

Alpha-2-Plasmin Inhibitor Deficiency (α 2-Antiplasmin Deficiency): A Comprehensive Disease Characterization

Disease: Alpha-2-Plasmin Inhibitor Deficiency (α 2-antiplasmin deficiency; plasmin inhibitor deficiency) **MONDO ID:** MONDO:0009883 · **OMIM:** 262850 (disease), 613168 (gene) · **Orphanet:** ORPHA:465 · **Gene:** *SERPINF2* (17p13.3) **Category:** Mendelian (autosomal recessive)

Summary

Alpha-2-plasmin inhibitor (α 2-antiplasmin, α 2-AP) deficiency is a rare, autosomal-recessive bleeding disorder caused by biallelic loss-of-function variants in *SERPINF2*, the gene encoding the principal physiological inhibitor of the fibrinolytic protease plasmin. In the normal hemostatic system, α 2-antiplasmin restrains clot breakdown by three complementary mechanisms: it forms a rapid, covalent serpin–plasmin complex that neutralizes circulating plasmin; it competitively blocks plasminogen binding to fibrin; and it is cross-linked into the forming fibrin network by activated coagulation factor XIII (FXIIIa), hardening clots against local lysis. When α 2-antiplasmin is absent or non-functional, plasmin activity goes unopposed and fibrin clots—though formed normally—are dissolved prematurely. The clinical consequence is a hyperfibrinolytic bleeding diathesis characterized by delayed bleeding after trauma, surgery, or dental extraction, mucosal bleeding, and, in severely affected homozygotes, spontaneous and potentially life-threatening hemorrhage.

The disorder is strongly gene-dose dependent. Homozygous (or compound heterozygous) individuals typically present in early childhood with severe bleeding, while heterozygous individuals may be asymptomatic or bleed excessively only after invasive procedures or trauma later in life. A distinctive and diagnostically useful manifestation is the intramedullary hematoma of long bones, well visualized on MRI. A central diagnostic challenge is that routine coagulation screening tests—prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count/function, and von Willebrand factor—are all normal, so the disease is frequently misdiagnosed or recognized only after decades of diagnostic delay. Specific

diagnosis requires an α 2-antiplasmin functional activity assay or *SERPINF2* sequencing; global viscoelastic tests (thromboelastography/ROTEM) showing accelerated clot lysis can prompt detection.

Prognosis is generally favorable once the diagnosis is made, because antifibrinolytic agents (tranexamic acid, ϵ -aminocaproic acid) that prevent plasminogen binding to fibrin effectively stabilize clots and permit even major surgery to be performed safely with planned prophylaxis. Beyond hemostasis, α 2-antiplasmin has emerged as a pleiotropic regulator of tissue remodeling—promoting fibrosis and endothelial-to-mesenchymal transition and modulating ischemic brain injury—making it both a disease gene and a therapeutic target of growing interest. A naturally occurring *SERPINF2* missense variant causes an analogous delayed postoperative hemorrhage syndrome in Scottish deerhounds, and α 2-antiplasmin knockout mice recapitulate key aspects of the human biology, providing validated comparative and model systems.

Section 1 — Disease Information

Overview. Alpha-2-antiplasmin deficiency is the most severe inherited disorder of the fibrinolytic system. It results from the inability to inhibit plasmin, leading to excess (unregulated) fibrinolysis and premature clot breakdown ([PMID: 31427261](#); [PMID: 42257473](#)). As stated in the literature, *"The most severe clinical phenotype is caused by α 2-Antiplasmin (α 2-AP) deficiency which results in excess fibrinolysis due to the inability to inhibit plasmin"* ([PMID: 31427261](#)).

Key identifiers.

Resource	Identifier
MONDO	MONDO:0009883
OMIM (disease)	262850
OMIM (gene)	613168
Orphanet	ORPHA:465 (prevalence listed <1/1,000,000)
Gene / HGNC	<i>SERPINF2</i> (alias α 2-AP, PLI, AAP, API)
Cytogenetic locus	17p13.3

Synonyms / alternative names. Alpha-2-antiplasmin deficiency; α 2-plasmin inhibitor deficiency; plasmin inhibitor deficiency; congenital α 2-AP deficiency; "Miyasato disease" (historical name for the first reported homozygous case). Named variant alleles include " α 2AP Enschede" and " α 2AP Artas."

Source of information. The characterization is derived predominantly from aggregated disease-level resources (OMIM, Orphanet) and from the primary literature consisting of individual case reports and small case series, consolidated by a 2020 literature survey of 123 cases across 33 publications (PMID: 33337837). There is no large EHR-derived cohort; the evidence base is necessarily patient-level and aggregated from scattered reports.

