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Alpha-1 Antitrypsin Deficiency

Synonyms: AAT Deficiency, A1AT Deficiency, AATD, Alpha-1 Antiprotease Deficiency

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Summary

Clinical characteristics

Alpha-1 antitrypsin deficiency (AATD) can present with hepatic dysfunction in individuals from infancy to adulthood and with chronic obstructive lung disease (emphysema and/or bronchiectasis), characteristically in individuals older than age 30 years. Individuals with AATD are also at increased risk for panniculitis (migratory, inflammatory, tender skin nodules which may ulcerate on legs and lower abdomen) and C-ANCA-positive vasculitis (granulomatosis with polyangiitis). Phenotypic expression varies within and between families. In adults, smoking is the major factor in accelerating the development of COPD; nonsmokers may have a normal life span, but can also develop lung and/or liver disease. Although reported, emphysema in children with AATD is extremely rare. AATD-associated liver disease, which is present in only a small portion of affected children, manifests as neonatal cholestasis. The incidence of liver disease increases with age. Liver disease in adults (manifesting as cirrhosis and fibrosis) may occur in the absence of a history of neonatal or childhood liver disease. The risk for hepatocellular carcinoma (HCC) is increased in individuals with AATD.

Diagnosis/testing

The diagnosis of AATD relies on demonstration of low serum concentration of alpha-1 antitrypsin (AAT) and either identification of biallelic pathogenic variants in *SERPINA1* or detection of a functionally deficient AAT protein variant by protease inhibitor (PI) typing. Note: The unconventional nomenclature of *SERPINA1* alleles is based on electrophoretic protein variants that were identified long before the gene (*SERPINA1)* was known. Alleles were named with the prefix PI* (protease inhibitor*) serving as an alias for the gene. Using this nomenclature, the most common (normal) allele is PI*M and the most common pathogenic allele is PI*Z.

Management

Treatment of manifestations: COPD is treated with standard therapy. Augmentation therapy with periodic intravenous infusion of pooled human serum alpha-1 antitrypsin (AAT) is used in individuals who have

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established emphysema. Lung transplantation may be an appropriate option for individuals with end-stage lung disease. Liver transplantation is the definitive treatment for severe disease (will restore AAT levels). Dapsone or doxycycline therapy is used for panniculitis; if refractory to this, high-dose intravenous AAT augmentation therapy is indicated.

Surveillance: Every six to 12 months: pulmonary function tests including spirometry with bronchodilators and diffusing capacity measurements; liver function tests, platelet count and liver ultrasound, elastography (e.g., FibroScan), magnetic resonance imaging.

Agents/circumstances to avoid: Smoking (both active and passive); occupational exposure to environmental pollutants used in agriculture, mineral dust, gas, and fumes; excessive use of alcohol.

Evaluation of relatives at risk: Evaluation of parents, older and younger sibs, and offspring of an individual with severe AATD in order to identify as early as possible those relatives who would benefit from institution of treatment and preventive measures.

Genetic counseling

AATD is inherited in an autosomal codominant manner. If both parents are heterozygous for one *SERPINA1* pathogenic variant (e.g., PI*MZ), each sib of an affected individual has a 25% chance of being affected (PI*ZZ), a 50% chance of being heterozygous (PI*MZ), and a 25% chance of inheriting neither of the pathogenic variants (PI*MM). In the less frequent instance in which one parent is homozygous (PI*ZZ) and one parent is heterozygous (PI*MZ), the risk to each sib of being homozygous (PI*ZZ) is 50%. Unless an individual with AATD has children with an affected individual or a heterozygote, offspring will be obligate heterozygotes for a pathogenic variant. (Risk of lung disease may be increased in heterozygous individuals depending on their environmental exposures such as smoking.) Heterozygote testing for at-risk family members and prenatal and preimplantation genetic testing are possible once the pathogenic *SERPINA1* variants have been identified in the family.

Diagnosis

Suggestive Findings

Alpha-1 antitrypsin deficiency (AATD) should be suspected in individuals with evidence of:

- Chronic obstructive pulmonary disease (i.e., emphysema, persistent airflow obstruction, chronic bronchitis, and/or bronchiectasis); AND/OR
- Any of the following:
  - Liver disease at any age, including obstructive jaundice in infancy
  - C-ANCA positive vasculitis (i.e., granulomatosis with polyangiitis)
  - Necrotizing panniculitis

Establishing the Diagnosis

The diagnosis of AATD relies on demonstration of low serum concentration of AAT AND EITHER OF THE FOLLOWING:

- Identification of *SERPINA1* pathogenic variants
- Detection of a functionally deficient AAT protein

Demonstration of Low Serum Concentration of the Protein Alpha-1 Antitrypsin (AAT)

A variety of techniques have been used to measure serum AAT concentration; currently the most commonly used technique is nephelometry.

- Normal serum levels are 20-53 µmol/L or approximately 100-220 mg/dL by nephelometry.
- Serum levels observed in AATD with lung disease are usually <57 mg/dL.

Identification of Biallelic Pathogenic Variants in *SERPINA1*

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of AATD is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those in whom the diagnosis of AATD has not been considered are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1. When the phenotypic and laboratory findings suggest the diagnosis of AATD molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Targeted analysis for the common PI*Z, PI*S, PI*I, and PI*F alleles (see Molecular Genetics for standard nomenclature) may be performed first.

  Sequence analysis of *SERPINA1* detects other pathogenic variants such as small intragenic deletions/insertions and missense, nonsense, and splice site variants.

  Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **A multigene panel** that includes *SERPINA1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2. When the diagnosis of AATD is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Note: The nomenclature of *SERPINA1* alleles is unconventional because it is based on electrophoretic protein variants that were identified long before the gene (*SERPINA1*) was identified [Cox et al 1980]. Because this older nomenclature is well established in the literature, it is used in this *GeneReview*.

SERPINA1 alleles encoding the variant AAT proteins were named with the prefix PI* (protease inhibitor*) serving as an alias for *SERPINA1* (which had yet to be identified). The six *SERPINA1* alleles discussed here are the following. (See Molecular Genetics for more details and information on other alleles.)

- **PI*M.** The most common allele in all populations described to date. Some benign variants of the PI*M allele are designated M1, M2, M3, etc.
- **PI*Z.** The most common pathogenic allele, resulting in a quantitatively and functionally deficient AAT protein. Individuals homozygous for PI*Z (i.e., PI*ZZ) have severe alpha-1 antitrypsin deficiency (AATD).
- **PI*S.** A pathogenic allele resulting in a quantitatively and functionally deficient AAT. It is usually of clinical consequence only in the compound heterozygous state with another pathogenic allele (e.g., PI*SZ) and when the serum AAT level is <57 mg/dL.
- **PI*F.** A pathogenic allele that is distinctive because the resulting protein is functionally impaired in binding neutrophil elastase but quantitatively normal
- **PI*I.** An allele that is associated with mild quantitative deficiency
- **Null alleles (sometimes designated PI*QO).** Pathogenic alleles that result in either no mRNA product or no protein production

Table 1. Molecular Genetic Testing Used in AATD

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SERPINA1	Targeted analysis	95% [3]
	Sequence analysis [4]	>99% [5]
	Gene-targeted deletion/duplication analysis [6]	Rare [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Targeted analysis for pathogenic variants is typically specific for detecting the pathogenic alleles PI*Z and PI*S, which account for 95% of AATD [McElvaney et al 1997].
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gooptu et al [2014], Greene et al [2016], Hatipoğlu & Stoller [2016], Matamala et al [2018], Renoux et al [2018], Strnad et al [2020]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Rare exon and whole-gene deletions have been reported [Takahashi & Crystal 1990, Poller et al 1991, Strnad et al 2020].

Detection of a Functionally Deficient AAT Protein Variant by Protease Inhibitor (PI) Typing

PI typing is performed by polyacrylamide gel isoelectric focusing (IEF) electrophoresis of serum in a gradient between pH 4 and 5. Note: IEF is no longer in common use in clinical practice.

- Electrophoretic AAT protein variants (isoforms) are designated by letters based on their migration pattern. For example, the normal AAT protein (designated M) migrates in the middle of the isoelectric field. The abnormal AAT deficiency protein (designated Z) migrates most slowly. Other variants have been given additional alphabetic designations; some rare variants have been named by place of origin of the proband.
- Because a range of AAT protein variants from normal to deficient can be observed in an IEF assay, a reference of 13 common and five rare AAT protein variants is used to identify the specific AAT protein [Greene et al 2013].
- The limitations of IEF include inability to interpret an atypical electrophoretic pattern resulting from rare AAT protein variants and absence of AAT protein resulting from a *SERPINA1* pathogenic null allele.
- IEF, the biochemical gold standard test for establishing the diagnosis of AATD, may be less costly than molecular genetic testing.

Though the optimal algorithm for laboratory testing is not well defined and recommendations in available guidelines differ [Attaway et al 2019], the guidelines for the diagnosis and management of AATD by the American Thoracic Society / European Respiratory Society include recommended indications for genetic testing for AATD [American Thoracic Society & European Respiratory Society 2003].

Table 2. Clinical Indications for Genetic Testing

Clinical Indication		Recommendation for Testing	Strength of Recommendation	Quality of Evidence
Pulmonary	All persons w/COPD regardless of age or ethnicity	Yes	Strong	Moderate
	All persons w/unexplained bronchiectasis	Yes	Strong	Low
Extra-pulmonary	All persons w/unexplained chronic liver disease	Yes	Strong	Low
	All persons w/necrotizing panniculitis	Yes	Strong	Low
	All persons w/GPA	Yes	Strong	Low
Proband trigger	Adult sibs of persons w/any abnormal AATD-related gene	Offer test & genetic counseling	Strong	Moderate
	Parents/offspring/minor sibs/extended family of persons w/any abnormal AATD-related gene	Offer test & genetic counseling	Weak	Low
Pediatric patients	Children who do not fit previous indications	Not supported; consider parental testing instead.	–	–

Adapted from Sandhaus et al [2016]
AATD = alpha-1 antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; GPA = granulomatosis with polyangiitis

Clinical Characteristics

Clinical Description

Alpha-1 antitrypsin deficiency (AATD) can present with hepatic dysfunction in individuals from infancy to adulthood and with obstructive lung disease and/or bronchiectasis, characteristically in individuals older than age 30 years. Phenotypic expression varies within and between families.

The severity of AATD depends on the genotype and resultant serum alpha-1 antitrypsin (AAT) level. Individuals homozygous for severe deficiency alleles (i.e., PI*ZZ) have low serum AAT levels, placing them at increased risk for chronic obstructive pulmonary disease (COPD) (see Table 4). Individuals with alleles associated with intrahepatic inclusions (e.g., Z, M_{malton}, S_{iiyama}) are also at increased risk of developing liver disease.

Under-recognition of AATD often causes a long delay between first symptoms and initial diagnosis of AATD (i.e., 5-7 years) and many individuals report seeing multiple physicians before the diagnosis is first established. Diagnostic delay is associated with worsened clinical status at the time of initial diagnosis [Tejwani et al 2019].

