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Complete Plasminogen Activator Inhibitor 1 Deficiency

Synonyms: Complete PAI-1 Deficiency, Homozygous PAI-1 Deficiency

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Summary

Clinical characteristics

Untreated complete plasminogen activator inhibitor 1 (PAI-1) deficiency is characterized by mild-to-moderate bleeding, although in some instances bleeding can be life-threatening. Most commonly, delayed bleeding is associated with injury, trauma, or surgery; spontaneous bleeding does not occur. While males and females with complete PAI-1 deficiency are affected equally, females may present more frequently with clinical manifestations or earlier in life than males due to menorrhagia and postpartum hemorrhage. Fewer than ten families with complete PAI-1 deficiency have been reported to date. The incidence of complete PAI-1 deficiency is higher than expected in the genetic isolate of the Old Order Amish population of eastern and southern Indiana due to a pathogenic founder variant. In one family from this Old Order Amish population, seven individuals were diagnosed to have cardiac fibrosis of varying degrees.

Diagnosis/testing

The diagnosis of complete PAI-1 deficiency is established in a proband when PAI-1 antigen is undetectable and PAI-1 activity is lower than 1 IU/mL and/or biallelic *SERPINE1* pathogenic variants are identified on molecular genetic testing. Note that because the normal range of functional PAI-1 activity assay starts at zero in most laboratories, the ability to discriminate between normal and abnormal levels of activity is limited.

Management

Treatment of manifestations: Management of the bleeding disorder by a team of experts in the treatment of individuals with bleeding disorders is highly recommended. Intravenous antifibrinolytics (e.g., epsilon-aminocaproic acid [EACA] and tranexamic acid) can be used for severe bleeding manifestations, including intracranial hemorrhage (with or without hematoma evacuation). Infusion of fresh-frozen plasma can be used as

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needed to increase PAI-1 activity prior to achieving therapeutic steady-state levels of antifibrinolytics. Heavy menstrual bleeding can often be managed with oral antifibrinolytics or hormonal suppression therapy. Since there is no specific treatment of cardiac fibrosis, symptomatic treatment as needed.

Prevention of primary manifestations: Antifibrinolytics should be used to prevent bleeding for surgical and dental procedures, childbirth, and other invasive procedures.

Surveillance: Regular follow up with a team of experts in the treatment of individuals with bleeding disorders is recommended. For all individuals with complete PAI-1 deficiency, screening echocardiogram and EKG for assessment of cardiac function and cardiac MRI for quantification of fibrosis is recommended at diagnosis with close monitoring by a cardiologist based on the initial findings. The age of onset of cardiac fibrosis is unknown; therefore, an initial normal evaluation does not rule out the need for further surveillance.

Agents/circumstances to avoid: Medications that affect coagulation including aspirin, ibuprofen, and some herbal remedies; high-risk activities such as contact sports.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an individual with complete PAI-1 deficiency in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Pregnancy management: Recommendations based on published findings during pregnancies in two women with complete PAI-1 deficiency are oral administration of either tranexamic acid or EACA for intermittent bleeding in the first and second trimester, continuous administration from 26 weeks' gestation through delivery to prevent preterm labor, and for at least two weeks postpartum to prevent postpartum bleeding. Note: Evidence that these recommendations would be effective in all pregnancies of women with complete PAI-1 deficiency is lacking; the teratogenicity of EACA and tranexamic acid is unknown and information regarding their safety during pregnancy and lactation is limited.

Genetic counseling

Complete PAI-1 deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *SERPINE1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *SERPINE1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk for complete PAI-1 deficiency, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Complete plasminogen activator inhibitor 1 (PAI-1) deficiency **should be suspected** in individuals with the following medical history and laboratory findings.

