Test Specific Guidelines

Alpha-1 Antitrypsin Deficiency Testing

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Introduction

Alpha-1 antitrypsin deficiency 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
Protease Inhibitor (PI) Typing	82104
SERPINA1 Sequencing	81479
SERPINA1 Targeted Mutation Analysis	81332

What Is alpha-1 Antitrypsin Deficiency?

Definition

Alpha-1 antitrypsin deficiency (AATD) is an inherited condition which may cause chronic obstructive pulmonary disease (COPD) and liver dysfunction. This condition is also referred to as AAT Deficiency and A1AT Deficiency.

Prevalence

It is estimated that 1 in 5000 to 1 in 7000 people in North America have AATD. AATD commonly affects individuals of Northern European heritage. This disorder is most common in Scandinavia, occurring in approximately 1 in 1500 to 1 in 3000 individuals there.[1] However, AATD is an under-recognized condition, with estimates that only 10% of those affected are actually diagnosed.[2]

Symptoms

The most common clinical manifestation is COPD, particularly emphysema.[1-3] Smoking is a major environmental risk factor for lung disease in AATD.[1,3]

AATD also increases the risk for neonatal or childhood liver disease, manifested by obstructive jaundice and hyperbilirubinemia, and early onset adult liver disease, usually cirrhosis and fibrosis.[1] Individuals are also at increased risk for

panniculitis (tender skin nodules which may be inflammatory and may ulcerate) and C-ANCA positive vasculitis.[1]

Cause

AATD results from mutations in the SERPINA1 gene, which codes for the enzyme alpha-1 antitrypsin (AAT).[1]

Inheritance

AATD is an autosomal recessive disorder.[1]

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

AATD may first be suspected based on reduced serum levels of AAT. Confirmatory testing includes either protease inhibitor typing or genetic testing for common mutations.[1] Sequence analysis may be indicated in certain situations.[1]

SERPINA1 targeted mutation analysis tests for the two common mutations in the gene (Z and S), which make up greater than 95% of the mutations.[1] The Z allele is by far the most common and more severe variant.[3]

SERPINA1 sequencing is available, but only appropriate in limited situations. The proportion of individuals with AATD that have a mutation identified by sequencing is unknown.[1]

Management

Individuals with COPD are treated with standard therapy. Individuals with emphysema may be treated with periodic human serum AAT by intravenous infusion. For individuals with end-stage lung disease, lung transplantation may be considered. Liver transplant may be considered as treatment for those with severe disease. “Dapsone or doxycycline therapy is used for panniculitis; if refractory to this, high-dose intravenous AAT augmentation therapy is indicated.”[1] Individuals are strongly encouraged to avoid exposure to active and passive smoking, environmental pollutants, and excessive alcohol use. Surveillance includes periodic pulmonary and liver function tests.[1]

Survival

The prognosis for individuals with AATD is dependent on the severity of the disease and lifestyle factors. Individuals with AATD may have a normal lifespan; however, those with exposure to cigarette smoke may experience earlier and faster progression of lung disease.[4]

Test Information

Introduction

Testing for AATD may include protease inhibitor typing, targeted mutation analysis, and/or next generation sequencing.

Protease Inhibitor Typing

Protease Inhibitor (PI) typing by isoelectric focusing to determine phenotype (PI*Z, PI*S).[1] PI typing can detect normal as well as variant alleles, but cannot detect null alleles[1,2]

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon patient ethnicity, phenotypic presentation, or other case-specific characteristics.

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.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to AATD testing.

American Thoracic Society and European Respiratory Society

The American Thoracic Society and the European Respiratory Society stated that testing for AATD is recommended for the following indications:[3]

- "symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators
- individuals with unexplained liver disease, including neonates, children, and adults, particularly the elderly
- asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors, examples include cigarette smoking and occupational exposure
- adults with necrotizing panniculitis, and
- siblings of an individual with AATD."

Selected Relevant Publications

The following selected relevant publications outlined recommendations for the diagnosis of AATD. When ambiguous results are obtained between quantification, genotype or phenotype assays, gene sequencing can identify rare variants or null alleles that would otherwise be missed.

Sandhaus et al. (2016)[5]

Sandhaus et al. (2016) provided recommendations for the diagnosis of AATD based on systematic review and expert scientist and clinician appraisal. For diagnostic testing of symptomatic individuals, the authors recommended "genotyping for at least the S and Z alleles. Advanced or confirmatory testing should include Pi-typing, AAT level testing, and/or expanded genotyping." The authors also recommended that the following groups be tested for AATD.

- "All individuals with COPD, regardless of age or ethnicity"
- "All individuals with unexplained chronic liver disease"
- "All individuals with necrotizing panniculitis, granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), or unexplained bronchiectasis"

In addition, the authors recommended that "adult siblings of individuals identified with an abnormal gene for AAT, whether heterozygote or homozygote, should be provided with genetic counseling and offered testing for AATD".

Graham et al. (2015)[6]

Graham et al. (2015) found pathogenic mutations with sequencing after PI and targeted mutation analysis were performed. They supported full gene

sequencing when there are discrepancies between clinical presentation and genotyping after PI and targeted mutation analysis.

Prins et al. (2008)[7]

Prins et al. (2008) sequenced exons 2, 3, and 5 of the SERPINA1 gene from 66 individuals with AAT concentration less than or equal to 1.0 g/L. They predicted that up to 22% of the disease-associated AATD alleles could be missed by S and Z genotyping or by phenotyping. They also identified rare alleles $M_{procida}$, $M_{palermo}$, $M6_{passau}$, $M_{wurzburg}$, $M_{heerlen}$ and the previously undescribed null alleles $Q0_{Soest}$ and $Q0_{amersfoort}$.

They found pathogenic mutations in 22% of those who had negative PI and targeted mutation testing. The authors recommended direct sequencing of the coding regions of the SERPINA1 gene for individuals with suspected AATD based on a serum AAT concentration ≤1.0 g/L.

Balderacchi et al. (2021)[8]

Balderacchi et al. (2021) reviewed various diagnostic algorithms described in the literature, with particular concern for false negatives. Inclusion of C-reactive protein levels, a marker of inflammation reported to impact observed AAT levels, can decrease the rate of false negative results in individuals with intermediate deficiency. They found the highest sensitivity by using an approach that evaluated all individuals for AAT levels, serum CRP levels, and genotyping of the S and Z alleles.

Criteria

Introduction

Requests for AATD testing are reviewed using these criteria.

Protease Inhibitor Typing or SERPINA1 Targeted Mutation Analysis

Protease inhibitor (PI) typing or SERPINA1 targeted mutation analysis (*S, *Z) may be considered in individuals who meet the following criteria:

- Abnormally low (less than 120mg/dL) or borderline (90-140mg/dL) alpha-1 antitrypsin (AAT) levels; AND
- At least one of the following:
  - Symptomatic adults with emphysema, chronic obstructive pulmonary disease (COPD), or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators; or
  - Individuals of any age with unexplained liver disease (including obstructive liver disease in infancy); or
  - Asymptomatic individuals with persistent obstruction on pulmonary function tests who have identifiable risk factors (e.g., cigarette smoking, occupational exposure); or

- C-ANCA positive vasculitis; or
- Adults with necrotizing panniculitis; or
- Siblings of an individual with AATD, AND

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

SERPINA1 Sequence Analysis

Sequencing of the SERPINA1 gene may be considered in individuals who meet the following criteria:

- There are discrepancies between clinical presentation, serum alpha-1 antitrypsin quantification, targeted mutation analysis, and/or PI typing; OR
- The presence of rare variants or null alleles (which cannot be identified by other methods) is suspected, 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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