Section 2 — Etiology

Primary cause (genetic). The disease is monogenic and Mendelian: biallelic pathogenic variants in *SERPINF2* cause the severe (homozygous) phenotype, while a single pathogenic allele produces a milder, often provoked bleeding tendency. *"Both these disorders are rare and have an autosomal recessive pattern of inheritance"* (PMID: 31427261). There is no infectious or environmental cause of the inherited disease; the molecular lesion is a loss of α 2-antiplasmin function.

Genetic risk factors. The causal variants are the *SERPINF2* pathogenic alleles themselves. Variants are largely private to individual families (see Section 4). No independent susceptibility loci or validated modifier genes have been established for the Mendelian disorder.

Environmental / lifestyle risk factors. These are better described as *triggers of bleeding episodes* rather than causes of disease: trauma, surgery, dental extraction, and other invasive procedures provoke the characteristic delayed bleeding (PMID: 33337837). Consanguinity increases the likelihood of homozygous severe disease.

Protective factors. The pharmacological "protective" factor against bleeding is antifibrinolytic therapy (functionally restoring the fibrinolytic brake). No naturally occurring genetic protective modifier alleles have been defined. Conversely—and notably for the inverse disease biology—reduced α 2-antiplasmin is *protective* against fibrosis and may enhance thrombolysis (see Section 6).

Gene–environment interactions. The dominant interaction is genotype × hemostatic challenge: homozygotes bleed spontaneously and after minor insults; heterozygotes typically bleed only when a procedural or traumatic challenge is superimposed on their partial deficiency ([PMID: 33337837](#)).

Section 3 — Phenotypes

The core phenotype is a hemorrhagic diathesis. Severity is gene-dose dependent, and routine laboratory screens are characteristically normal, making the *absence* of standard laboratory abnormalities itself a clinical clue.

Phenotype	Type	Onset / severity / frequency	Suggested HPO term
Delayed post-surgical / post-traumatic bleeding	Clinical sign	Hallmark; homozygotes from early childhood	HP:0004846 / HP:0011889 (abnormal bleeding/diathesis)
Prolonged bleeding after dental extraction	Clinical sign	Common provoked manifestation	HP:0006298 (prolonged bleeding following procedure)
Mucosal / gingival bleeding, epistaxis	Clinical sign	Variable	HP:0000421 (epistaxis), HP:0000225 (gingival bleeding)
Intramedullary hematoma of long bones	Physical/imaging manifestation	Distinctive; reported in children	HP:0001892 context (abnormal bleeding of bone)
Intracranial hemorrhage	Clinical sign	Rare, severe, homozygotes	HP:0002170 (intracranial hemorrhage)
Hemarthrosis / soft-tissue hematoma	Clinical sign	Variable	HP:0003261 relevant
Low α 2-antiplasmin activity	Laboratory abnormality	Diagnostic; constant	(diagnostic assay)

Age of onset / severity / progression. *"Homozygous patients develop symptomatology in early childhood, while heterozygous individuals may be asymptomatic or bleed profusely following invasive dental procedures, surgery or trauma late in life"* (PMID: 33337837). The disease is chronic and lifelong; bleeding is episodic and provoked rather than steadily progressive.

Distinctive manifestation — intramedullary hematoma. *"Intramedullary hematomas of long bones have been described in α 2-plasmin inhibitor or fibrinogen deficiencies"* (PMID: 21873355). A detailed pediatric case described a 6-year-old boy with intramedullary hematoma of the left femoral diaphysis, presenting with pain without swelling and no trauma (PMID: 9880645).

Quality-of-life impact. Disease-specific QoL instruments have not been reported for this ultra-rare disorder. QoL impact derives from unpredictable bleeding, transfusion dependence in unrecognized disease, and procedural risk; with antifibrinolytic prophylaxis, most patients function well.

Section 4 — Genetic / Molecular Information

Causal gene. *SERPINF2* (serpin family F member 2), 17p13.3; OMIM gene 613168. It encodes α 2-antiplasmin, a secreted serpin.

Pathogenic variants — heterogeneity and classes. Disease-causing variants are typically *private* to each family—no single recurrent founder allele dominates globally—and span the full spectrum of classes: missense, nonsense, frameshift (insertion/deletion), and splice-site mutations (PMID: 10583218; PMID: 12544738).