Medical History

Bleeding disorder that typically presents as:

- Delayed bleeding following injury, trauma, or surgery
- In females, menorrhagia and abnormal bleeding with pregnancy

Absence of other known bleeding disorders including:

- von Willebrand disease

- Deficiencies of factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XIII, or factor V & VIII
- Alpha-2-antiplasmin deficiency
- Factor XIII deficiency
- Platelet function disorders (including Scott syndrome and Quebec platelet disorder)

Laboratory Findings

Normal. Common tests of coagulation including prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin clotting time (TCT)

Abnormal. Tests indicative of a hyperfibrinolytic state; these may include the following:

- Free tissue plasminogen activator (tPA) in the absence of PAI-1 is cleared faster, leading to lower levels of tPA antigen in individuals with PAI-1 deficiency. Low PAI-1 activity with normal or increased tPA antigen is usually due to prolonged application of the tourniquet during blood draw, leading to increased tPA in the sample and falsely low PAI-1 activity.
- Shortened euglobin lysis time (ECLT) in plasma. Note: While ECLT is shortened due to excessive fibrinolysis in individuals with complete PAI-1 deficiency, and ECLT and whole blood clotting assays (e.g., thromboelastogram) can be helpful in diagnosis of hyperfibrinolytic states, these tests are insufficient to confirm or exclude the diagnosis of complete PAI-1 deficiency.

PAI-1 specific assays:

- PAI-1 antigen assay (to determine the level of PAI-1 antigen) can be helpful in identifying complete PAI-1 deficiency if no PAI-1 is produced, but is not helpful if dysfunctional protein is produced [Gupta et al 2014].
- PAI-1 activity assay can be used to exclude a diagnosis of complete PAI-1 deficiency when PAI-1 activity levels are clearly within the normal range. Because the normal range of the functional PAI-1 activity assay starts at zero in most laboratories, the ability to discriminate between normal and abnormal levels of activity is limited [Fay et al 1997, Mehta & Shapiro 2008].

Note: If the PAI-1 antigen level is normal and PAI-1 activity is decreased, the phenotype is referred to as qualitative PAI-1deficiency or dysfunctional PAI-1 [Fay et al 1997, Mehta & Shapiro 2008].

Establishing the Diagnosis

The diagnosis of complete PAI-1 deficiency **is established** in a proband when [Fay et al 1997, Iwaki et al 2011]:

- PAI-1 antigen is undetectable and PAI-1 activity is lower than 1 IU/mL.

  Note: (1) Because the majority of PAI-1 activity assays are used to detect increased PAI-1 activity rather than decreased PAI-1 activity, they lack the sensitivity to differentiate between low-normal activity and complete deficiency. Thus, a PAI-1 activity level of zero is often reported to be within the normal limits. (2) PAI-1 activity also demonstrates diurnal variation: because higher levels are observed in the morning and lower levels in the afternoon, the activity should be assayed in a sample drawn in the morning.

AND/OR

- Biallelic *SERPINE1* pathogenic (or likely pathogenic) variants are identified on molecular genetic testing (see Table 1). See also Molecular Genetics.

  Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic

and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *SERPINE1* variants of uncertain significance (or of one known *SERPINE1* pathogenic variant and one *SERPINE1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *SERPINE1* is performed first. If only one or no *SERPINE1* pathogenic variant is identified, gene-targeted deletion/duplication analysis can be considered; however, to date no *SERPINE1* exon or whole-gene deletions/duplications have been reported.

  Note: Targeted analysis for the c.699_700dupTA pathogenic variant can be performed first in individuals from the Old Order Amish community of eastern and southern Indiana. Note: This variant has not been identified in other Old Order Amish populations.

- **A multigene panel** that includes *SERPINE1* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Complete Plasminogen Activator Inhibitor 1 Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
SERPINE1	Sequence analysis [3]	<100% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	None reported [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. 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.
4. One reported individual with a lifelong history of bleeding associated with surgery and trauma had a heterozygous missense *SERPINE1* variant; the authors ultimately concluded that a second pathogenic variant was present but undetectable [Zhang et al 2005].
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson 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. To date, no exon or multiexon *SERPINE1* deletions/duplications have been reported in individuals with complete plasminogen activator inhibitor 1 deficiency [Stenson et al 2020].

