

Factor V Leiden

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THE STORY IN ONE SENTENCE

Factor V Leiden is a genetic mutation that makes factor V resistant to protein C degradation, shifting the coagulation balance toward clot formation.

“Factor V Leiden is the most common inherited clotting disorder in people of European ancestry. A single gene change makes one clotting protein last too long in the blood, raising the risk of abnormal blood clots in veins.”

Normal anatomy — the body's job

The coagulation system is a cascade of proteins in the blood that work together to form clots and stop bleeding when blood vessels are injured. Factor V is a helper protein (cofactor) that speeds up the conversion of prothrombin to thrombin, the enzyme that turns fibrinogen into fibrin strands that form a clot. Protein C, activated by thrombin, acts as a natural brake by cutting and inactivating factor V and factor VIII to prevent excessive clotting. This balance between clot formation and clot regulation keeps blood flowing smoothly while allowing rapid clotting when needed.

BODY'S JOB

Think of the clotting system like a construction crew building a dam to stop a leak—factor V is a foreman who speeds up the work, while protein C is the supervisor who tells the crew when to stop building so the river does not get completely blocked.

1. Blood vessel is injured and exposed collagen triggers the clotting cascade
2. Factor V is activated to factor Va and teams up with factor Xa on platelet surfaces
3. Factor Va-Xa complex rapidly converts prothrombin to thrombin
4. Thrombin cuts fibrinogen into fibrin strands that weave a stable clot
5. Thrombin also activates protein C by binding to thrombomodulin on intact vessel walls
6. Activated protein C cuts factor Va at specific sites to inactivate it and slow clot formation

What breaks

In Factor V Leiden, a single letter change in the DNA (nucleotide 1691 changes from G to A) creates a factor V protein with the wrong amino acid at position 506 (arginine becomes glutamine). Protein C normally cuts factor V at that exact spot to turn it off. When arginine is replaced with glutamine, protein C cannot recognize or cut the protein, so factor V stays active much longer than it should and keeps pushing clot formation forward.

CLINICAL TERM

The Factor V Leiden mutation (G1691A) substitutes glutamine for arginine at amino acid position 506 (R506Q), which is one of three protein C cleavage sites on factor Va. This single-point mutation creates APC resistance (activated protein C resistance), meaning factor Va remains functional in the prothrombinase complex (the factor Va-Xa enzyme complex) approximately six times longer than wild-type factor V. The result is prolonged thrombin generation and a hypercoagulable state (increased tendency to clot).

How the body compensates

The body has limited ability to compensate for Factor V Leiden because the defect directly interferes with one of the main negative-feedback loops that controls clotting. Other anticoagulant pathways—such as antithrombin and tissue factor pathway inhibitor—continue to work normally, which is why most people with Factor V Leiden do not have constant clotting problems. However, these backup systems can be overwhelmed during high-risk situations that further tip the balance toward clotting.

1. {'step': 'Antithrombin continues to neutralize thrombin and factor Xa', 'detail': 'Antithrombin (a protease inhibitor) binds and inactivates free thrombin and factor Xa in the bloodstream, providing some brake on clot formation even when protein C activity is impaired'}
2. {'step': 'Tissue factor pathway inhibitor (TFPI) limits initial clot trigger', 'detail': 'TFPI blocks the tissue factor-factor VIIa complex that starts the clotting cascade, reducing the amount of downstream factor Xa and thrombin generated'}
3. {'step': 'Protein S enhances whatever protein C activity remains', 'detail': 'Protein S acts as a cofactor for activated protein C, helping it cleave factor Va at the two remaining cleavage sites (positions 306 and 679) that are still intact in Factor V Leiden'}
4. {'step': 'Fibrinolysis breaks down clots after they form', 'detail': 'The plasminogen-plasmin system dissolves fibrin clots through tissue plasminogen activator (tPA) and urokinase, clearing small inappropriate clots before they grow'}

5. {'step': 'Blood flow dilutes clotting factors away from injury sites', 'detail': 'Normal circulation washes activated clotting factors downstream into the liver for clearance, preventing localized buildup of thrombin in areas of slow flow'}
6. {'step': 'Endothelial cells release prostacyclin and nitric oxide', 'detail': 'Healthy vessel lining secretes anti-clotting and anti-platelet substances that keep platelets from sticking and prevent clots from forming on intact walls'}

