

Test Specific Guidelines

Dentatorubral-Pallidoluysian Atrophy **Genetic Testing**

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Introduction

Dentatorubral-pallidoluysian atrophy genetic testing is addressed by this guideline.

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.

<u>Procedure addressed by this guideline</u>	<u>Procedure code</u>
<u>ATN1 Expansion Analysis</u>	<u>81177</u>

What Is Dentatorubral-Pallidoluysian Atrophy?

Definition

Dentatorubral-pallidoluysian atrophy (DRPLA) is a progressive neurologic disorder. DRPLA is also known as Naito-Oyanagi Disease; Haw River Syndrome;¹ Myoclonic Epilepsy with Chorea, Chorea, Seizures, and Dementia; and Dentatorubropallidoluysian atrophy.²

Incidence

Although initially thought to be a disorder of the Japanese population, DRPLA has been diagnosed in people from a variety of other ethnic backgrounds.³ DRPLA is most commonly recognized in populations of Japanese ancestry with an incidence of 2-7 per million.⁴

Symptoms

The age of onset ranges from one year of age to 72 years of age; the mean age of onset is 31.5 years of age.¹

In adults (over ~age 20 years), DRPLA presents as ataxia, choreoathetosis, and dementia or character changes.¹

In people under ~age 20 years, DRPLA typically manifests with progressive intellectual deterioration, behavior changes, ataxia, myoclonus, and seizures.¹

Neuropathology demonstrates degeneration of the dentatorubral and pallidoluysian systems.⁵ In addition, white matter lesions have been described.¹

Cause

DRPLA is caused by expansion of a CAG trinucleotide repeat in the ATN1 gene.

Normal alleles typically have a repeat length of 6 to 35.¹

Individuals with DRPLA have a full penetrance allele with repeat length greater than or equal to 48 repeats, usually 48-93.¹

Alleles of 35–47 repeat length ("mutable normal alleles") are incompletely penetrant and have been associated with a milder DRPLA clinical phenotype in a small number of cases.⁴ Mutable normal alleles are unstable and may increase in size when transmitted to offspring.¹

The age of onset and clinical presentation is inversely correlated with the size of the expansion. On average, people with large expansions have earlier onset than those with a smaller number of repeats.^{1,5}

Although the size of the trinucleotide repeat is inversely correlated with the age of onset, the number of repeats cannot be used for specific prediction of symptoms or age of onset in an asymptomatic person. Repeat length is estimated to account for 50-68% of the variability in age of onset, the other contributing factors are not known.⁶

Inheritance

DRPLA is an autosomal dominant disorder.

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.

Most individuals with DRPLA have inherited the mutation from a parent. The parent may not have had signs of DRPLA because the number of repeats he or she had were below the "threshold" for manifesting symptoms ("mutable normal" or "intermediate" alleles) or the number of repeats was within the disease-causing range, but small in number thus the parent with the abnormal allele has not yet developed symptoms.¹

Unaffected persons with mutable normal or intermediate alleles may pass this allele to offspring and the allele may undergo intergenerational expansion to a disease-causing range. The amount of that expansion depends upon the size of the repeat and gender of the transmitting parent. When the expansion is inherited from the father, increase in size of the expansion tends to be larger than when the disease-causing allele is inherited from the mother.¹ As a result,

individuals who inherit the mutation from their father tend to have onset of disease 26-29 years earlier than their affected parent; when inheritance is from the mother, the onset of disease is about 14-15 years earlier.¹

Diagnosis

The diagnosis of DRPLA is based on presenting findings and family history of DRPLA or by the results of molecular genetic testing demonstrating an expansion of the CAG trinucleotide/polyglutamine tract in ATN1.¹ A repeat length of greater than or equal to 48 confirms the diagnosis of disease. Testing is >99% accurate.¹

Management

There is no cure for DRPLA. Some pharmacologic treatments may be effective in decreasing some of the associated symptoms, such as seizures, ataxia, and psychiatric manifestations.¹

Survival

The mean age of death is 49 years.⁴ Individuals, on average, pass away with 13 years from the onset of symptoms.²

Test Information

Introduction

Testing for DRPLA includes trinucleotide repeat testing to determine the number of CAG repeats in the ATN1 gene.