Clinical Characteristics

Clinical Description

Untreated complete plasminogen activator inhibitor 1 (PAI-1) deficiency is characterized by mild-to-moderate bleeding, although in some instances bleeding can be life-threatening. Most commonly, delayed bleeding is associated with injury, trauma, or surgery; spontaneous bleeding episodes such as those observed in classic hemophilia A and hemophilia B do not occur.

While males and females with complete PAI-1 deficiency are affected equally, females may present with clinical manifestations more frequently or earlier in life than males, due to menorrhagia and postpartum hemorrhage. In addition, females experience bleeding with pregnancy and can have difficulty carrying a pregnancy to term.

Bleeding disorder. Mucocutaneous bleeding, a hallmark of complete PAI-1 deficiency, includes oral bleeding, epistaxis, and (in females) menorrhagia and postpartum bleeding.

Post-traumatic bleeding can include joint bleeds and hematomas [Schleef et al 1989, Diéval et al 1991, Minowa et al 1999]. Affected members of the kindred from the Old Order Amish community of eastern and southern Indiana developed knee and elbow hemarthroses after minor trauma, extensive subperiosteal bleeding after minor jaw trauma, and epidural hematoma (in an infant) after a head injury [Fay et al 1997].

The male reported by Zhang et al [2005] experienced soft tissue hematomas of the leg and hip following minor leg trauma that required treatment; he subsequently manifested muscle atrophy.

A 17-year-old male with molecularly confirmed complete PAI-1 deficiency experienced a recurrent iliopsoas bleed over several years. He had a previous history of liver hematoma after a fall at age seven years [Prabhudesai et al 2020].

Postsurgical bleeding has been reported in individuals with a molecularly confirmed diagnosis of complete PAI-1 deficiency:

- A child age five years experienced postoperative bleeding following surgical repair of a ventricular septal defect [Iwaki et al 2011].
- A member of the Old Order Amish community had delayed bleeding after surgical repair of an inguinal hernia [Fay et al 1997].
- Delayed bleeding was reported after total hip arthroplasty [Hirose et al 2016].

Prolonged bleeding after dental extraction has been reported in individuals with a molecularly confirmed diagnosis of complete PAI-1 deficiency [Fay et al 1997, Iwaki et al 2011].

A palatal hemorrhage complicated a dental abscess, requiring hospitalization and transfusion [Fay et al 1992].

Prolonged wound healing occurred in one individual [Iwaki et al 2011].

Menorrhagia is a consistent characteristic of complete PAI-1 deficiency [Minowa et al 1999, Mehta & Shapiro 2008, Iwaki et al 2011]. In some instances, treatment with transfusion of packed red blood cells [Mehta & Shapiro 2008] or whole blood is required [Iwaki et al 2011].

In one woman rupture of an ovarian follicle resulted in hemoperitoneum requiring hospitalization, treatment with antifibrinolytics, and red blood cell transfusion.

Pregnancy can be complicated by sporadic antenatal bleeding, preterm labor, postpartum bleeding, and miscarriage. Gupta et al [2014] (full text) followed two women with complete PAI-1 deficiency through a total of seven pregnancies that resulted in six live-born premature infants and one miscarriage. Bleeding, which began

between eight and 19 weeks' gestation and recurred prior to delivery, was treated with epsilon-aminocaproic acid (EACA). Postpartum bleeding was treated with EACA for up to six weeks (see Pregnancy Management). A third woman, not included in the review by Gupta et al [2014], has had four pregnancies. In the first two pregnancies noncompliance and inconsistent EACA treatment resulted in preterm labor and presentation with hemorrhage and disseminated intravascular coagulation necessitating emergency cæsarean section at 35 weeks' gestation. In the last two pregnancies, compliance with EACA treatment resulted in normal vaginal deliveries at term [Authors, personal observation]. Iwaki et al [2012] also reported on three pregnancies in a woman with complete PAI-1 deficiency in which antenatal bleeding, preterm labor, and miscarriage were complications.