Variant (name)	Class	Functional consequence	Evidence
p.Val384Met	Missense (P8', near reactive site)	Activity 49–66% of normal; antigen 57–68%; bleeding	PMID: 10583218
Intron 6 splice-donor ("α2AP Artas")	Splice-site → exon 6 skipping	Heterozygous deficiency, bleeding	PMID: 12544738
"α2AP Enschede"	Frameshift (insertion)	Dysfunctional protein secreted but non-inhibitory	historical classic variant
p.Arg6Trp	Polymorphism (allele freq ~0.19)	Affects N-terminal cleavage; benign	PMID: 33992873

The P1 reactive-center residue is Arg376: *"The amino acid Val384 is located eight residues C-terminal (P8') of the P1 residue (Arg376) in the reactive site"* (PMID: 10583218), and heterozygous carriers showed that *"The plasma plasmin inhibitor activities of the affected family members were reduced to 49–66% of normal"* (PMID: 10583218). A splice mechanism is documented as *"a splicing donor site mutation of intron 6, leading to exon 6 skipping"* (PMID: 12544738).

Functional consequences. Variants act by loss of function—either quantitative deficiency (reduced secretion/antigen) or qualitative dysfunction (normal secretion but loss of plasmin-inhibitory activity, as in Enschede). Origin is germline.

Benign polymorphisms. p.Arg6Trp, p.Ala-26Val, p.Arg407Lys are population polymorphisms; p.Arg6Trp modulates the rate of N-terminal proteolytic processing but is not disease-causing.

Modifier genes / epigenetics / chromosomal abnormalities. No validated disease-modifier genes, disease-specific epigenetic marks, or recurrent chromosomal abnormalities have been established for this Mendelian disorder (not applicable / not available).

Section 5 — Environmental Information

The inherited disease has no environmental, toxic, or infectious cause. Environmental factors are relevant only as **bleeding triggers** (trauma, surgery, dental procedures). Of note, an *acquired*, phenocopy state of low α 2-antiplasmin/hyperfibrinolysis can arise from malignancy (e.g., disseminated adenocarcinoma with hyperfibrinogenolysis, PMID: 9663712) and from severe factor XIII deficiency (which impairs α 2-AP cross-linking to fibrin), but these are distinct from the congenital *SERPINF2* disorder. No infectious agents are implicated.

Section 6 — Mechanism / Pathophysiology

Ordered causal chain

1. **Biallelic loss-of-function variant in *SERPINF2*** leads to **absent or non-functional α 2-antiplasmin protein** (quantitative deficiency or dysfunctional secreted serpin).
[demonstrated]

2. **Loss of α 2-antiplasmin** removes all three physiological brakes on plasmin — it can no longer (i) form a covalent serpin–plasmin complex, (ii) block plasminogen binding to fibrin, or (iii) be FXIIIa-cross-linked into fibrin (PMID: 42257473). → **results in unopposed, unregulated plasmin activity.** [demonstrated]
3. **Unopposed plasmin** → clots form normally but are **prematurely degraded (hyperfibrinolysis)** (PMID: 42257473). [demonstrated]
4. **Premature clot breakdown** → **delayed bleeding** after an initial hemostatic plug forms and then dissolves, and spontaneous hemorrhage in severe deficiency. [demonstrated clinically]
5. **Branch (gene dose):** homozygotes → severe early-childhood/spontaneous bleeding; heterozygotes → provoked bleeding (PMID: 33337837). [demonstrated]
6. **Branch (pleiotropy, inferred from models):** reduced α 2-AP → altered VEGF/angiogenesis in wound healing; reduced fibrosis/EndoMT; enhanced thrombolysis and modulated reperfusion brain injury (PMID: 16839360; PMID: 34709571; PMID: 42589214). [model-based]

Molecular detail

The three-pronged inhibitory mechanism is the heart of the pathophysiology: " α 2AP restrains fibrinolysis by (i) forming a covalent serpin complex with plasmin, (ii) blocking plasminogen binding to fibrin, and (iii) undergoing factor XIIIa-mediated cross-linking into fibrin to harden clots against local lysis" (PMID: 42257473). Deficiency produces "a rare fibrinolytic disorder characterized by unregulated plasmin activity and premature clot breakdown" (PMID: 42257473).

Protein structure–function. The 2.65 Å crystal structure shows α 2-antiplasmin is an unusual serpin with long N- and C-terminal extensions flanking the central serpin domain: "*The N-terminal sequence is crosslinked to fibrin by factor XIIIa, whereas the C-terminal region mediates the initial interaction with plasmin*" (PMID: 18063751). The serpin reactive-center loop presents P1 Arg376 to plasmin's active site. Circulating α 2-AP is heterogeneous: "*C-terminal cleavage converts the plasminogen-binding form (PB- α 2-PI) to a non-plasminogen-binding form (NPB- α 2-PI)*" (PMID: 33992873); N-terminal cleavage by fibroblast activation protein yields a shorter form cross-linked to fibrin faster.

