Test Specific Guidelines

Ataxia-Telangiectasia Genetic Testing

MOL.TS.130.A
v1.0.2023

Introduction

Ataxia-telangiectasia 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.

Procedures addressed by this guideline	Procedure codes
ATM Deletion/Duplication Analysis	81479
ATM Known Familial Mutation Analysis	81403
ATM Sequencing	81408

What Is Ataxia-telangiectasia?

Definition

Ataxia-telangiectasia (A-T) is a progressive neurological disorder. Individuals with A-T also have an increased risk for immunodeficiency, frequent infections, and malignancy. Additionally, they are unusually sensitive to ionizing radiation.[1]

Prevalence

The prevalence of A-T is approximately 1 in 40,000 to 1 in 100,000 live US births.[1-3] The estimated pan-ethnic carrier frequency of mutations in the ATM gene is approximately 1% in the general population.[4,5]

Symptoms

The onset of symptoms of A-T is typically between the ages of 1 and 4 years.[1,3] Signs and symptoms of A-T include[1,6]

- **progressive cerebellar atrophy and dysfunction, which can present with the following symptoms at a young age:**
  - **truncal and gait ataxia,**
  - **ocular apraxia,**

  - slurred speech, and
  - head tilting, after the age of 6 months;
- conjunctival telangiectasias;
- immunodeficiencies and frequent non-opportunistic infections;
- malignancies, especially leukemias and lymphomas; and
- radiation sensitivity.

Cause

A-T is caused by biallelic mutations in the ATM gene.

Inheritance

A-T is an autosomal recessive disorder.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

The diagnosis may be suspected based on clinical symptoms and preliminary laboratory data.[1] Individuals with A-T often have an elevated serum alpha-fetoprotein (AFP) level and immunoblotting may demonstrate reduce or absent ATM protein.[1] A diagnosis of A-T is established in an individual with characteristic clinical features and/or biallelic pathogenic mutations in ATM.

Sequence analysis of the ATM gene can identify 90-95% of A-T mutations in affected individuals.[1]

Deletion and duplication analysis of the ATM gene can identify another 1-2% of mutations.[1]

Management

Individuals with A-T are best cared for by a multidisciplinary team. Management and treatment includes addressing the neurological and immunodeficiency symptoms while also monitoring for malignancy.[1]

Survival

Although individuals with A-T live to adulthood, they are at an increased risk for early death. Currently, most individuals live beyond 25 years, with some surviving into their 50s.[1] Cause of death is associated with A-T associated cancers, infection, and pulmonary failure.[7]

Related Conditions

Individuals with a single ATM mutation are carriers. ATM carriers may be at an increased risk for breast cancer, especially women with a strong family history of breast cancer.[2,4,5,7,8] Epidemiological data has also suggested an increased risk for cardiovascular disease in carriers.[5,7] Therefore, the detection of carriers can have medical management implications for breast cancer and cardiovascular disease screening.

Test Information

Introduction

Testing for A-T may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and

losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to A-T testing.

International Workshop on A-T

The Eighth International Workshop on Ataxia-telangiectasia (A-T) was convened in 1999. The workshop described ATM mutations and cancer risk in carriers, and potential therapeutic approaches. Genetic testing strategies were not described.[9] A subsequent workshop in 2012 provided updated information about the cancer risks and potential treatment options, but still did not address genetic testing strategies.[10]

Criteria

Introduction

Requests for A-T testing are reviewed using these criteria.

ATM Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation(s), AND
- Carrier Screening Individuals:
  - Known family mutation in ATM in 1st, 2nd, or 3rd degree biologic relative(s), OR
- Prenatal Testing for At-Risk Pregnancies:
  - ATM mutations identified in both biologic parents, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

ATM Sequencing

- Genetic Counseling:

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

- Previous Genetic Testing:
  - No previous ATM gene sequencing, and
  - No known ATM mutation in family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Elevated alpha-fetoprotein (AFP) levels, or
  - Decreased ATM protein detected by immunoblotting, and
  - Progressive cerebellar ataxia, or
  - Truncal and gait ataxia, or
  - Oculomotor apraxia, OR
- Testing for Individuals with Family History or Partners of Carriers:
  - 1st, 2nd, or 3rd, degree relative diagnosed with Ataxia-Telangiectasia clinical diagnosis, family mutation unknown, and testing unavailable, or
  - Partner is monoallelic or biallelic for ATM mutation, and
  - Has living children with this partner, or
  - Has the potential and intention to reproduce, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

ATM Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous deletion/duplication analysis of ATM, and
  - No mutations detected in full sequencing, or
  - Heterozygous for mutation and individual is expected to be affected (eg, elevated alpha-fetoprotein levels, decreased ATM protein detected by immunoblotting (if performed), other features of disorder are present), 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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