Cardiac fibrosis. Mouse models have shown that PAI-1 deficiency has a deleterious effect on cardiac matrix remodeling leading to cardiac fibrosis [Flevaris & Vaughan 2017]. In humans, cardiac fibrosis has only been reported in an Old Order Amish kindred with complete PAI-1 deficiency, which is – to the authors' knowledge – the largest number of affected individuals with this finding reported to date [Flevaris et al 2017, Khan et al 2021]. Of the initial eight individuals identified with cardiac fibrosis (ages 15 to 35 years), one individual suffered sudden cardiac death. Thus, to date, information about cardiac fibrosis in complete PAI-1 deficiency is limited.

Genotype-Phenotype Correlations

Because data on the phenotype associated with biallelic *SERPINE1* pathogenic variants are limited, no genotype-phenotype correlations can be made at this time.

Nomenclature

Complete PAI-1 deficiency, the topic of this *GeneReview*, is defined as undetectable PAI-1 antigen levels and undetectable PAI-1 activity. Complete PAI-1 deficiency may also be referred to as quantitative PAI-1 deficiency or homozygous PAI-1 deficiency.

Qualitative PAI-1 deficiency, not addressed in this *GeneReview*, refers to normal PAI-1 antigen levels and decreased PAI-1 activity and is thought to be associated with either a heterozygous *SERPINE1* pathogenic variant (i.e., the carrier state for an autosomal recessive disorder) or compound heterozygosity for variants that produce a reduced amount of protein that is nonetheless sufficient to avoid complete deficiency. The clinical significance of qualitative PAI-1 deficiency is unknown. See also Molecular Genetics.

Prevalence

The prevalence of complete PAI-1 deficiency is unknown, in large part because of the inability of the majority of tests of PAI-1 activity to differentiate between low-normal activity and complete deficiency (see Establishing the Diagnosis).

Fewer than ten families with complete PAI-1 deficiency have been reported to date.

Complete PAI-1 deficiency has no known racial or ethnic predominance. It has been reported in North America, Europe, and Asia.

Of note, the incidence of complete PAI-1 deficiency is higher than expected in the genetic isolate of the Old Order Amish population of eastern and southern Indiana due to a pathogenic founder variant (see Molecular Genetics). To date, this pathogenic variant has not been found in other Old Order Amish communities.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SERPINE1*.

Differential Diagnosis

Table 2 lists genetic, mild-to-moderate bleeding disorders in the differential diagnosis of complete plasminogen activator inhibitor 1 (PAI-1) deficiency. With the exception of alpha-2-antiplasmin deficiency, bleeding in these disorders is typically associated with injury, surgery, or dental procedures.

Table 2. Genes of Interest in the Differential Diagnosis of Complete Plasminogen Activator Inhibitor 1 Deficiency

Gene(s)	Disorder	MOI
ANO6 *GP1BA* *GP1BB* *GP9* *ITGA2B* *ITGB3*	Platelet function defects (OMIM 177820, 187800, 231200, & 262890)	AD AR
F13A1 *F13B*	Factor XIII deficiency (OMIM 613225 & 613235)	AR
F2	Factor II (prothrombin) deficiency (OMIM 613679)	AR
F5	Factor V deficiency (OMIM 227400)	AR
	East Texas bleeding disorder [1]	AD
F10	Factor X deficiency (OMIM 227600)	AR
PLAU	Quebec platelet disorder (OMIM 601709)	AD
SERPINF2	Alpha-2-antiplasmin deficiency [2] (OMIM 262850)	AR
VWF	von Willebrand Disease (VWD)	AD AR

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; PLI = plasmin inhibitor

1. Peterson et al [2022]

2. The moderate bleeding seen in alpha-2-antiplasmin deficiency is not characteristically associated with injury, surgery, or dental procedures.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with complete plasminogen activator inhibitor 1 (PAI-1) deficiency, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Questions to elicit an individual's history of:
  - Epistaxis
  - Poor wound healing
  - Bleeding in association with injury or trauma
  - Bleeding with dental extractions
  - Additional oral bleeding
  - Postsurgical bleeding
  - In females: heavy menstrual bleeding, postpartum bleeding, bleeding during pregnancy, preterm delivery, and bleeding in association with ovulation

- History of therapies tried in the past and the response to each specific therapy

  Note: Response to antifibrinolytic therapy may support the diagnosis of complete PAI-1 deficiency (see Treatment of Manifestations).