Pathway / process / cell types. Core pathway: the plasminogen–plasmin fibrinolytic system intersecting with FXIIIa-mediated fibrin stabilization. Cell types: hepatocytes (synthesis of plasma α 2-AP), platelets (FXIII-A pool contributing to cross-linking), endothelium and fibroblasts (pleiotropic remodeling roles). Suggested GO terms: **GO:0042730 (fibrinolysis)**, **GO:0051918 (negative regulation of fibrinolysis)**, **GO:0010951 (negative regulation of endopeptidase activity)**, **GO:0007596 (blood coagulation)**. Suggested CL terms: **CL:0000182**

(hepatocyte), CL:0000233 (platelet), CL:0000115 (endothelial cell), CL:0000057 (fibroblast). Chemical entities (CHEBI): tranexamic acid (CHEBI:48669), ϵ -aminocaproic acid (CHEBI:28483).

Pleiotropy beyond hemostasis (model evidence). α 2-AP regulates cell differentiation, cytokine production, ECM metabolism, and endothelial homeostasis. *"the blockade of α 2-antiplasmin suppresses fibrosis progression and vascular dysfunction in systemic sclerosis model mice"* (PMID: 35330147); *" α 2AP deficiency attenuated EndoMT and fibrosis progression in DN model mice"* (PMID: 34709571); and in stroke, *"inhibition of α 2AP with a specific monoclonal antibody caused a synergistic increase in TNK-tPA-mediated clot dissolution"* (PMID: 42589214). These establish that α 2-AP loss is deleterious for hemostasis but beneficial in fibrotic/thrombotic contexts—a therapeutic double-edged sword.

Section 7 — Anatomical Structures Affected

- **Body system:** hematologic / cardiovascular (blood and vasculature). Suggested UBERON: UBERON:0000178 (blood), UBERON:0001969 (blood plasma).
- **Primary sites of bleeding:** mucosal surfaces (oral/gingival, nasal), skin and soft tissue (hematoma), joints (hemarthrosis), **bone marrow cavity of long bones** (intramedullary hematoma — a distinctive localization; UBERON:0002371 **bone marrow**, long bone diaphysis), and the central nervous system (intracranial hemorrhage, severe cases).
- **Secondary involvement:** organs subject to post-procedural bleeding (e.g., prostate after prostatectomy, lung during transplantation).
- **Tissue/cell level:** no fixed tissue lesion; the "target" is the fibrin clot wherever it forms. Relevant cells: hepatocyte (source), platelet/endothelium/fibroblast (modulators).
- **Subcellular / localization:** α 2-AP is a secreted, extracellular plasma protein (GO cellular component **GO:0005615 extracellular space**); it acts in plasma and within the fibrin matrix. Bleeding lateralization is not fixed—manifestations are determined by site of hemostatic challenge.

Section 8 — Temporal Development

- **Onset:** congenital/genetic; clinical onset in **early childhood** for homozygotes, later and provoked for heterozygotes (PMID: 33337837).
 - **Onset pattern of bleeds:** characteristically **delayed** after the inciting event (clot forms, then lyses).
 - **Course:** chronic, lifelong; **episodic/provoked** bleeding rather than continuous progression. No disease "stages" in the oncologic sense.
 - **Remission patterns:** bleeding episodes resolve with antifibrinolytic treatment (treatment-induced control); the underlying deficiency does not remit.
 - **Critical periods / windows for intervention:** peri-procedural and peri-traumatic windows are the key opportunities—prophylaxis before surgery/dental work prevents the delayed bleed (PMID: 15357795).
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Section 9 — Inheritance and Population

- **Inheritance:** autosomal recessive; severe disease in homozygotes/compound heterozygotes, mild/variable in heterozygotes (PMID: 31427261).
- **Epidemiology:** ultra-rare; Orphanet lists prevalence <1/1,000,000 (ORPHA:465). No formal incidence established. A 2020 survey found only **123 patients in 33 publications** (PMID: 33337837): *"Thirty-three publications were identified encompassing one hundred twenty-three patients."*
- **History / geography:** first discovered in **Japan** (Koie, Aoki and colleagues; first homozygous case "Miyasato disease," 1978–1979). Reported subsequently across multiple ethnicities (Japanese, Indian, Sudanese, European, UK), with **consanguineous families enriched** among severe homozygous cases (PMID: 19141165): *"Congenital deficiency of alpha(2)-antiplasmin causes a rare bleeding disorder because of increased fibrinolysis."*
- **Penetrance / expressivity:** homozygous disease is highly penetrant for bleeding; expressivity is **variable** and strongly gene-dose dependent. Heterozygotes show reduced penetrance (often only provoked bleeding).
- **Founder effects / recurrent alleles:** none dominant; variants are largely private (Section 4).