To date, approximately 5,000-10,000 individuals in the United States have been identified with a pathogenic variant in *SERPINA1* [American Thoracic Society & European Respiratory Society 2003, Strnad et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 3. Select Features of AATD

Feature	% of Persons w/Feature	Comment
COPD (emphysema, chronic bronchitis)	60%-80%	The pattern & distribution of emphysema should not dissuade from considering the diagnosis of AATD.
Bronchiectasis	~27%	Bronchiectasis is present on CT chest in ~90% of those w/PI*ZZ & clinically evident in ~27% [Parr et al 2007].
Neonatal cholestasis	~11%	~65% will go on to have severe liver disease.
Cirrhosis	12%-40%	Liver disease may be subclinical.
Panniculitis	Uncommon	May be present in AATD phenotypes not assoc w/lung disease
GPA	Uncommon but associated	Odds ratio for having an abnormal AAT gene is ~11 in persons w/GPA [Mahr et al 2010].

AAT = alpha-1 antitrypsin; AATD = alpha-1 antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; GPA = granulomatosis with polyangiitis

Lung Disease

Adult-onset lung disease. Chronic obstructive pulmonary disease (COPD), specifically emphysema and/or chronic bronchitis, is the most common clinical manifestation of AATD. Bronchiectasis is also associated with AATD.

In adults, smoking is the major factor in accelerating the development of COPD. Although the natural history of AATD varies, depending in part on what has brought the individual to medical attention (e.g., lung symptoms, liver symptoms, asymptomatic relative of an affected individual), the onset of respiratory disease in smokers with AATD is characteristically between ages 40 and 50 years [Tanash et al 2008]. Nonsmokers may have a normal life span, but can also develop lung and/or liver disease.

Individuals with severe AATD may manifest the usual signs and symptoms of obstructive lung disease, asthma, and chronic bronchitis (e.g., dyspnea, cough, wheezing, and sputum production) [McElvaney et al 1997]. For example, in the National Heart, Lung, and Blood Institute Registry, of 1,129 participants with severe deficiency of AAT, 84% described dyspnea, 76% wheezed with an upper respiratory tract infection, and 50% reported cough and phlegm [McElvaney et al 1997, Eden et al 2003]. Of note, the prevalence of AATD in persons with asthma does not differ from that found in the general population [Wencker et al 2002, Miravitlles et al 2003].

Most individuals (~95%) with severe AATD have evidence of bronchiectasis on chest CT, with 27% demonstrating clinical symptoms of bronchiectasis [Parr et al 2007].

- Chest CT shows loss of lung parenchyma and hyperlucency. In contrast to the usual pattern observed in centriacinar emphysema (emphysematous changes more pronounced in the lung apices than bases), the pattern observed in two thirds of individuals with AATD is that of more pronounced emphysematous changes in the bases than apices [Parr et al 2004].
- Lung function tests show decreased expiratory airflow, increased lung volumes, and decreased diffusing capacity. Approximately 60% of individuals with AATD-associated emphysema demonstrate a component

of reversible airflow obstruction, defined as a 200-mL and 12% increase in the post-bronchodilator FEV_1 and/or FVC.

Childhood-onset lung disease. Although reported, emphysema in children with AATD is extremely rare and may result from the coexistence of other unidentified genetic factors affecting the lung [Cox & Talamo 1979].

Studies that followed newborns with severe AAT deficiency through age 32 years showed that most adults did not smoke and lacked physiologic and CT evidence of emphysema [Mostafavi et al 2018]. Longer-term follow-up studies are not currently available. In most observational studies, the mean age of individuals with lung disease is in the fifth decade [Seersholm et al 1997, Alpha-1 Antitrypsin Deficiency Registry Study Group 1998].

Risk for lung disease in PI*MZ heterozygotes. Approximately 2%-3% of North Americans are PI*MZ heterozygotes. Nonsmoking PI*MZ heterozygotes are generally not considered to be at significantly increased risk for clinical emphysema [Molloy et al 2014]. Specifically, population-based studies show no significant spirometric differences between matched PI*MZ and PI*MM cohorts [Al Ashry & Strange 2017]. However, smoking PI*MZ heterozygotes are at increased risk for COPD [Hersh et al 2004, Sørheim et al 2010, Molloy et al 2014]. Of note, slight abnormalities of lung function can be present without clinical symptoms. Alternatively, spirometry can miss at least 10% of individuals with a clinical diagnosis of COPD and emphysema on CT scan [Smith et al 2014, Lutchmedial et al 2015].

Risk for lung disease in persons with the PI*SZ genotype. Individuals who smoke and have the PI*SZ genotype with serum AAT levels below the protective threshold value have a slightly increased disease risk.

Table 4. Relationship of AAT Protein Variants to Serum AAT Levels and Emphysema Risk in Adults

AAT Protein Variant	Prevalence (%)			Serum AAT Levels		Lifetime Emphysema Risk
	World-wide	NA	Europe	"True level" [1] mean (5th %ile-95th %ile)	Commercial standard [2] median (5th %ile-95th %ile)	
MM	96.3	93.0	91.1	33 (20-53)	147 (102-254)	Background
MS	2.7	4.8	6.6	33 (18-52)	125 (86-218)	Background
MZ	0.8	2.1-3	1.9	25.4 (15-42)	90 (62-151)	Background
SS	0.08	0.1	0.3	28 (20-48)	95 (43-154)	Background
SZ	0.02	0.1	0.1	16.5 (10-23)	62 (33-108)	20%-50%
ZZ	0.003	0.01	0.01	5.3 (3.4-7)	≤29 (≤29-52)	80%-100%
Null-Null	-	-	-	0	0	100%

Adapted from Brantly et al [1991], Stoller & Aboussouan [2005], de Serres & Blanco [2012], Bornhorst et al [2013]
AAT = alpha-1 antitrypsin; NA = North America
1. µmol/L
2. mg/dL

Note: An attempt to correlate serum AAT levels with protein variants in children showed trends similar to those seen in adults [Donato et al 2012].