- Evaluation by a hematologist with expertise in disorders of coagulation
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of complete PAI-1 deficiency in order to facilitate medical and personal decision making

Treatment of Manifestations

Bleeding disorder. Management by a team of experts in the treatment of individuals with bleeding disorders is highly recommended. In the United States, such teams are often identified through the federally funded hemophilia treatment center network.

Severe bleeding manifestations, including intracranial hemorrhage (with or without hematoma evacuation), have been successfully managed with intravenous antifibrinolytics. Response to both epsilon-aminocaproic acid (EACA) and tranexamic acid have been documented.

If PAI-1 activity needs to be increased prior to achieving the therapeutic steady-state level of antifibrinolytics, infusion of fresh-frozen plasma (FFP) (10-15 mL/kg) can be used. Duration of use of FFP is individualized based on clinical course and response to therapy. Of note, monitoring PAI-1 levels is not recommended during treatment with FFP; assessment of clinical response should guide therapy decisions. Note: The use of FFP does not appear to be effective in pregnancy for the prevention of bleeding in women with complete PAI-1 deficiency [Iwaki et al 2012]. FFP to replace PAI-1 during pregnancy may be difficult due to the PAI-1 level achieved with plasma, the volume required, and the need for repeated infusion, all of which may be associated with risk of volume overload and/or infusion reactions [Gupta et al 2014].

Heavy menstrual bleeding can often be effectively managed with continuous or intermittent prophylactic use of the antifibrinolytics tranexamic acid and EACA and/or hormonal suppression therapy (oral contraceptives).

Occasionally, individuals with complete PAI-1 deficiency experience excessive menstrual bleeding or bleeding following a procedure or trauma that requires infusion of packed red blood cells to manage the acute blood loss.

Education regarding bleeding manifestations and when to seek treatment includes the following:

- For females, anticipatory counseling regarding onset of menses and potential complications
- Prompt reporting of injuries and planned procedures to allow early initiation of treatment to prevent significant bleeding

Cardiac fibrosis. There is currently no specific treatment for cardiac fibrosis associated with complete PAI-1 deficiency. Treatment is symptomatic as recommended by the treating cardiologist.

Prevention of Primary Manifestations

Antifibrinolytics should be used to prevent bleeding for surgical and dental procedures, childbirth, and other invasive procedures. Antifibrinolytics can be administered intravenously, orally, or topically, the latter especially during dental procedures.

Surveillance

Bleeding disorder. Regular follow up with a team of experts in the treatment of individuals with bleeding disorders is recommended. Such teams are often identified through the federal hemophilia treatment center network in the US.

For menstruating females:

- Regular monitoring of hemoglobin and/or hematocrit and iron studies including ferritin for possible iron deficiency and/or anemia
- Assessment of the effectiveness of therapeutic interventions such as antifibrinolytics or hormonal suppressive agents (oral contraceptives)

Cardiac fibrosis. Because of limited clinical experience with cardiac fibrosis in persons with complete PAI-1 deficiency [Flevaris et al 2017, Khan et al 2021], screening echocardiogram and EKG to assess cardiac function and cardiac MRI (to quantify cardiac fibrosis) can be considered at the time of diagnosis. The age of onset for cardiac fibrosis is not known in this population and follow-up screening should be considered [Ghosh et al 2010; Ghosh et al 2013; Authors, personal observation].

