

# Huntington Disease

## Indications for Ordering

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- Diagnostic confirmation in a symptomatic individual
- Presymptomatic testing for adults with a family history of Huntington disease (HD)
  - Presymptomatic individuals are strongly urged to be tested through a counseling program approved by the [Huntington Disease Society of America](http://hdsa.org/) (hdsa.org/)

## Test Description

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Chimeric PCR followed by capillary electrophoresis to detect CAG repeat length

## Tests to Consider

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### [Huntington Disease \(HD\) Mutation by PCR 0040018](#)

- Informed consent is required for testing
  - See [ARUP Genetics Consent Forms](http://aruplab.com/genetics/resources/consent) (aruplab.com/genetics/resources/consent)
- Testing of minors (<18 years of age) is not available at ARUP

## Disease Overview

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### Age of onset

- Typically 35-44 years of age
  - May range from 18 months through the ninth decade of life
- Juvenile onset (<21 years of age) – 5% of cases

### Symptoms

- Progressive neurodegenerative disorder characterized by cognitive, motor, and psychiatric disturbances
  - Early signs – irritability, depressed mood, difficulty in mental planning, subtle coordination changes, mild memory loss, small involuntary movements
  - Disease progression includes worsening chorea, difficulty walking, dysarthria and dysphagia, cognitive decline, aggressive behavior, social disinhibition
  - Late-stage disease – severe motor and cognitive disabilities, total dependence on others
  - Juvenile onset – clumsiness, hyperreflexia, oculomotor disturbances, falls, rigidity, mental deterioration, epilepsy, rapid decline
- Median survival after disease onset – 15-20 years

## Treatment

- Currently, no cure or treatment slows disease progression
- Treatments are available for suppressing psychiatric disturbances, rigidity, and chorea

## Diagnostic issues

- Suicide and suicide ideation are common in individuals with HD, especially just prior to receiving a formal diagnosis and later when disease symptoms begin to compromise independence
- Due to significant psychological risks associated with learning one's genetic status for HD, informed consent must be obtained prior to testing
- Predictive HD testing protocols should include neurological and psychological examinations with pre- and posttest genetic counseling
- The Huntington Disease Society of America recommends against testing asymptomatic minors

## Genetics

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### Gene – *HTT*

### Inheritance

- Autosomal dominant
- Exhibits paternal expansion and anticipation
  - Allele sizes may increase from father to offspring
  - Earlier age of onset in successive generations is often observed
- Rare apparent de novo cases may be explained by
  - Death of a parent before symptom onset
  - Unrecognized diagnosis in family member
  - Intermediate, reduced penetrance allele resulting in absent or late-onset symptoms in family member
  - Nonpaternity

### Structure/function

- The encoded protein, huntingtin, is expressed in neural and nonneural tissues
  - Mutant protein is suspected to cause localized neuronal loss in the caudate and putamen

## Pathogenic variants

- Expansion of the polyglutamine tract (CAG repeat expansion) causes 99% of cases
- Allele sizes are classified by the number of CAG repeats
  - Normal
    - ≤26 CAG repeats
    - Individual not at risk for developing or transmitting HD
  - Mutable normal
    - 27-35 CAG repeats
    - Individual unaffected, but males have a 2.5% risk of having offspring with CAG expansion in disease-causing range
    - Approximately 1-2% of the general population carries an allele of this size
- Reduced penetrance
  - 36-39 CAG repeats
  - May or may not develop HD symptoms
  - Offspring also at risk for HD
- Full penetrance
  - ≥40 CAG repeats
  - Disease causing
  - Offspring at 50% risk for developing HD
- Higher numbers of CAG repeats are associated with earlier disease onset but not possible to predict specific age of onset, severity, and rate of disease progression from number of CAG repeats

## Test Interpretation

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### Sensitivity/specificity

- Clinical sensitivity/specificity – 99%
- Analytical sensitivity – 99%

## Results

- Negative – 2 normal alleles detected
  - Individual is not at risk for developing or transmitting HD
- Mutable (intermediate) – 1 normal and 1 mutable allele detected
  - Individual is not at risk for developing HD
  - CAG repeats may expand in transmission to offspring
- Reduced penetrance – 1 normal allele and 1 reduced penetrance allele detected
  - Individual may or may not develop disease symptoms
  - Offspring are at risk for inheriting a disease-causing allele
- Full penetrance – 1 or 2 disease-causing alleles detected
  - Individual is predicted to develop HD
  - Offspring have a 50% chance of inheriting the disease allele
  - No difference in age of onset, disease symptoms, or progression in individuals with 1 or 2 fully penetrant alleles
- Mosaicism may be detected; however, the level is typically not significant to compromise interpretation of disease status

## Limitations

- Rarely, Southern blot analysis is needed to accurately size large CAG expansions (generally >80 CAG repeats)
- Neurodegenerative conditions unrelated to HD will not be detected
- Rare, previously unreported variants may interfere with PCR amplification

## References

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- Kremer B, Goldberg P, et al. A worldwide study of the Huntington's disease mutation: the sensitivity and specificity of measuring CAG repeats. *New Eng. J. Med.* 1994; 330: 1401-1406
- Wild EJ, Tabrizi SJ. Huntington's disease phenocopy syndromes. *Curr Opin Neurol.* 2007;20(6):681-687