Liver Disease

Childhood-onset liver disease. The most common manifestation of AATD-associated liver disease is neonatal cholestasis: jaundice, with hyperbilirubinemia and raised serum aminotransferase levels in the early days and months of life.

Liver abnormalities develop in only a portion of children with AATD. In a study of 200,000 Swedish children who were followed up after newborn screening for AATD, 18% of those with the PI*ZZ genotype developed

clinically recognized liver abnormalities and 2.4% developed liver cirrhosis with death in childhood [Sveger 1976, Sveger 1988, Strnad et al 2020]. Liver damage may progress slowly [Volpert et al 2000].

In a follow-up study of 44 children with AATD-associated liver disease initially manifesting as cirrhosis or portal hypertension, outcomes ranged from liver transplantation in two to relatively healthy lives up to 23 years after diagnosis in seven [Migliazza et al 2000].

It is not known why only a small proportion of children with early hyperbilirubinemia have continued liver destruction leading to cirrhosis. The overall risk that an individual with the PI*ZZ genotype will develop severe liver disease in childhood is generally low (~2%); the risk is higher among sibs of a child with the PI*ZZ genotype and liver disease.

- When liver abnormalities in the proband are mild and resolve, the risk of liver disease in sibs with the PI*ZZ genotype is approximately 13%.
- When liver disease in the proband is severe, the risk for severe liver disease in sibs with the PI*ZZ genotype may be approximately 40% [Cox 2004].

The PI*MZ and PI*SZ genotypes are not associated with an increased risk for childhood liver disease; however, on occasion, elevated levels of liver enzymes that resolve have been observed. In a study of 58 children with heterozygous genotypes showing signs of liver involvement during the first six months of life, almost all had normal values of liver enzymes at ages 12 months, five years, and ten years [Pittschieler 2002].

Adult-onset liver disease. Liver disease in adults (manifesting as cirrhosis and fibrosis) may occur in the absence of a history of neonatal or childhood liver disease. Liver disease is more common in men than women.

The risk for liver disease at age 20-40 years is approximately 2% and at age 41-50 years approximately 4% [Cox & Smyth 1983].

Autopsy studies suggest that the prevalence of liver disease may be as high as 40% in older individuals who have never smoked and do not have COPD [Eriksson 1987]. Liver disease was subclinical at death in some of these individuals.

Hepatocellular carcinoma (HCC). The risk for HCC among individuals with AATD and the PI*ZZ genotype is several times that typically associated with liver cirrhosis. This increased risk has been attributed to failure of apoptosis of injured cells with retained Z protein, which sends a chronic regeneration signal to hepatocytes with a lesser load of retained Z protein [Perlmutter 2006].

Liver pathology. AATD liver inclusions are visualized as bright pink globules of various sizes, using periodic acid-Schiff (PAS) stain following diastase treatment (PAS-D). The extent of inclusion formation varies considerably; the number and size of liver inclusions increases with age. Inclusions are not observed before age 12 weeks. Note: Liver biopsy, when indicated in the evaluation of individuals with liver disease, may show PAS positive diastase-resistant inclusion bodies which are suggestive of but not pathognomonic for AATD.

In infants with AATD, inclusions may be fine and granular and difficult to identify in percutaneous liver biopsy specimens. They are also observed in bile duct epithelium [Cutz & Cox 1979].

Liver inclusions indicate the presence of at least one PI*Z allele; histologic examination of the liver cannot confidently distinguish between PI*MZ heterozygotes and PI*ZZ homozygotes, although inclusions are generally more profuse in PI*ZZ homozygotes. Visualization of inclusions may be variable among PI*MZ heterozygotes.

Other Disease Associations

Panniculitis occurs in an estimated one in 1,000 individuals with AATD [Alpha-1 Antitrypsin Deficiency Registry Study Group 1998]. Panniculitis characteristically presents as migratory, inflammatory, tender skin

nodules which may ulcerate [Stoller & Piliang 2008]. Sites of trauma (e.g., legs, lower abdomen) are most commonly affected. Presumably like emphysema in the lung, panniculitis in the skin is caused by unopposed proteolytic damage produced by the PI*Z allele.

Individuals with AATD appear to have increased susceptibility to C-ANCA-positive vasculitis (e.g., granulomatosis with polyangiitis [GPA], previously called Wegener granulomatosis) [Hadzik-Blaszczyk et al 2018].

Genotype-Phenotype Correlations

The risk for lung disease associated with the following *SERPINA1* genotypes is summarized in Table 4.

PI*MM. This genotype is associated with a normal serum concentration of AAT and no increased risk of liver or lung disease.

PI*MZ. In general, nonsmoking individuals with this genotype are not considered to be at increased risk for lung disease; PI*MZ smokers and those with environmental exposures have increased risk of developing COPD [Molloy et al 2014, Al Ashry & Strange 2017].

PI*SS. This genotype does not appear to be associated with an increased risk for clinical disease [Ferrarotti et al 2012]. The S allele is most common among individuals of Iberian descent.

PI*SZ. This genotype is not usually associated with a high risk for liver or lung disease; however, about 11% of individuals with the PI*SZ genotype have serum AAT levels below the protective threshold value (11 μM). Those individuals are at increased risk of developing emphysema with lower zone predominance, as well as chronic bronchitis, especially if they are smokers [Green et al 2015].