Agents/Circumstances to Avoid

The following should be avoided:

- Medications that affect coagulation including aspirin, ibuprofen, and some herbal remedies
- High-risk activities such as contact sports

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an individual with complete PAI-1 deficiency in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures. Evaluations can include:

- Molecular genetic testing if the *SERPINE1* pathogenic variants in the family are known;
- Measurement of PAI-1 antigen levels and PAI-1 activity if the *SERPINE1* pathogenic variants in the family are not known.

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

Pregnancy Management

Recommendations based on published findings during pregnancies in two women with complete PAI-1 deficiency are administration of either tranexamic acid (25 mg/kg per dose, maximum 1,300 mg, orally 3-4 times per day) or epsilon-aminocaproic acid (EACA) (100 mg/kg per dose, maximum 3 g, orally 4 times per day) for intermittent bleeding in the first and second trimester, continuous treatment from 26 weeks' gestation through delivery to prevent preterm labor, and for at least two weeks postpartum to prevent postpartum bleeding [Heiman et al 2014]. Note that evidence that these recommendations would be effective in all pregnancies of women with complete PAI-1 deficiency is lacking.

A woman with complete PAI-1 deficiency was treated with FFP during three pregnancies at eight to 11 weeks' gestation two to three times per week; FFP treatment was increased to daily at 20 to 28 weeks' gestation. The first pregnancy ended in miscarriage at 19 weeks. The second and third pregnancies were delivered at 32 and 27 weeks' gestation, respectively, as a result of uncontrollable contractions and placental abruption [Iwaki et al 2012].

Of note, the teratogenicity of EACA and tranexamic acid is unknown and information regarding their safety during pregnancy and lactation is limited. There is a need to establish dosing guidelines for the use of antifibrinolytics during pregnancy and the postpartum period.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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

Complete plasminogen activator inhibitor 1 (PAI-1) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *SERPINE1* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *SERPINE1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing complete PAI-1 deficiency.

Sibs of a proband

- If both parents are known to be heterozygous for a *SERPINE1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing complete PAI-1 deficiency.

Offspring of a proband

- Unless an affected individual's reproductive partner also has complete PAI-1 deficiency or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *SERPINE1*.
- The incidence of complete PAI-1 deficiency is higher than expected in the genetic isolate of the Old Order Amish population of eastern and southern Indiana due to a pathogenic founder variant, increasing the

risk that an affected individual may have a reproductive partner who is heterozygous for a *SERPINE1* pathogenic variant (see Prevalence). The offspring of an affected individual and a heterozygous reproductive partner are at 50% risk of being affected and 50% risk of being heterozygous.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *SERPINE1* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *SERPINE1* pathogenic variants in the family.

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.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers. This includes issues related to pregnancy in affected women and the risk to the fetus due to risk of prematurity (see Pregnancy Management).
- Carrier testing for reproductive partners of known carriers should be considered, particularly if both partners are of the same ethnic background. The incidence of complete PAI-1 deficiency is higher than expected in the genetic isolate of the Old Order Amish population of eastern and southern Indiana due to a pathogenic founder variant (see Prevalence).

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 *SERPINE1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for complete PAI-1 deficiency are possible.

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.

- **Rare Coagulation Disorders Resource Room**
  Plasminogen Activator Inhibitor Type 1 Deficiency

- **Rare Coagulation Disorders Resource Room**
  Patient Advocacy and Support Groups
- **National Hemophilia Foundation**
  Phone: 212-328-3700; 888-463-6643
  Email: info@hemophilia.org
  www.hemophilia.org

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. Complete Plasminogen Activator Inhibitor 1 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SERPINE1	7q22.1	Plasminogen activator inhibitor 1	SERPINE1 database	SERPINE1	SERPINE1

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 Complete Plasminogen Activator Inhibitor 1 Deficiency (View All in OMIM)

173360	SERPIN PEPTIDASE INHIBITOR, CLADE E (NEXIN, PLASMINOGEN ACTIVATOR INHIBITOR TYPE 1), MEMBER 1; SERPINE1
613329	PLASMINOGEN ACTIVATOR INHIBITOR-1 DEFICIENCY

Molecular Pathogenesis

Plasminogen activator inhibitor 1 (PAI-1), a protein that is a member of the serine protease inhibitor (SERPIN) superfamily, is involved in a variety of pathophysiologic systems including embryogenesis, angiogenesis, ovulation, inflammation, and tumor metastasis. These observations suggest that the plasminogen activation system is an important mediator of tissue remodeling and cell migration [Gupta et al 2014] (full text).

