Clinical Phenotype in Carriers of Intermediate Alleles in the Huntingtin Gene

Daniel Savitt, DO and Joseph Jankovic, MD
Baylor College of Medicine

Background

Huntington disease (HD) is caused by a mutation in the *HTT* gene consisting of ≥40 CAG trinucleotide repeats. Since our original case report of pathologically proven HD with 29 CAG repeats[1], a growing body of evidence has accumulated supporting the observation that individuals with intermediate alleles (IA) (27-35 CAG repeats) may exhibit clinical, imaging, and pathologic features of HD. About 6% of the general population has CAG repeats in the IA range in at least one allele of the *HTT* gene[2]. The presence of IA is a challenge for genetic counseling.

Objectives

To describe the phenotype of individuals with IA CAG repeat length in the *huntingtin* (*HTT*) gene seen at the Parkinson's Disease Center and Movement Disorders Clinic at Baylor College of Medicine.

Methods

Medical records of patients with IAs seen at the PDCMDC at BCM from January 2008 to the present were reviewed to assess age at symptom onset, dominant clinical features and presence of psychiatric and cognitive symptoms.

Table

Case	Gender	Age at Symptom Onset, y	Dominant Movement Disorder(s)	Cognitive/Behavioral Symptoms	CAG Repeats
1	M	Late 40s	▪ Chorea of face and hands that progressed to generalized chorea (face, trunk, and limbs) with a dystonic component affecting the face ▪ Wide-based dancing gait ▪ Mild dysarthria ▪ Motor tics comprised of sniffing, throat-clearing, and coughing	▪ Paranoid delusions ▪ Visual hallucinations ▪ Irrational behavior and irritability	30/17
2	F	40	▪ Leg tapping stereotypies ▪ "Pill-rolling" stereotypies ▪ Essential tremor	▪ Anxiety	29/17
3	F	34	▪ Psychogenic tremor ▪ Psychogenic dystonia ▪ Mild chorea of face and hands	▪ Bipolar disorder ▪ Anxiety ▪ ADD	29/17
4	F	35	▪ Psychogenic paroxysmal dystonia ▪ Psychogenic Parkinsonism	▪ Depression	29/17
5	F	45	▪ Chorea of face then limbs ▪ Gait disturbance with occasional falls ▪ Stereotypies including finger rubbing and toe tapping	▪ Depression ▪ Irritability ▪ Difficulty with concentration	29/17
6	M	78	▪ Progressive chorea of arms and legs ▪ Dysarthria	▪ Irritability ▪ Behavioral change ▪ MoCA 25/30	32/29
7	M	37	▪ Chorea in the legs that progressed to head, trunk, and arms	▪ Anxiety ▪ Panic attacks ▪ Short-term memory impairment	27/19
8[1]	M	60	▪ Mild generalized chorea ▪ Intermittent frontalis contraction ▪ Shuffling gait	▪ Depression ▪ Cognitive impairment	29/20

Results

Four men and four women were found to have IAs (range: 27-32) in the course of their evaluation at the PDCMDC. The age at onset of clinically evident symptoms ranged from 27 to 78 years. Six individuals had chorea, three had gait disturbances, two had stereotypies, and one had multiple motor tics. All eight had psychiatric symptoms, with depression being the most common.

Conclusions

Our series of eight individuals with IA in the *HTT* gene exhibit a variety of motor and non-motor features that overlap with the HD phenotype. These individuals and their offspring should be considered at risk for development of progressive HD.

References

1. Kenney C, Powell S, Jankovic J. Autopsy-proven Huntington's disease with 29 trinucleotide repeats. *Mov Disord*. 2007;22(1):127-30.
2. Kay C, Collins JA, Wright GEB, et al. The molecular epidemiology of Huntington disease is related to intermediate allele frequency and haplotype in the general population. *Am J Med Genet B Neuropsychiatr Genet*. 2018;177(3):346-57.

Disclosures

The authors do not have anything to disclose.

Download poster