Test Specific Guidelines

Huntington Disease

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Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure addressed by this guideline	Procedure code
HTT Gene Analysis; evaluation to detect abnormal (eg, expanded) alleles	81271
HTT Gene Analysis; characterization of alleles (eg expanded size)	81274

What Is Huntington Disease?

Definition

Huntington disease (HD) is a neurodegenerative disorder causing progressive cognitive, motor, and psychiatric disturbances.[1]

Prevalence

The prevalence of HD ranges from 9.71 to 17 per 100,000 people in populations of European descent.[1]

It is less frequent in individuals of Chinese, Japanese, Korean, Finnish or indigenous South African descent. The prevalence of HD is believed to be highest in individuals living in the Lake Maracaibo region of Venezuela.[1]

Symptoms

HD is characterized by choreic movements, cognitive decline, and psychiatric issues.[2]

The mean age of onset of symptoms is 35-44 years of age.[1] 1 Approximately 5-10% of individuals with HD have onset of symptoms before 20 years of age.[1] This is known as juvenile HD. Juvenile HD most commonly results from paternally inherited HD mutations with larger CAG repeats.

Cause

HD is caused by expansion of a CAG trinucelotide repeat mutation in the HTT gene. This expansion causes the resulting protein to fold incorrectly.[2] The number of CAG repeats is typically associated with the severity of disease

When a person has this number of CAG repeats ...	Then the person ...
26 or fewer	is unaffected.
27 to 35	is in the intermediate range and is typically not affected with HD. However, any offspring are at risk for HD. The CAG repeat number can expand over generations due to instability with unknown probability.[1,3]
36 to 39	is at risk for HD but may not develop symptoms.[1]
40 or more	will develop HD symptoms.[1]

Inheritance

HD is an autosomal dominant condition.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Typically, as the disease passes through generations:

severity of HD symptoms increases, and

age of onset decreases.

This is seen more often when inherited through a male. This phenomenon is known as anticipation.[1]

Diagnosis

HD should be suspected in individuals with the following presentations:[1]

"Progressive motor disability featuring chorea. Voluntary movement may also be affected."

"Mental disturbances including cognitive decline, changes in personality, and/or depression"

"Family history consistent with autosomal dominant inheritance".

Diagnosis of HD is established by a combination of clinical assessment of molecular testing.[1] CAG repeat analysis has a mutation detection rate greater than 99%, but detection of the expansion is not currently possible by sequence-based technologies.[1]

Symptomatic HD testing is appropriate for individuals who have a known or suspected diagnosis of HD based on clinical symptoms.[3]

Predictive HD testing is appropriate for adults who have a known family history of HD, and wish to know their HD mutation status. Predictive testing should be performed in the context of thorough counseling (described below in Guidelines/Evidence).[3-5] Predictive HD testing is generally not recommended for minors or for testing of pregnancies.[3-9] Guidelines for Preimplantation Genetic Diagnosis (PGD) for testing of future pregnancies have been published (See *Preimplantation Genetic Screening and Diagnosis* guideline for medical necessity guidance).[1,3,4] Predictive testing for HD cannot accurately predict progression of behavioral symptoms.[1] However, an estimate of age of onset is possible based on the number of CAG repeats detected.[10] Additionally, the number of CAG repeats may be helpful to predict age of death (but not the duration of symptoms) and the rate of cognitive, motor, and functional decline.[11,12]

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Management

There is no cure for HD. Some pharmacologic treatments may be effective in decreasing some of the associated symptoms, such as chorea, rigidity and psychiatric disturbances.[1]

Survival

Median survival time is 15-18 years after onset.[1]

Test Information

Introduction

Testing for HD may include CAG trinucleotide repeat testing.

Trinucleotide Repeat Testing

Repeat expansion genetic testing allows for the determination of the size of a repeated DNA sequence. This testing may involve more than one test methodology. Smaller repeat expansions are typically identified using certain types of polymerase chain reaction (PCR), while larger expansions may require Southern blot. More comprehensive repeat expansion testing that utilizes next generation sequencing and exome sequencing methods is under development.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Huntington disease testing.

American College of Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2020) technical standard and guideline for Huntington disease stated:[2,13]

"CAG repeat expansion mutations account for >99% of cases of HD. Therefore, tests that effectively detect and measure the CAG repeat region of the HTT gene are >99% sensitive."

"The absence of HD pathology has not been documented in any individual with an HD allele size of ≥40 CAG repeats who died, disease free, after living up to or past the normal life expectancy. Therefore, positive results (at least one allele of 40 CAG repeats or more) are 100% specific. Allele sizes of 26 CAG repeats or less have never been associated with an HD phenotype in the US survey or in any published study."

"Detection of CAG expansion is used for both confirmatory and predictive testing. Positive results for both confirmatory and predictive testing are considered diagnostic."

"It is strongly suggested that predictive testing not be offered to individuals until they are at least 18 years old. A formal multidisciplinary predictive testing protocol is offered at many sites for individuals desiring determination of their carrier status."

United States Huntington's Disease Genetic Testing Group

The United States Huntington's Disease Genetic Testing Group (2016)[4] has guidelines regarding genetic testing for Huntington disease.

Symptomatic testing

"Confirmatory testing by analysis of the HD gene [HTT] is offered at or after the time of the clinical diagnosis of HD. The presence of a CAG repeat expansion in a person with HD symptoms confirms the clinical impression and supports a diagnosis of HD."

Predictive testing

Asymptomatic (predictive) testing is supported in the context of a predictive testing protocol that includes

optional neurological exam

mental health assessment,

pre- and post-test counseling regarding implications of positive and negative test results, and

documented informed consent.

Predictive Testing Protocol Support

The predictive testing protocol is also supported by guidelines from

the International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea (1994),[5]

the American Society of Human Genetics,[9]

the American College of Medical Genetics and Genomics,[6] and

the National Society of Genetic Counselors.[6]

Criteria

Introduction

Requests for Huntington disease testing are reviewed using these criteria.

Criteria

Clinical Consultation:

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Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), and

Examination by a geneticist or physician familiar with genetic movement disorders, AND

Previous Genetic Testing:

No previous genetic testing of HTT, AND

Diagnostic Testing for Symptomatic Individuals:

For individuals 18 years of age or older, at least 2 of the following must be present:

Progressive motor disability featuring involuntary movements (chorea) and gait disturbance, and/or

Behavioral disturbances including:

Personality change

Depression

Cognitive decline, and/or

Family history of Huntington disease, OR

For individuals 17 years of age or younger, at least 2 of the following must be present:

Progressive motor disability featuring involuntary movements (chorea) and gait disturbance, and/or

Cognitive decline, and/or

Stiffness or rigidity, and/or

Epilepsy/myoclonus and tremor, and/or

Family history of Huntington disease, OR

Predictive Testing for Presymptomatic/Asymptomatic At-Risk Individuals:

For individuals 18 years of age or older:

Known CAG trinucleotide repeat expansion in HTT in 1st, 2nd, or 3rd degree biologic relative, or

One or more 1st degree biologic relative(s) with clinical diagnosis of HD and mutation unknown/not yet tested, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

References

Introduction

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