In hemostasis, PAI-1 regulates fibrinolysis (i.e., the degradation of thrombi) [Gupta et al 2014]. PAI-1 is an inhibitor of tissue-type plasminogen activators (tPA) and urokinase-type plasminogen activators (uPA), which convert plasminogen to plasmin, the primary protease responsible for fibrinolysis. Thus, complete PAI-1 deficiency results in excessive fibrinolysis manifesting as mild-to-moderate bleeding [Heiman et al 2014]. Physiologic fibrinolysis occurs exclusively on the clot surface within a blood vessel and not in the circulation [Gupta et al 2014] (see Figure 1).

Heterozygous pathogenic variants in *SERPINE1* may be associated with qualitative PAI-1 deficiency (i.e., normal PAI-1 antigen levels and decreased PAI-1 activity). However, the significance of reports of families with qualitative PAI-1 deficiency and a heterozygous *SERPINE1* variant should be interpreted with caution because (1) the PAI-1 activity assays used in these families lack the sensitivity to differentiate between low-normal activity and complete deficiency, and (2) the clinical significance of a heterozygous *SERPINE1* variant is uncertain.

Although beyond the scope of diagnostic laboratories, studies to determine the functional consequences of a *SERPINE1* variant may be of value in these circumstances. Of note, in vitro expression analyses demonstrated that the c.699_700dupTA variant of the Old Order Amish community resulted in the synthesis of an insoluble,

unstable protein [Fay et al 1992]. However, currently there are no clinically useful functional PAI-1 assays. Note: A fibrinolysis assay with a euglobulin clot lysis time is not sensitive or specific to PAI-1.

Mechanism of disease causation. Complete PAI-1 deficiency may result from either complete plasma protein deficiency (absence of PAI-1 activity and antigen) or a dysproteinemic state with presence of the antigen but absence of activity.

***SERPINE1*-specific laboratory technical considerations.** The *SERPINE1* c.-820_-817G(4_5) (commonly known as 4G/5G) benign variant is a common insertion/deletion of four or five guanine residues in the *SERPINE1* promoter region; the 4G allele is associated with higher plasma PAI-1 activity. An elevation in plasma PAI-1 activity leads to depressed fibrinolytic activity and a theoretically increased risk for arterial and venous thrombosis, a significant risk factor for coronary artery disease, myocardial infarction, and recurrent miscarriage [Huang et al 2017]. This benign variant is mentioned only to point out that testing for the 4G/5G variant will *not* aid in diagnosing an individual with complete PAI-1 deficiency.

Table 3. Notable *SERPINE1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change [2]	Comment [Reference]
NM_000602.4	c.-820_-817G(4_5) [3] (4G/5G)	--	Modulator variant
NM_000602.4 NP_000593.1	c.699_700dupTA	p.Thr234IlefsTer45	Founder variant in Old Order Amish community of eastern & southern Indiana [Fay et al 1997]

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
2. Numbering relative to full-length protein
3. Not associated with the complete plasminogen activator inhibitor 1 (PAI-1) deficiency phenotype but can affect measured PAI-1 activity levels. A 1-bp guanine deletion/insertion variant in the *SERPINE1* promoter region (rs587776796) is associated with higher transcription and activity levels and other phenotypes, including coronary artery disease (OMIM 173360).