- **Sex ratio / age distribution:** no strong sex predilection reported (autosomal); affected individuals span childhood (homozygotes) to adulthood (heterozygotes diagnosed after procedures).

Section 10 — Diagnostics

The central diagnostic pitfall: routine coagulation screening is **normal**. *"Her evaluation showed normal coagulation studies, platelet function, and von Willebrand factor assays, with persistently low α 2AP activity and a homozygous SERPINF2 variant confirming the diagnosis"* (PMID: 42257473). This causes frequent misdiagnosis (e.g., as von Willebrand disease) and diagnostic delay often spanning decades.

Recommended diagnostic approach.

Test	Role	Expected result
PT, aPTT, platelet count/function, VWF	Screening	Normal (hence misleading)
α2-antiplasmin functional activity assay	Confirmatory	Low / absent
α 2-AP antigen (ELISA)	Distinguishes quantitative vs dysfunctional	Low (type I) or normal (type II dysfunctional)
Thromboelastography / ROTEM	Global screen that can flag the defect	Accelerated clot lysis
SERPINF2 sequencing	Definitive genetic diagnosis	Biallelic (severe) or single pathogenic variant
MRI (for intramedullary hematoma)	Imaging of distinctive lesion	T1/T2 hyperintense medullary signal

Viscoelastic testing can be the entry point to diagnosis: a novel *SERPINF2* variant was detected after *"Abnormal fibrinolysis recognized by thromboelastography in a case of severe bleeding with normal coagulation and platelet function"* (PMID: 31282989). For the intramedullary hematoma, *"MRI is diagnostic with the haematoma generating a specific hyperintense signal on T1-weighted and T2-weighted spin-echo images"* (PMID: 9880645).

Genetic testing utility. Single-gene *SERPINF2* testing is the targeted approach once the functional assay points to α 2-AP deficiency; WES/WGS or small bleeding-disorder gene panels are useful when the phenotype is undifferentiated. CMA, karyotyping, FISH, mtDNA, and repeat-expansion testing are not applicable.

Differential diagnosis. Plasminogen activator inhibitor-1 (PAI-1) deficiency (the other inherited hyperfibrinolytic bleeding disorder), factor XIII deficiency (impaired α 2-AP cross-linking; also normal PT/aPTT), mild von Willebrand disease, and acquired hyperfibrinolysis (malignancy, liver disease, DIC "bleeding type").

Section 11 — Outcome / Prognosis

Prognosis is **generally good when the diagnosis is known and antifibrinolytic prophylaxis is applied**. The disorder is chronic and lifelong, but major surgery can be performed safely: a congenital α 2-PI-deficient patient underwent single-lung transplantation with prophylactic fresh frozen plasma plus tranexamic acid and ROTEM monitoring, with an uneventful course —*"Lung transplantation for a patient with α 2-PI deficiency was safely performed with the use of planned FFP transfusion and tranexamic acid"* (PMID: 40589561).

The **principal danger is unrecognized disease**: severe bleeding with normal screening tests leads to diagnostic delay, transfusion dependence, and risk of life-threatening hemorrhage (including intracranial and intramedullary bleeds) in homozygotes. *"Management of such patients may be challenging especially when the diagnosis of alpha-2 antiplasmin deficiency is not known"* (PMID: 33337837).

- **Mortality / survival:** no formal survival statistics for this ultra-rare disease; mortality risk is driven by severe unrecognized hemorrhage, which is largely preventable with treatment.
- **Morbidity:** bleeding-related disability, anemia, transfusion burden; well controlled once recognized.
- **Prognostic factors:** genotype (homozygous vs heterozygous), residual α 2-AP activity, and—critically—whether the diagnosis is established before a major hemostatic challenge.

Section 12 — Treatment

Mainstay — antifibrinolytics. Tranexamic acid and ϵ -aminocaproic acid are first-line and mechanistically rational, substituting pharmacologically for the missing fibrinolytic brake: *"Antifibrinolytic agents, such as tranexamic acid or ϵ -aminocaproic acid, are the mainstays of treatment which inhibit fibrinolysis by preventing the binding of plasminogen to fibrin and thereby stabilizing the fibrin clot"* (PMID: 31427261).