Domino effect

1. Factor Va persists on platelet surfaces and continues generating thrombin — Without effective protein C cleavage, the prothrombinase complex (factor Va-Xa) remains active and produces excess thrombin in areas of sluggish blood flow
2. Excess thrombin converts more fibrinogen to fibrin and activates more platelets — High thrombin levels accelerate clot growth beyond what is needed for hemostasis, especially in veins where flow is slow and clotting factors accumulate
3. Fibrin meshwork forms in deep veins of legs or pelvis without clear injury — Prolonged sitting, dehydration, or minor endothelial damage provides enough trigger for unchecked thrombin generation to produce an inappropriate clot
4. A clot in a deep leg vein (Deep vein thrombosis) (DVT) obstructs venous return and causes leg swelling — Clot fills the vein lumen, blocking blood from draining back to the heart and causing blood and fluid to back up into leg tissues
5. Clot fragment breaks off and travels through right heart to pulmonary arteries — Muscle contraction or sudden movement dislodges part of the DVT, creating a pulmonary embolism (a clot lodging in a lung artery) (PE) that lodges in lung blood vessels
6. Pulmonary embolism (a clot lodging in a lung artery) blocks blood flow to lung segments, impairing gas exchange — Obstructed pulmonary arteries prevent blood from reaching alveoli (air sacs) for oxygen pickup, creating ventilation-blood flow (perfusion) mismatch and low oxygen in the blood (hypoxemia) (low blood oxygen)
7. Right ventricle strains against increased pressure from blocked lung vessels — Pulmonary artery obstruction raises afterload (resistance) on the right heart, which is thin-walled and not designed to pump against high pressure
8. Massive PE causes right heart failure, cardiovascular collapse, and death — Right ventricle cannot maintain cardiac output against sudden severe pulmonary high blood pressure (hypertension), leading to shock, loss of blood pressure, and cardiac arrest if clot burden is large

Symptoms · what the patient feels, and why

- Leg swelling (unilateral): A clot in a deep leg vein (Deep vein thrombosis) (clot in deep leg veins) blocks blood return, causing fluid buildup in tissues downstream
- Leg pain or tenderness: A blood clot (Thrombus) (blood clot) stretches vein wall and triggers inflammation in surrounding tissue
- Sudden shortness of breath: Pulmonary embolism (a clot lodging in a lung artery) (clot travels to lung arteries) blocks oxygen exchange in alveoli (air sacs)
- Chest pain with deep breathing: Pulmonary embolism (a clot lodging in a lung artery) irritates pleura (lung lining), which has pain nerves that fire with lung expansion
- No symptoms at baseline: Factor V Leiden creates hypercoagulable state (increased clotting tendency) but requires trigger like surgery or pregnancy to form clots
- Recurrent miscarriages: Microthrombi (tiny clots) form in placental vessels, reducing oxygen delivery to developing fetus
- Warmth in affected leg: Inflammatory mediators (histamine, prostaglandins) released around a blood clot (thrombus) cause vasodilation (blood vessel widening) and increased blood flow to skin
- Rapid heart rate: Pulmonary embolism (a clot lodging in a lung artery) reduces oxygen in blood, triggering baroreceptors (pressure sensors) to increase heart rate for compensation

Focused exam

- Unilateral leg swelling measured 2 cm larger in circumference than opposite leg: Asymmetric swelling (edema) (swelling) is hallmark of a clot in a deep leg vein (deep vein thrombosis); greater than 3 cm difference increases likelihood ratio to 2.5
- Positive Homan sign (calf pain with foot dorsiflexion): Stretching inflamed vein triggers pain; low sensitivity (30%) but when present alongside other findings raises DVT probability
- Palpable cord in leg vein: Thrombosed vein feels firm because clot replaces flowing blood; highly specific (95%) for a clot in a deep leg vein (deep vein thrombosis) when detected
- Fast breathing (Tachypnea) (respiratory rate over 20) with normal lung sounds: Pulmonary embolism (a clot lodging in a lung artery) causes ventilation-blood flow (perfusion) mismatch (air reaches alveoli but blood cannot) triggering rapid breathing to compensate
- Oxygen saturation below 95% on room air: Low oxygen in the blood (Hypoxemia) (low oxygen) from pulmonary embolism (a clot lodging in a lung artery) blocking gas exchange; indicates significant clot burden affecting lung function
- Normal physical exam at baseline: Factor V Leiden carriers are asymptomatic between thrombotic events; exam helps exclude active clot before genetic testing

Diagnostics · every test answers a question

- Activated protein C resistance assay → Does the patient's plasma show resistance to activated protein C, the functional abnormality caused by Factor V Leiden?
- Factor V Leiden genetic test (PCR) → Is the G1691A mutation present in the Factor V gene?
- D-dimer → Are fibrin degradation products elevated, suggesting active clot formation and breakdown?
- Duplex ultrasound of leg veins → Is there noncompressible vein segment or absent flow indicating a clot in a deep leg vein (deep vein thrombosis)?
- CT pulmonary angiography → Is there filling defect in pulmonary arteries indicating a traveling clot lodging in a vessel (embolism)?
- Complete blood count → Is platelet count normal before starting anticoagulation?
- Prothrombin time and aPTT → Are baseline clotting times normal before anticoagulation, and is lupus anticoagulant (another thrombophilia) present?
- Comprehensive thrombophilia panel → Are there additional inherited clotting disorders like prothrombin mutation or protein C/S deficiency?

