

# Huntington Disease (HD)

## FOR DIAGNOSTIC OR PRESYMPTOMATIC TESTING IN ADULTS

### Disease Overview

- HD is an inherited, progressive, neurodegenerative disorder characterized by cognitive, motor, and psychiatric disturbances.
    - Early signs of HD include irritability, depressed mood, difficulty in mental planning, subtle coordination changes, mild memory loss, and small involuntary movements.
    - Disease progression involves worsening chorea, difficulty walking, dysarthria and dysphagia, cognitive decline, aggressive behavior, and social disinhibition.
    - During late-stage disease, individuals have severe motor and cognitive disability, and are mute, incontinent, and totally dependent on others.
  - Onset typically occurs between 35 and 44 years of age, but can range from 18 months through the ninth decade of life. Median survival after disease onset is 15–20 years.
  - Juvenile onset (before 21 years of age) represents about 5 percent of cases and is characterized by clumsiness, hyperreflexia, oculomotor disturbances, falls, rigidity, mental deterioration, speech and language delay, epilepsy, and rapid decline.
  - There is currently no cure or treatment to slow disease progression; however, effective treatments for suppressing psychiatric disturbances, rigidity, and chorea are available.
  - Suicide and suicide ideation are common in individuals with HD. Critical periods for suicide include just prior to receiving a diagnosis and when disease symptoms begin to compromise independence.
  - Significant psychological risks may be associated with learning one's genetic status for HD, and informed consent must be obtained prior to testing. Predictive HD testing protocols should include neurological and psychological examinations with pre- and post-test genetic counseling.
  - The Huntington Disease Society of America (HDSA) recommends against testing asymptomatic minors.
- Reduced penetrance: 36–39 CAG repeats; at risk for developing symptoms of HD; offspring also at risk for HD.
  - Full penetrance:  $\geq 40$  CAG repeats; disease-causing; offspring at 50 percent risk for developing HD.
- Higher numbers of CAG repeats are associated with earlier disease onset; however, it is not possible to predict the specific age at onset, severity, and rate of disease progression from the number of CAG repeats.
  - Most individuals with HD have an affected parent; apparent de novo cases may be explained by the following:
    - Death of a parent before symptom onset.
    - Unrecognized diagnosis in family member.
    - Intermediate, reduced penetrance allele resulting in absent or late-onset symptoms in a parent.
    - Non-paternity.
  - Allele sizes may increase during paternal transmission, and anticipation (earlier age of onset in successive generations) is often observed in families.

### Indications for Ordering

- Diagnostic confirmation in a symptomatic individual.
- Presymptomatic testing for adults with a family history of HD.

### Contraindications

- Prenatal testing.
- Testing for minors; ARUP no longer tests minors whether or not they are symptomatic.

### Additional Ordering Notes

- Informed consent is required prior to diagnostic or presymptomatic testing. An HD Consent Form is available at [www.aruplab.com/genetics/resources/consent](http://www.aruplab.com/genetics/resources/consent).
- If there is a positive family history of HD, please provide information on the relationship of the proband to the individual being tested and the number of CAG repeats in the affected relative, if known.
- Presymptomatic individuals are strongly urged to be tested through a counseling program approved by the Huntington Disease Society of America, (800) 345-4372, [www.hdsa.org](http://www.hdsa.org).

### Interpretation

- Negative: Detection of two normal alleles; individual is not at risk for developing or transmitting HD.
- Mutable (intermediate): Detection of one normal and one mutable allele; individual is not at risk for developing HD but may have offspring with an allele in the disease-causing range.
- Reduced penetrance: Detection of one normal allele and one reduced penetrance allele; individual may or may not develop disease symptoms; offspring are at risk for inheriting a disease-causing allele.

### Epidemiology

Prevalence: one in 15,000 in Western European populations; less frequent in Japanese, Chinese, Finnish, and African individuals.

### Genetics

- Autosomal dominant.
- Greater than 99 percent of cases result from an expanded number of CAG repeats in exon 1 of the HD (*HTT*) gene.
- The encoded protein, huntingtin, is expressed in neural and non-neural tissues; however, mutant protein is suspected to cause localized neuronal loss in the caudate and putamen.
- Allele sizes are classified by the number of CAG repeats.
  - Normal:  $\leq 26$  CAG repeats; not at risk for developing or transmitting HD.
  - Mutable normal: 27–35 CAG repeats; unaffected, but males have a 2.5 percent risk for CAG expansion in offspring to disease-causing range. Approximately 1–2 percent of the general population carries an allele of this size.

- Full penetrance: Detection of one or two disease-causing alleles; individual is predicted to develop HD, and offspring have a 50 percent chance of inheriting the disease allele. There is no difference in age of onset, disease symptoms, or progression in individuals with one or two fully penetrant alleles.
- Mosaicism may be detected; however, the level is typically not significant to compromise interpretation of disease status.

### Methodology

- Polymerase chain reaction (PCR) using fluorescence-labeled chimeric primers followed by gel electrophoresis to detect CAG repeat length.
- To confirm apparent homozygosity for a normal allele detected by PCR, Southern blot analysis may be performed as reflex testing.
- Clinical sensitivity and specificity are 99 percent.
- Analytical sensitivity and specificity are 99 percent.

### Limitations

- Huntington gene mutations, other than CAG expansions, will not be detected by this assay.
- Neurodegenerative conditions unrelated to HD will not be detected.

### References

1. Huntington Disease Society of America. [www.hdsa.org](http://www.hdsa.org) (accessed on August 10, 2009).
2. Online GeneTests: Huntington Disease. [www.genetests.org](http://www.genetests.org) (accessed on August 10, 2009).
3. Potter NT, et al. Technical standards and guidelines for Huntington disease testing. *Genet Med* 2004;6(1):61–5.
4. Langbehn DR, et al. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin Genet* 2004;65:267–77.

## Test Information

**0040018**

### Huntington Disease (HD) Mutation with Reflex to Southern Blot

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

### AUTHORS

Elaine Lyon, PhD

Chris Miller, MS, LCGC