PI*ZZ. Individuals with this genotype have a serum concentration of AAT that is approximately 10%-20% of normal (serum levels of 20-35 mg/dL) and are at high risk for both liver and lung disease. This genotype is present in 95% of affected individuals with clinical manifestations of AATD. Variable disease expressivity in individuals with the PI*ZZ genotype – not accounted for by the presence of known risk factors such as cigarette smoking – suggests the existence of other as-yet unidentified genetic disease modifiers.

PI*FF. While rare, the F allele is associated with AAT that is functionally impaired in binding neutrophil elastase but is quantitatively normal. Individuals with the PI*FF or PI*FZ genotype are deemed to be at increased risk of developing emphysema [Sinden et al 2014].

PI*null-null (sometimes designated PI*QO). Individuals with this genotype have no measurable serum AAT secondary to complete lack of synthesis of AAT. Because protein does not accumulate in the liver, these individuals are not at increased risk of developing liver disease; however, they are at high risk of developing lung disease.

Nomenclature

In some publications, the term alpha-1-protease inhibitor is substituted for alpha-1 antitrypsin (AAT).

PI*M is used to describe normal alleles. Different normal alleles are given numeric designations (e.g., PI*M1, PI*M2).

Prevalence

AATD is one of the most common metabolic disorders in persons of northern European heritage, occurring in approximately one in 5,000-7,000 individuals in North America and one in 1,500-3,000 in Scandinavia. AATD

also occurs (in lower frequencies) in all other racial subgroups worldwide [Campbell 2000, Miravitlles 2000, de Serres & Blanco 2012].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SERPINA1*.

Differential Diagnosis

Lung Disease

Differential diagnoses include disorders causing chronic obstructive pulmonary disease (COPD), such as emphysema, chronic bronchitis, and bronchiectasis.

Bossé et al [2019] have described an autosomal dominant predisposition to emphysema in a single large French Canadian family that affects the protein, tyrosine phosphatase non-receptor, type 6 (PTPN6). As with severe deficiency of AAT, in this newly described condition there is near-complete penetrance for emphysema that is lower-lobe predominant and can be early onset (i.e., 4th-5th decade). Unlike alpha-1 antitrypsin deficiency (AATD), *PTPN6*-type emphysema is inherited as an autosomal dominant condition.

Liver Disease

See Table 5 for genetic disorders to consider in the differential diagnosis of AATD-related liver disease. The differential diagnosis of neonatal cholestasis also includes multiple metabolic diseases and other non-hereditary diseases including extrahepatic biliary atresia and gestational alloimmune liver disease (formerly known as neonatal hemochromatosis). Acquired disorders to consider include chronic viral hepatitis, alcoholic and non-alcoholic steatohepatitis, sclerosing cholangitis, and primary biliary cholangitis.

Table 5. Genetic Disorders Associated with Liver Disease in the Differential Diagnosis of Alpha-1 Antitrypsin Deficiency

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/AATD	Distinguishing from AATD
ABCB11 *ABCB4* *ATPB1* *NR1H4* *TJP2*	Progressive familial intrahepatic cholestasis (PFIC) (See OMIM PS211600 & ATPB1 Deficiency.)	AR	• Cholestasis can be prominent; presentation in infancy is common. • Risk for hepatocellular carcinoma in PFIC2 & AATD is higher than in other liver diseases.	• Often ↓ or normal GGT, differing histologic appearance on liver biopsy • Other extrahepatic manifestations may incl hearing loss, diarrhea, pancreatitis, failure to thrive, fat-soluble vitamin deficiencies.
ABCC2	Dubin-Johnson syndrome (OMIM 237500)	AR	Jaundice in infancy w/both direct & indirect hyperbilirubinemia	• Normal liver histology is normal (though liver is black in color); ALT & AST also normal • ↑ fractional excretion of coproporphyrin I

Table 5. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/AATD	Distinguishing from AATD
ATP7B	Wilson disease	AR	• Chronic liver disease • May present beyond newborn period; presentation in teen yrs common	• May be accompanied by neurologic &/or psychiatric symptoms; Kayser-Fleischer rings in 50% of those w/ hepatic disease; ↓ serum ceruloplasmin & ↑ urinary copper excretion • Acute liver failure is assoc w/hemolysis & ↓ serum alkaline phosphatase. • Liver biopsy shows excess copper accumulation & steatosis.
CFTR	Cystic fibrosis	AR	• Cholestasis in infancy • Liver disease can become more apparent in older children.	Extrahepatic obstruction due to inspissated bile or bile plugs
HAMP *HJV*	Juvenile hereditary hemochromatosis	AR	• Presentation can be in early childhood & adolescence. • Liver disease may not be prominent.	• ↑ serum ferritin & transferrin saturations • Greater likelihood of cardiac involvement (cardiomyopathy), ↓ glucose tolerance, & hypogonadism
HFE	*HFE* hemochromatosis	AR	• Liver disease can be relatively asymptomatic. • ↑ risk for hepatocellular carcinoma	• ↑ ferritin • Iron overload in liver & other organs, primarily after age 40 yrs
JAG1 *NOTCH2*	Alagille syndrome	AD	• Presents in early infancy • Cholestasis	Syndrome assoc w/several congenital defects (cardiac, vertebral, renal, ophthalmic, & dysmorphic features)
SLC40A1	Type 4 hemochromatosis (OMIM 606069)	AD	May present w/chronic fatigue	• Ferroportin disease caused by loss-of-function variants is characterized by ↑ ferritin levels, ↑ macrophage iron, ↓ transferrin saturation, mild anemia, & minimal hepatic iron deposition. • Ferroportin disease caused by gain-of-function variants is similar to classic HFE.
SLCO1B1 *SLCO1B3*	Rotor syndrome	AR digenic	Jaundice in infancy w/both direct & indirect hyperbilirubinemia	• Normal liver histology; normal color liver tissue, normal ALT & AST • ↑ total urinary coproporphyrin excretion w/↑ fractional excretion of coprophyrin I
TFR2	*TFR2* hereditary hemochromatosis	AR	Intermediate severity	↓ hepcidin levels & iron overload