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 DRPLA testing. Of note, no U.S. guidelines exist for genetic testing for DRPLA.

Selected Relevant Publications

A 2018 expert-authored review stated:⁴

"No established clinical diagnostic criteria have been established for DRPLA, with the genetic diagnosis typically made during the investigation of symptomatic individuals."

"Diagnostic genetic testing should be considered in any individual with an autosomal dominant pattern of family history involving cognitive impairment, dementia, or movement disorder."

"Consensus guidance on testing within adult-onset ataxia for DRPLA focuses on clinical findings, Asian ancestry, and family history as being important factors to consider."

"Genetic testing is typically via polymerase chain reaction amplification across the ATN1 CAG repeat region followed by gel or capillary electrophoresis, which identifies 100% of pathogenic expansions of ≥ 48 CAG repeats. Although next-generation sequencing technologies are promising they have not been widely used or validated for the ATN1 repeat expansion and diagnosis of DRPLA, and repetitive genomic elements remain problematic to assay via short-read next generation sequencing technologies."

A 2016 expert-authored review stated:¹

Dentatorubral-pallidoluysian atrophy (DRPLA) should be suspected in individuals with the following:

"Clinical features (by age):

Age <20 years: Ataxia, myoclonus, seizures, progressive intellectual deterioration

Age >20 years: Ataxia, choreoathetosis, dementia, psychiatric disturbance

Brain MRI findings: Cerebellar and brain stem atrophy

Family history: Consistent with autosomal dominant inheritance and Asiatic (mainly Japanese) familial origin. Note: (1) Absence of a family history of DRPLA does not preclude the diagnosis. (2) DRPLA is extremely rare outside of Asiatic populations."

"The diagnosis of DRPLA is established in a proband with suggestive clinical findings and a family history of DRPLA or by the identification of a heterozygous pathogenic CAG trinucleotide expansion in ATN1 by molecular genetic testing. The CAG repeat length in individuals with DRPLA ranges from 48 to 93."

"Most individuals diagnosed with DRPLA have an affected parent. It is appropriate to evaluate both parents of an affected individual with molecular genetic testing even if they are asymptomatic."

"It is appropriate to consider testing symptomatic individuals regardless of age in a family with an established diagnosis of DRPLA."

"Testing of asymptomatic at-risk adults for DRPLA in the presence of nonspecific or equivocal symptoms is predictive testing, not diagnostic testing. When testing

at-risk individuals for DRPLA, it is helpful to test for the CAG expansion in an affected family member to confirm the molecular diagnosis in the family."

"Testing of asymptomatic, healthy at-risk adults for DRPLA can be performed, taking into consideration their autonomy of choice and right to privacy."

"Potential consequences of such testing [predictive testing] (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing."

"Predictive testing of minors for adult-onset disorders for which no treatment exists is not considered appropriate. Such testing negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause."

"If the disease-causing mutation has been identified in the family, prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis (usually performed at ~15-18 weeks' gestation) or chorionic villus sampling (usually performed at ~10-12 weeks' gestation)."

"Once the ATN1 (DRPLA) CAG trinucleotide repeat expansion has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for DRPLA are possible."

Criteria

Introduction

Requests for DRPLA testing are reviewed using these criteria.

Genetic Counseling:

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

Previous Testing:

No previous ATN1 expanded repeat testing for DRPLA, AND

Diagnostic Testing for Symptomatic Individuals:

less than 20 years of age and 2 or more of the following:

Ataxia

Myoclonus

Seizures

Progressive intellectual deterioration/behavior changes

Brain MRI demonstrating cerebellar and brain stem atrophy

Affected 1st degree biologic relative or Japanese/Haw River descent, OR

20 years of age or older and 2 or more of the following:

Ataxia

Choreoathetosis

Dementia/psychiatric disturbance

Brain MRI demonstrating cerebellar and brain stem atrophy

Affected 1st degree biologic relative or Japanese/Haw River descent, OR

Predisposition Testing for Presymptomatic/Asymptomatic Individuals:

ATN1 CAG trinucleotide expansion detected in 1st degree biologic relative, or

Suspected DRPLA in a deceased 1st, 2nd or 3rd degree biologic relative who was not genetically diagnosed, AND

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

References

Introduction

These references are cited in this guideline.

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