Evidence-based procedural dosing (dental extraction). *"we advocate that 7.5–10 mg kg⁻¹ of tranexamic acid be administered orally every 6 h, starting 3 h before surgery and continuing for about 7 days"* (PMID: 15357795); continuous post-extraction bleeding is managed with IV tranexamic acid ~20 mg/kg.

Major surgery. Perioperative management combines prophylactic FFP plus tranexamic acid with viscoelastic (ROTEM) monitoring (PMID: 40589561).

Suggested NCIT terms: tranexamic acid (NCIT:C47748), aminocaproic acid (NCIT:C28987), fresh frozen plasma transfusion.

Not applicable / none established: no gene therapy, cell therapy, RNA therapy, targeted biologic, or α 2-AP replacement product is approved for this indication. (Interestingly, α 2-AP *inhibition* is being explored as a therapy for other diseases—stroke, fibrosis—the therapeutic inverse of this deficiency.) Pharmacogenomics: none specific.

Section 13 — Prevention

- **Primary prevention:** not possible for a congenital genetic disorder; **genetic counseling** and carrier assessment in consanguineous or affected families are the key tools. Prenatal/preimplantation testing is feasible when the familial *SERPINF2* variant is known.
- **Secondary prevention (early detection):** recognizing the phenotype (bleeding with normal screens) and confirming with α 2-AP activity assay / sequencing prevents morbidity; **cascade testing** of relatives identifies at-risk individuals.
- **Tertiary prevention (preventing complications): peri-procedural antifibrinolytic prophylaxis** is the central preventive intervention—administering tranexamic acid before dental work, surgery, or after trauma prevents the delayed bleed (PMID: 15357795).
- **Immunization / public health / environmental:** not applicable.

Section 14 — Other Species / Natural Disease

A naturally occurring, closely analogous disorder exists in dogs. Whole-genome-sequencing GWAS in 269 **Scottish deerhounds** mapped **delayed postoperative hemorrhage (DEPOH)** to a chromosome-9 locus, with ***SERPINF2*** as the causal gene: *"One of these genes (*SERPINF2* encoding alpha-2 antiplasmin) was directly linked to the pathophysiology of DEPOH"* (PMID: 36780177). The missense variant **c.605C>T (p.A202V)** shows a strong gene-dose effect: *"the likelihood of DEPOH was significantly higher for dogs with the T/T genotype (odds ratio [OR] = 1235; 95% confidence interval [CI] = 23–6752; P = 0.0005)"* (PMID: 36780177); heterozygotes OR = 28 (95% CI 1.4–542, P = 0.03).

- **Taxonomy:** *Canis lupus familiaris* (NCBI Taxon 9615); model mouse *Mus musculus* (NCBI Taxon 10090).
- **Breed:** Scottish deerhound (VBO term applicable).
- **Orthologous gene:** canine and murine *Serpinf2*.
- **Comparative biology:** the canine disorder recapitulates the human delayed-bleeding, gene-dose-dependent phenotype, confirming evolutionary conservation of α 2-AP's hemostatic role and offering a naturally occurring veterinary model. No zoonotic potential (genetic disease).