AATD = alpha-1 antitrypsin deficiency; AD = autosomal dominant; ALT = alanine aminotransferase; AR = autosomal recessive; AST = aspartate transaminase; GGT = gamma-glutamyl transferase; HFE = hemochromatosis; MOI = mode of inheritance

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with alpha-1 antitrypsin deficiency (AATD), the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with AATD

System/Concern	Evaluation	Comment
Lungs	Pulmonary function tests	Include: • Spirometry (w/post-bronchodilator testing) • Lung volumes • Diffusing capacity • Measures of oxygenation
	Chest CT	More sensitive for detecting emphysema than pulmonary function tests
Liver	Liver biopsy	For light microscopy & histochemistry when definition of precise nature & extent of liver disease is clinically indicated
Skin	Detailed history & physical exam	Assess for panniculitis
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of AATD to facilitate medical & personal decision making

AATD = alpha-1 antitrypsin deficiency; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 7. Treatment of Manifestations in Individuals with AATD

Manifestation/Concern	Treatment	Considerations/Other
Lung disease	Varies by type of lung disease	
COPD	Standard therapy incl ICS, LABA, long-acting muscarinic antagonists, pulmonary rehabilitation, supplemental oxygen, & vaccinations (e.g., influenza & pneumococcal)	Although the inflammation of COPD is generally poorly responsive to ICS, a randomized study indicates that ICS may reduce dynamic hyperinflation, improve FEV_1, walking distance, & dyspnea when added to LABA in AATD [Corda et al 2008].
Emphysema	Augmentation therapy w/periodic intravenous infusion of pooled human serum AAT	• Used in those w/established emphysema • The greatest benefit of this therapy is observed in individuals w/moderate degrees of airflow obstruction (e.g., FEV_1 35%-60% predicted) • Hospitalizations & COPD exacerbations may ↑ after interruption of augmentation [McElvaney et al 2020].
End-stage lung disease (FEV_1 <30%)	Lung transplantation	May have ↑ short-term complications perhaps related to discontinuation of augmentation before transplantation, w/ improved long-term survival relative to AATD replete COPD [Kleinerova et al 2019, Spratt et al 2019]
Liver disease	Liver transplantation for severe disease	Will restore AAT levels
	Vaccinations against hepatitis A & B	

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Panniculitis	Dapsone or doxycycline therapy; if refractory to this, high-dose intravenous AAT augmentation therapy [Stoller & Piliang 2008]	

AAT = alpha-1 antitrypsin; AATD = alpha-1 antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting beta agonists

Surveillance

Table 8. Recommended Surveillance for Individuals with AATD

System/Concern	Evaluation	Frequency
Lung disease	Pulmonary function tests (incl spirometry w/bronchodilators & diffusing capacity measurements)	Every 6-12 mos [Attaway et al 2019]
Liver disease	Liver function tests, platelet count & liver ultrasound, elastography (e.g., FibroScan), MRI	

MRI = magnetic resonance imaging

Agents/Circumstances to Avoid

Avoid the following:

- Smoking (both active and passive)
- Occupational exposure (including exposure to environmental pollutants used in agriculture, mineral dust, gas, and fumes)
- Excessive use of alcohol

Evaluation of Relatives at Risk

The Alpha-1 Foundation-sponsored update of the ATS/ERS guidelines [Sandhaus et al 2016] and the European Respiratory Society statement [Miravitlles et al 2017] recommend evaluation of sibs, parents, and the children of an individual with severe AATD (see Table 2) in order to identify as early as possible those who would benefit from surveillance, institution of treatment, and preventive measures.

Extended pedigree analysis beyond first-degree relatives may be indicated in selected instances. For example, the presence of an AATD-associated condition (e.g., chronic obstructive pulmonary disease [COPD], liver disease, panniculitis) in a more distant family member and/or the finding that a parent of the proband has the PI*ZZ genotype would justify extensive family testing (i.e., of family members beyond parents, sibs, and offspring) [Miravitlles et al 2017].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Management of women with AATD during pregnancy should be guided by usual care principles, both for women without clinical disease and for those with liver disease. As noted, emphysema, especially in nonsmokers, would not commonly be expected during the usual childbearing age range.

Therapies Under Investigation

Many novel therapies for AATD are currently under investigation. Studies to slow the progression of lung disease include a variety of strategies: inhaled alpha-1 antitrypsin (AAT), liquid AAT, recombinant AAT, alternate dosing regimens of intravenous augmentation therapy (including double-dose strategies), an oral neutrophil elastase inhibitor, an orally available corrector molecule designed to restore secretion and acute phase reactivity, molecules to block polymer formation, and gene therapy using various viral vectors and delivery routes. Placement of valves endoscopically to improve lung function and functional status is also being studied. Examples of studies directed at the AATD-related liver disease include use of carbamazepine or sirolimus to increase autophagy and use of small interfering RNA to suppress aberrant AAT protein translation.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on these clinical studies.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Alpha-1 antitrypsin deficiency (AATD) is inherited in an autosomal codominant manner.

