Huntington Disease

Huntington disease (HD) is a progressive neurodegenerative disorder characterized by uncontrolled movements (Huntington chorea), cognitive decline, and psychiatric disturbances. The majority of affected individuals have adult-onset disease with the first symptoms beginning between 30 and 50 years of age. Juvenile HD is more rare, in which symptoms begin in childhood or adolescence. Both forms of HD are caused by expansion of a trinucleotide CAG repeat in the *HTT* gene. This condition is inherited in an autosomal dominant manner, and the size of the CAG repeat may expand when transmitted from parent to child.

Tests to Consider

Huntington Disease (HD) Mutation by PCR
0040018

Method: Polymerase Chain Reaction/Fragment Analysis

- Informed consent is required for testing
  - See ARUP Genetics Consent Forms
- Testing of minors (<18 years of age) is not available at ARUP

Indications for Ordering

- Diagnostic confirmation in a symptomatic individual
- Presymptomatic testing for adults with a family history of HD
- Presymptomatic individuals are strongly urged to be tested through a counseling program approved by the Huntington Disease Society of America

Disease Overview

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 Considerations

- 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

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
  - Intermediate (mutable normal) allele
    - 27-35 CAG repeats
    - Individual unaffected, but males have an increased 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 allele
  - 36-39 CAG repeats
  - May or may not develop HD symptoms
  - Offspring also at risk for HD
- Full penetrance allele
  - ≥40 CAG repeats
  - Disease causing
  - Offspring at 50% risk for developing HD
- Higher numbers of CAG repeats are associated with earlier disease onset, but it is not possible to predict specific age of onset, severity, and rate of disease progression from the number of CAG repeats

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity/specificity: 99%
- Analytical sensitivity: 99%
  - Repeat sizing precision is +/- 2 for alleles ≤50 repeats, +/- 3 for alleles with 51 to 75 repeats, and +/- 4 for alleles greater than 75 repeats

Results

- Negative: two normal alleles detected
  - Individual is not at risk for developing or transmitting HD
- Intermediate (mutable normal): one normal and one intermediate allele detected
  - Individual is not at risk for developing HD
  - CAG repeats may expand in transmission to offspring
- Reduced penetrance: one normal allele and one reduced penetrance allele detected
  - Individual may or may not develop disease symptoms
  - Offspring are at risk for inheriting a disease-causing allele
- Affected (full penetrance): one or two 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

- Other neurodegenerative disorders will not be detected.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.

Additional Resources

Huntington's Disease Society of America (HDSA). [Accessed: Dec 2019]

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ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
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