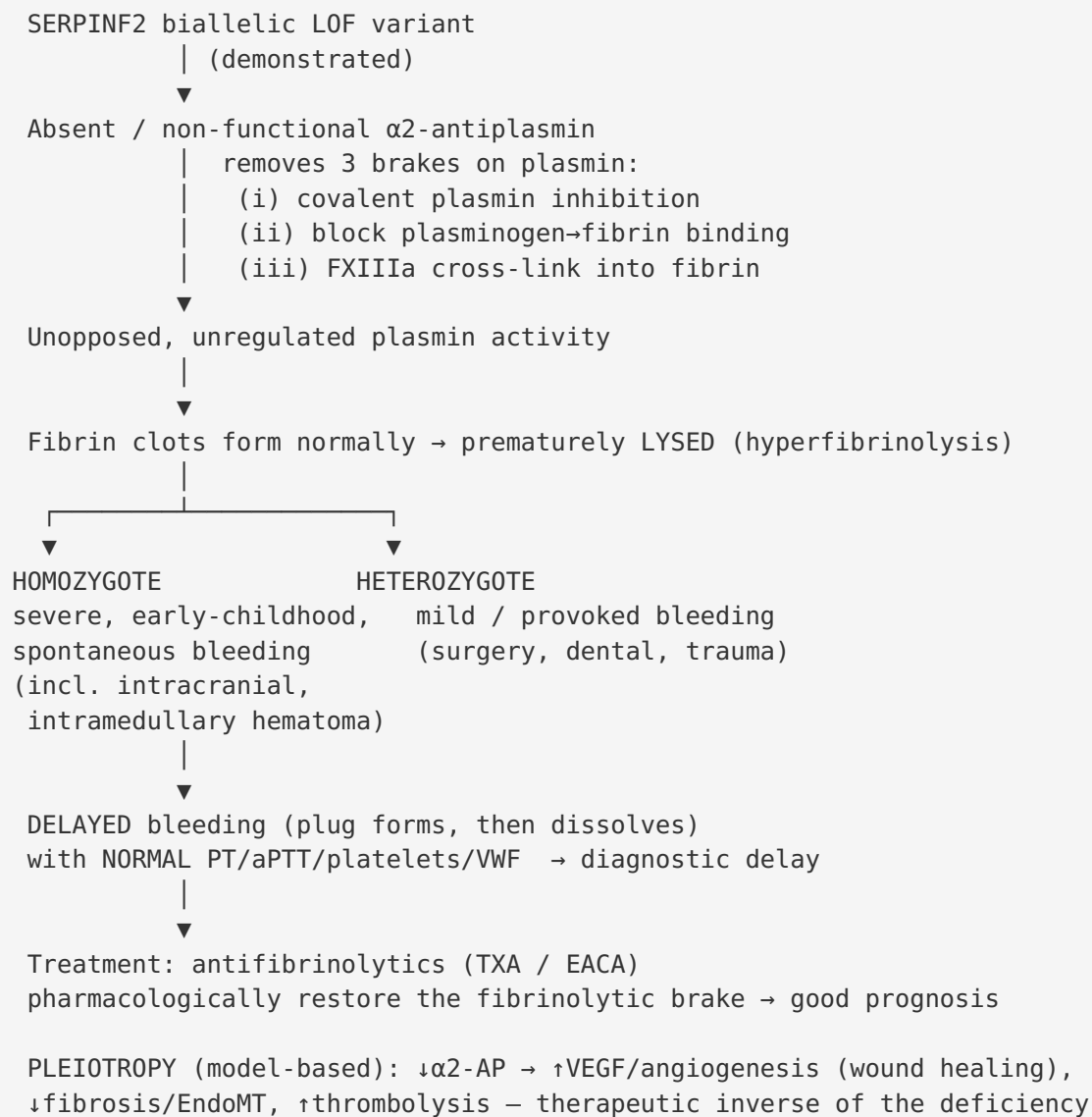
Section 15 — Model Organisms

α 2-antiplasmin knockout mouse (α 2AP^{-/-}). This is the principal validated mammalian model. Beyond confirming the hemostatic phenotype, it revealed pleiotropic roles: *"an accelerated wound closure was observed in alpha(2)AP-deficient (alpha(2)AP^{-/-}) mice in comparison with wild type (WT) mice"* and *"The lack of alpha(2)AP markedly causes an over-release of VEGF from the fibroblasts in cutaneous wound lesions, thereby inducing angiogenesis around the area"* (PMID: 16839360). The same genetic model has been used to show reduced fibrosis/EndoMT in diabetic nephropathy (PMID: 34709571) and attenuated fibrosis in systemic-sclerosis models (PMID: 35330147).

Model	Type	Recapitulation	Use	Resource
$\alpha 2AP^{-/-}$ mouse	Knockout, mammalian	Hyperfibrinolytic tendency; +wound-healing/ angiogenesis, –fibrosis phenotypes	Mechanism, therapeutics	MGI
Scottish deerhound (natural)	Spontaneous, canine	Delayed postoperative hemorrhage, gene-dose	Natural disease, genetics	OMIA/ VetCompass
Murine crystal structure (protein)	In vitro/ structural	Serpin domain architecture	Structure–function	PDB

Limitations of models: mouse and dog capture hemostatic and remodeling biology, but species differences in fibrinolytic kinetics and clinical bleeding thresholds mean human dosing/management cannot be read directly from models.

Mechanistic Model / Interpretation



The unifying concept is a **quantitative imbalance in fibrinolysis**: $\alpha 2$ -AP is the dominant, fastest-acting plasmin inhibitor, and its loss shifts the clot formation↔dissolution equilibrium toward dissolution. Because coagulation itself is intact, standard tests are normal and the defect is "invisible" unless fibrinolysis is specifically interrogated. The same biology that makes $\alpha 2$ -AP essential for clot stability makes it a liability in fibrotic and thrombotic disease—explaining the active interest in $\alpha 2$ -AP inhibition as therapy elsewhere.