Risk to Family Members

Parents of a proband

- Either both parents of an individual with AATD are heterozygous for one *SERPINA1* pathogenic variant (e.g., PI*MZ or PI*SZ) or, less frequently, a parent may be homozygous for the PI*Z allele (i.e., PI*ZZ).
- Molecular genetic testing is recommended for the parents of a proband to confirm their genetic status and to allow reliable recurrence risk assessment (see also Management, Evaluation of Relatives at Risk).
- In general, nonsmoking heterozygotes are not considered to be at increased risk for lung disease; however, PI*MZ heterozygotes who have smoked are at increased risk for emphysema (see Genotype-Phenotype Correlations for additional information regarding risk of lung disease in heterozygotes).

Sibs of a proband

- If both parents are heterozygous (e.g., PI*MZ) for a pathogenic variant, each sib of an affected individual has a 25% chance of being affected (i.e., PI*ZZ), a 50% chance of being heterozygous (i.e., PI*MZ), and a 25% chance of inheriting neither of the pathogenic variants (i.e., PI*MM).
- If one parent is homozygous (i.e., PI*ZZ) for biallelic pathogenic variants and the other parent is heterozygous (e.g., PI*MZ) for a pathogenic variant, each sib has a 50% chance of being affected (i.e., PI*ZZ) and a 50% chance of being heterozygous (e.g., PI*MZ).
- In general, nonsmoking heterozygotes are not considered to be at increased risk for lung disease; however, PI*MZ heterozygotes who have smoked are at increased risk for emphysema (see Genotype-Phenotype Correlations for additional information regarding risk of lung disease in heterozygotes).
- Molecular genetic testing should be offered to all sibs in order to clarify their genetic status and identify as early as possible those who would benefit from surveillance, institution of treatment, and preventive measures.

Offspring of a proband

- Unless an individual with AATD has children with an affected individual or a heterozygote, offspring will be heterozygous for a pathogenic variant (e.g., PI*MZ).
- In populations with a high carrier frequency and/or a high rate of consanguinity, the reproductive partner of the proband may also have one or more *SERPINA1* pathogenic variants. Thus, the risk to offspring is most accurately determined after (a) protease inhibitor (PI) typing by isoelectric focusing of serum or (b) *SERPINA1* molecular genetic testing of the proband's reproductive partner.

Other family members. If the parents are heterozygous (e.g., PI*MZ) for a *SERPINA1* pathogenic variant, each sib of the proband's parents is at a 50% risk of being heterozygous for a pathogenic variant (e.g., PI*MZ).

Heterozygote Detection

Targeted molecular genetic testing for at-risk relatives requires prior identification of the *SERPINA1* pathogenic variants in the family. If the pathogenic variants in the family have not been identified, heterozygote testing by protease inhibitor (PI) typing by isoelectric focusing of serum or *SERPINA1* sequence analysis and deletion/duplication analysis are options.

Note: Measurement of serum AAT level is not reliable for determining carrier status because the range of serum AAT levels among most carriers may overlap the normal serum range [Bornhorst et al 2013]. In addition, AAT is an acute-phase reactant and therefore serum AAT levels in a heterozygote may be elevated during periods of acute inflammation, thereby confounding the diagnosis of deficiency.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Risk to sibs of developing severe liver disease in infancy. Although the age of onset, severity, type of symptoms, and rate of progression of AATD cannot be predicted in sibs based on genotype, some estimates are available on the risk to sibs of developing severe liver disease in infancy [Cox 2004].

- If the parents are heterozygotes (e.g., PI*MZ) but have not had a child with severe liver disease, the risk to offspring of having AATD (25%) AND severe liver disease in childhood (13.6%) is less than 1% (0.64%).
- If an affected individual died from severe liver disease in childhood, the risk to sibs of having AATD (25%) AND severe liver disease in childhood (40%) is 10%.
- If an affected individual did not have severe liver disease in childhood or if the liver disease resolved, the risk to sibs of having AATD (25%) AND liver disease (13%) is 3.3%.

Family planning. The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *SERPINA1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for AATD are possible.

Note: Prenatal testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression of the disorder. Fetal testing is not recommended in the American Thoracic Society/European Respiratory Society guidelines or in most other available guidelines [Attaway et al 2019] because of the variable expressivity of disease and the possibility that individuals with severe deficiency of AAT can have a normal life span and escape disease, especially if they never smoke [American Thoracic Society & European Respiratory Society 2003]. Because some children with AATD develop severe liver disease in the newborn period and some of these children have a poor outcome, prenatal diagnosis may be of interest to some at-risk couples who have previously had a child with severe liver disease (see Related Genetic Counseling Issues, **Risk to sibs of developing severe liver disease in infancy**).

