Huntington Disease (HD) CAG Repeat Expansion

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Huntington disease (HD) is a progressive neurodegenerative disorder characterized by uncontrolled movements (Huntington chorea), cognitive decline, and psychiatric disturbances.[1] The majority of affected individuals have adult-onset disease.[1] Juvenile HD, in which symptoms begin in childhood or adolescence, is less common.[1] Both forms of HD are caused by expansion of a trinucleotide CAG repeat in the *HTT* gene.[1] This condition is inherited in an autosomal dominant manner, and the size of the CAG repeat may expand when transmitted from parent to child.[1]

Featured ARUP Testing

Huntington Disease (HD) CAG Repeat Expansion 3016908

Method: Polymerase Chain Reaction (PCR) / Capillary Electrophoresis

- Use to confirm the diagnosis of HD in symptomatic individuals.
- Use for presymptomatic testing in adults with a family history of HD.
  - Testing through a counseling program approved by the Huntington Disease Society of America is strongly encouraged for presymptomatic individuals.
- Informed consent is required for testing.
  - Required form: Informed Consent for Huntington Disease (HD) DNA Testing
- Testing is not available at ARUP for individuals <18 years of age.

Huntington Disease (HD) CAG Repeat Expansion, Fetal 3019937

Method: Polymerase Chain Reaction (PCR) / Capillary Electrophoresis / Fragment Analysis

- Use for prenatal diagnostic HD testing.
- Documentation of a full penetrance HD-causing allele in a biological parent is required.
- Informed consent is required for testing.
  - Required form: Informed Consent for Huntington Disease (HD) DNA Testing
- Fetal HD testing will not be performed without prior approval; please contact an ARUP genetic counselor at 800-242-2787 ext. 2141.

Disease Overview

Age of Onset

- Typically 35-44 years of age[1]
  - Onset after 50 years of age: approximately 25% of cases
  - Juvenile onset (<20 years of age): 5-10% of cases

Symptoms

- Progressive neurodegenerative disorder characterized by cognitive, motor, and psychiatric disturbances[1]
  - Early stage: coordination changes, delusions or hallucinations, irritability, loss of inhibition, loss of sense of smell, mood changes (anxiety, apathy, depression), small involuntary movements (e.g., eye movements)
  - Middle stage: continued cognitive decline, difficulty walking, dysarthria, dysphagia, weakness, weight loss, worsening chorea
  - Late stage: severe motor and cognitive disabilities, total dependence on others
  - Juvenile onset: similar but more severe and rapidly progressing cognitive, motor, and psychiatric changes; epilepsy may be present
- Median survival after disease onset: 15-18 years[1]

Treatment

- Currently, no cure or treatment slows disease progression.
- Treatments are available for suppressing chorea, psychiatric disturbances, and rigidity.[1]

Diagnostic Considerations

- Suicide and suicidal ideation are common in individuals with HD, especially just before receiving a formal diagnosis and later when disease symptoms begin to compromise independence.[1]
- 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.[2]

Genetics

Gene/Variant

HTT; expansion of the CAG polyglutamine tract (CAG repeat expansion)

Inheritance

- Autosomal dominant[1]
- Exhibits paternal expansion and anticipation[1]
  - 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[1]
  - Nonpaternity or nonmaternity[1]

Test Interpretation

Methodology

Triplet repeat-primed polymerase chain reaction (PCR) followed by size analysis using capillary electrophoresis

Sensitivity/Specificity

- Clinical sensitivity/specificity: 99%
- Analytic sensitivity: 99%
  - Repeat sizing precision is +/- 2 for alleles <50 repeats, +/- 3 for alleles with 50 to 75 repeats, and +/- 4 for alleles >75 repeats.[3]
- Mosaicism may be detected; however, the level of mosaicism is typically not enough to compromise interpretation of disease status.

Results

Huntington Disease (HD) Mutation by PCR Results Interpretation		
Allele Type	**Number of CAG Repeats**	**Clinical Significance**
Normal	≤26	Not at risk for developing or transmitting HD
Intermediate (mutable normal)	27-35	Not at risk for developing HD Males have increased risk of having offspring with CAG expansion in disease-causing range
Reduced penetrance	36-39	At risk for HD, but may not develop symptoms Offspring at risk for developing HD
Full penetrance	≥40	Causes HD, assuming normal life span Offspring at 50% risk for developing HD Juvenile onset HD typically associated with CAG repeat sizes >60

- 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 for full penetrance or reduced penetrance alleles.

Limitations

- Other neurodegenerative disorders will not be detected.
- Only the *HTT* CAG repeat expansion will be interrogated.
- 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.
- Prenatal specimens with maternal cell contamination may give false-negative or false-positive results.

References

1. Caron NS, Wright GEB, Hayden MR. Huntington disease. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews*. University of Washington, Seattle. Updated Jun 2020; accessed Jul 2023.

2. Huntington's Disease Society of America (HDSA). Accessed Jul 2023.

3. Bean L, Bayrak-Toydemir P. American College of Medical Genetics and Genomics Standards and Guidelines for Clinical Genetics Laboratories, 2014 edition: technical standards and guidelines for Huntington disease. *Genet Med*. 2014;16(12):e2.

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