype and progression of individuals among those who have an intermediate CAGn repeat expansion.

Objective

To evaluate the clinical phenotype and longitudinal progression of individuals at risk for HD who carry an intermediate CAGn repeat expansion.

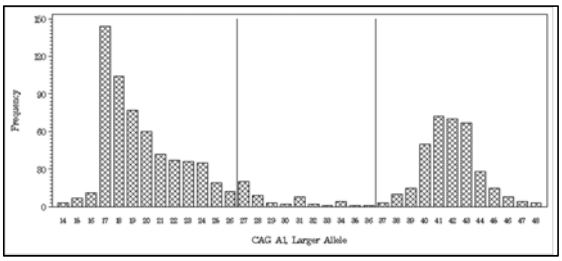
Methods

- 1001 participants at risk for HD but unaware of their gene status were enrolled in PHAROS beginning in 1999; all domains of the UHDRS were completed at baseline and every 9 months.
- All investigators and participants remained unaware of individual gene status.
- All PHAROS participants with available CAGn data and NOT rated as having unequivocal motor features of HD at baseline were included in this analysis (n=983).
- Data were analyzed by CAG expanded (≥37) intermediate (27-36) and non-expanded (≤26).
- A repeated measures analysis adjusted for age and gender measured select motor, cognitive, behavioral, and functional UHDRS assessments at baseline and over time.

Results

Mean follow up 5.6 years (2.7); maximum 10 years.

Distribution of CAG A1 (larger allele), with three grouping categories indicated



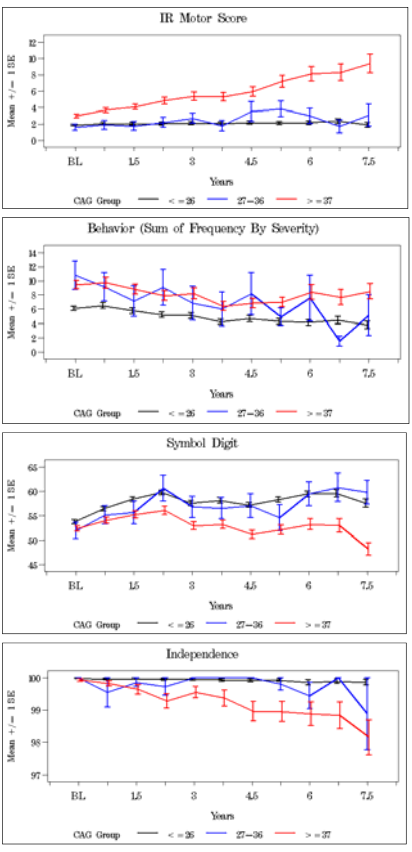
Distribution of subjects by CAGn category by visit

VISIT	CAG ≤ 26	CAG 27-36	CAG ≥ 37
Baseline	587 (59.7%)	51 (5.1%)	345 (35.1%)
2 (9 months)	555	46	320
3 (18 months)	505	40	279
4 (27 months)	473	38	256
5 (36 months)	432	36	233
6 (45 months)	383	25	213
7 (54 months)	372	27	207
8 (63 months)	346	27	195
9 (72 months)	304	28	158
10 (81 months)	245	23	128
11 (90 months)	185	18	110

Diagnostic confidence at baseline by CAGn category

Baseline diagnostic confidence	CAG ≤ 26 (n=587)	CAG 27-36 (n=51)	CAG ≥ 37 (n=345)
0 (normal)	387 (66%)	36 (71%)	180 (52%)
1 (non-specific, <50%)	170 (29%)	14 (27%)	113 (33%)
2 (may be, 50-89%)	24 (4%)	0 (0%)	34 (10%)
3 (likely, 90-98%)	5 (1%)	1 (2%)	18 (5%)

Longitudinal UHDRS change by CAGn expansion category



Conclusions

- Individuals in a cohort at risk for HD who had intermediate CAGn expansions (27-36) behave similarly over time compared with those without the expansion; however, they have behavioral symptoms similar to individuals with expanded CAGn
- Shorter expansions than traditionally considered pathologic may influence the behavioral phenotype in HD
- Confirmation in larger cohorts, possibly using different groupings (≤26, 27-35, 36-39, and ≥40), and over longer periods of time may be necessary to determine the effect of intermediate expansions on clinical phenotypes and the risk of developing manifest disease in this population.

References

•Kenney C, et al. *Mov Disord*. 2007;22:127-130. The Huntington Study Group PHAROS Investigators.*Arch Neurol*. 2006;63:991-998.