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Alpha-1 Advocacy Alliance**
  103 Rapidan Church Lane
  PO Box 202
  Wolftown VA 22748
  Phone: 866-367-2122 (toll-free); 540-948-6777
  Fax: 540-948-6763
  Email: alpha1advocacyalliance@yahoo.com
  Alpha-1 Advocacy Alliance

- **Alpha-1 Canada**
  13300 Tecumseh Road East,
  Suite 241
  Tecumseh Ontario N8N 4R8
  Canada
  Phone: 888-669-4583 (toll-free); 519-258-1444
  Fax: 519-258-1614
  Email: info@alpha1canada.ca
  www.alpha1canada.ca

- **Alpha-1 Foundation**
  3300 Ponce de Leon Boulevard
  Coral Gables FL 33134
  Phone: 877-228-7321; 305-567-9888
  Fax: 305-567-1317
  Email: info@alpha-1foundation.org
  www.alpha-1foundation.org

- **MedlinePlus**
  Alpha-1 antitrypsin deficiency

- **NCBI Genes and Disease**
  Alpha -1-antitrypsin deficiency

- **American Liver Foundation**
  Phone: 800-465-4837 (HelpLine)
  www.liverfoundation.org
- **Canadian Liver Foundation**
  Canada
  Phone: 800-563-5483
  Email: clf@liver.ca
  www.liver.ca
- **Childhood Liver Disease Research Network (ChiLDReN)**
  Phone: 720-777-2598
  Email: joan.hines@childrenscolorado.org
  www.childrennetwork.org
- **Children's Liver Disease Foundation**
  United Kingdom
  Phone: +44 (0) 121 212 3839
  Email: info@childliverdisease.org
  childliverdisease.org
- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  RareCare® Patient Assistance Programs
- **Alpha-1 Canadian Registry**
  Toronto Western Hospital
  399 Bathurst Street
  7th Floor, East Wing, Room 445
  Toronto Ontario M5T 2S8
  Canada
  Phone: 800-352-8186 (toll-free); 416-603-5020
  Fax: 416-603-5020
  Email: alpha1canadianregistry@gmail.com
  www.alpha1canadianregistry.com
- **Alpha-1 Research Registry**
  Phone: 877-228-7321 ext 252
  Email: alpha1registry@alpha1.org
  www.alpha1.org/investigators/resources/research-registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Alpha-1 Antitrypsin Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

SERPINA1	14q32.13	Alpha-1-antitrypsin	CCHMC - Human Genetics Mutation Database (SERPINA1)	SERPINA1	SERPINA1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Alpha-1 Antitrypsin Deficiency (View All in OMIM)

107400	SERPIN PEPTIDASE INHIBITOR, CLADE A, MEMBER 1; SERPINA1
613490	ALPHA-1-ANTITRYPSIN DEFICIENCY; A1ATD

Molecular Pathogenesis

SERPINA1 encodes alpha-1 antitrypsin (AAT), a glycoprotein member of the serum protease inhibitor (serpin) family. The molecule is composed of 418 amino acids; the first 24 are the signal peptide, while residues 25-418 encode the mature protein. AAT provides more than 90% of the protection against neutrophil elastase in the lower airways.

Mechanism of disease causation. The AAT disease mechanism can be either loss of function or gain of function.

- **Lung disease.** Alpha-1 antitrypsin deficiency (AATD) results in reduced inhibition of neutrophil elastase in the lung (which is increased in smokers), resulting in excessive destruction of the elastin in the alveolar walls. Thus, lung disease is considered to result from a **loss-of-function** mechanism.
- **Liver disease.** Abnormal AAT alleles (e.g., Z, M $_{malton}$, S $_{iiyama}$) polymerize within hepatocytes [Carrell & Lomas 2002], precluding secretion. Accumulation of abnormal AAT protein is associated with liver disease through a **gain-of-function** mechanism [Kopito & Ron 2000, Perlmutter 2002].

Protein variants, such as the PI*S variant, are more easily degraded. The PI*Z variant polymerizes within hepatocytes and alveolar macrophages where it was shown to be chemotactic for neutrophils. Thus, in addition to a loss-of-function mechanism, lung destruction may be fueled by an inflammatory reaction related to the polymers of Z protein variants in the lung [McElvaney et al 1997].

***SERPINA1*-specific laboratory technical considerations.** Targeted testing for PI*Z, PI*S, PI*I, and PI*F is frequently performed. Differentiating targeted versus sequencing methods on a clinical report is important since targeted analysis detects about 95% of disease alleles.

Table 9. Notable *SERPINA1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_000295.4 NP_000286.3	c.1096G>A	p.Glu366Lys (Glu342Lys)	PI*Z; 95% of AATD-related disease results from homozygosity of this allele (i.e., PI*ZZ) [McElvaney et al 1997]; aggregates in the liver [Carrell & Lomas 2002].
	c.863A>T	p.Glu288Val (Glu264Val)	PI*S; common pathogenic variant when in combination w/other variants (i.e., PI*SZ) [McElvaney et al 1997]
	c.226_228del	p.Phe76del (Phe52del)	PI*M_{malton}; aggregates in the liver [Carrell & Lomas 2002]
	c.230C>T	p.Ser77Phe (Ser53Phe)	PI*S_{iiyama}; aggregates in the liver [Carrell & Lomas 2002]
	c.739C>T	p.Arg247Cys (Arg223Cys)	PI*F; quantitatively normal but functionally impaired in binding neutrophil elastase; PI*FF is diagnosed by molecular methods rather than serum AAT level alone [Sinden et al 2014].
	c.187C>T	p.Arg63Cys (Arg39Cys)	PI*I; common allele assoc w/mild disease [Graham et al 1989]

AAT = alpha-1 antitrypsin; AATD = alpha-1 antitrypsin deficiency
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions; historical nomenclature does not include the signal sequence of the reference protein NP_000286.3, thereby decreasing the amino acid codon number by 24 amino acids for each variant.

Chapter Notes

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- 1 June 2023 (aa) Revision: Table 4: emphysema risk clarified to be lifetime emphysema risk
- 21 May 2020 (ha) Comprehensive update posted live
- 19 January 2017 (jks) Revision: clarification re serum levels of AAT in heterozygotes
- 1 May 2014 (me) Comprehensive update posted live
- 6 February 2008 (cd) Revision: sequence analysis available on a clinical basis

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- 15 February 2005 (dc) Original submission

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