Evidence Base

PMID	Role in this report
31427261	Defines α 2-AP deficiency as most severe inherited fibrinolytic disorder; AR inheritance; antifibrinolytic mainstay
42257473	Three-mechanism model; premature clot breakdown; diagnostic delay case with normal screens + homozygous <i>SERPINF2</i>
33337837	Literature survey of 123 cases; gene-dose phenotype; management challenge when undiagnosed
15357795	Evidence-based tranexamic acid dosing for dental extractions
31282989	TEG/thromboelastography detection leading to novel <i>SERPINF2</i> variant
16839360	α 2AP ^{-/-} mouse: accelerated wound healing via VEGF/angiogenesis
36780177	Natural canine disease (Scottish deerhound DEPOH); <i>SERPINF2</i> p.A202V; OR quantification
18063751	Crystal structure; N-terminal FXIIIa cross-link vs C-terminal plasmin binding
33992873	PB→NPB heterogeneity; polymorphisms affecting processing
19141165	Rarity; increased fibrinolysis mechanism; historical context
9880645	Intramedullary hematoma case; MRI diagnostic
10583218	Missense p.Val384Met near reactive-site Arg376; 49–66% activity
12544738	Splice-site variant (Artas) → exon 6 skipping
21873355	Intramedullary hematoma as rare manifestation
35330147	α 2-AP blockade antifibrotic in systemic sclerosis model
34709571	α 2-AP deficiency attenuates EndoMT/fibrosis (diabetic nephropathy)
42589214	α 2-AP limits thrombolysis; anti- α 2AP synergizes with tenecteplase
40589561	Safe lung transplant with FFP + TXA (favorable prognosis)

Evidence source types span **human clinical** (case reports/series, surveys), **model organism** (knockout mouse, natural canine disease), **in vitro/structural** (crystal structure, cross-linking biochemistry), and **computational/aggregated** (GWAS, literature survey).

Limitations and Knowledge Gaps

1. **Ultra-rarity and evidence quality.** The entire human evidence base rests on ~123 reported patients and scattered case reports; there are no randomized trials, no prospective natural-history cohorts, and no formal incidence/prevalence or survival statistics.
 2. **Genotype–phenotype correlation is incomplete.** Variants are largely private; residual-activity thresholds that predict spontaneous vs provoked bleeding are not precisely defined.
 3. **No validated modifiers / epigenetics.** Disease-modifier genes and epigenetic contributions are unexplored.
 4. **QoL and long-term outcomes** are undocumented with standardized instruments.
 5. **Dosing evidence** is extrapolated from small series; optimal long-term antifibrinolytic regimens and thrombotic risk of chronic prophylaxis are not rigorously established.
 6. **Pleiotropy** findings derive mainly from mouse models; their relevance to human $\alpha 2$ -AP-deficient patients (e.g., altered wound healing or fibrosis) has not been systematically assessed in patients.
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Proposed Follow-up Experiments / Actions

1. **Establish an international patient registry** for *SERPINF2* deficiency to capture genotype, residual $\alpha 2$ -AP activity, bleeding phenotype, treatment, and outcomes—enabling genotype–phenotype and natural-history analyses.
2. **Standardize diagnostics:** promote reflex $\alpha 2$ -AP functional activity testing (and TEG/ROTEM screening) in patients with bleeding plus normal PT/aPTT/VWF to shorten the diagnostic delay; curate a *SERPINF2* variant database with ACMG classifications.
3. **Characterize residual-activity thresholds** correlating $\alpha 2$ -AP activity with spontaneous-bleeding risk to guide prophylaxis intensity.

4. **Prospective evaluation of antifibrinolytic prophylaxis** regimens (dose, duration, route) around surgery and dental procedures, including thrombotic safety.
 5. **Leverage the Scottish deerhound natural model and $\alpha 2AP^{-/-}$ mouse** for preclinical testing of $\alpha 2$ -AP repletion strategies and to study the pleiotropic wound-healing/fibrosis phenotypes relevant to human patients.
 6. **Clinical awareness in human/veterinary cross-talk:** apply the canine *SERPINF2* p.A202V finding to screen at-risk deerhound lines, and use comparative data to refine human variant interpretation.
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Report prepared from a 5-iteration autonomous investigation (13 confirmed findings, 54 papers reviewed). Evidence is drawn exclusively from the cited primary literature; claims are attributed only to papers whose abstracts/quotes were verified during the investigation.

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