Chapter Notes

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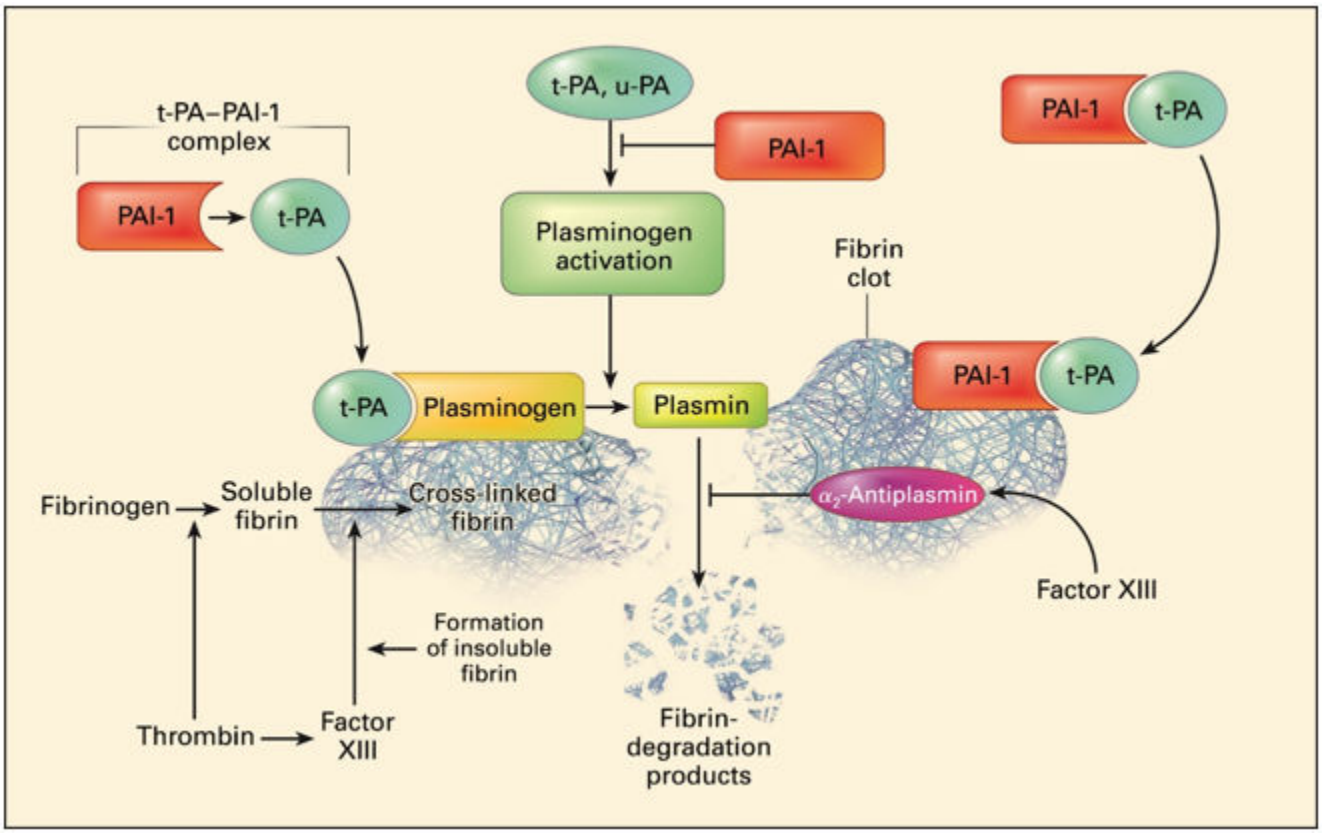

Figure 1. Plasminogen activators – urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA) – circulate in plasma as a reversible complex with plasminogen activator inhibitor 1 (PAI-1). When the fibrin clot is formed, plasminogen and tPA or uPA bind to the clot and form plasmin, resulting in lysis of the cross-linked fibrin-to-fibrin degradation products. PAI-1 also binds to fibrin and, when bound, can irreversibly inhibit plasminogen activators.

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