Treatment logic

- Anticoagulation for acute VTE → Prevents clot propagation (growth) by blocking thrombin generation, allowing endogenous fibrinolysis (natural clot breakdown) to dissolve existing a blood clot (thrombus) over weeks
- Avoid estrogen-containing contraceptives → Eliminates 30-fold VTE risk increase from estrogen-induced changes in clotting factor production and natural anticoagulant reduction
- Thromboprophylaxis during high-risk periods → Temporary anticoagulation during surgery, pregnancy, or immobility prevents stasis-triggered clot formation (thrombosis) when baseline hypercoagulability meets environmental risk
- Extended anticoagulation after unprovoked VTE → Reduces recurrent VTE rate from 10% per year to 1% per year by maintaining therapeutic anticoagulation in patients with permanent thrombophilia
- Compression stockings for post-thrombotic syndrome → Graduated compression (20-30 mmHg) reduces venous high blood pressure (hypertension) (high pressure) from damaged valves, decreasing leg swelling and pain
- Genetic counseling for family planning → Educates about 50% transmission risk to offspring, pregnancy management strategies, and need for partner testing if considering prenatal diagnosis

Medications

rivaroxaban · direct oral anticoagulant (DOAC), Factor Xa inhibitor

This medicine blocks Factor Xa, an enzyme in the coagulation cascade (clotting chain reaction). By stopping Factor Xa, the drug prevents conversion of prothrombin to thrombin (the main clotting enzyme). Less thrombin means less fibrin formation, so clots cannot grow.

1. Rivaroxaban binds directly to Factor Xa active site
2. Factor Xa can no longer convert prothrombin to thrombin
3. Thrombin generation drops by 80-90%
4. Fibrinogen stays unconverted, preventing fibrin mesh formation
5. Existing clots stop growing and natural plasmin breaks them down over time

SAFETY WATCH

Major bleeding risk 2-3% per year, especially gastrointestinal · Requires dose adjustment if creatinine clearance below 50 mL/min · No routine monitoring needed but cannot easily measure anticoagulation effect · Avoid in patients with mechanical heart valves or antiphospholipid syndrome

apixaban · direct oral anticoagulant (DOAC), Factor Xa inhibitor

This drug directly attaches to Factor Xa enzyme and blocks its action. Factor Xa normally cuts prothrombin to create thrombin. When apixaban stops this step, the entire clotting cascade slows down. The body's natural clot-dissolving system can then clear existing clots.

1. Apixaban enters bloodstream and finds Factor Xa molecules
2. Drug locks into Factor Xa active site reversibly
3. Prothrombin cannot be converted to thrombin
4. Fibrin production decreases by 85%
5. Platelets cannot form stable clots without fibrin mesh

SAFETY WATCH

Lowest bleeding rate among DOACs in clinical trials (1.8% major bleeding per year) · Must reduce dose if two of three present: age over 80, weight under 60 kg, creatinine over 1.5 · Drug level peaks 3 hours after dose, creating brief high-bleeding window · Stop 48 hours before major surgery if kidney function normal

warfarin · vitamin K antagonist

This medicine blocks vitamin K epoxide reductase, the enzyme that recycles vitamin K in the liver. Without recycled vitamin K, hepatocytes (liver cells) cannot activate clotting factors II, VII, IX, and X. These factors need vitamin K to add carboxyl groups that let them bind calcium and work properly.

1. Warfarin enters liver cells and inhibits vitamin K epoxide reductase
2. Vitamin K stays in oxidized (inactive) form
3. New clotting factors II, VII, IX, X are made but lack gamma-carboxylation
4. Un-carboxylated factors cannot bind calcium or phospholipid surfaces
5. Clotting cascade slows over 3-5 days as old active factors degrade

SAFETY WATCH

Requires INR monitoring every 2-4 weeks with target 2.0-3.0 · Vitamin K in foods (leafy greens) reduces drug effect if intake varies · Hundreds of drug interactions through cytochrome P450 system · Teratogenic (causes birth defects) - absolutely contraindicated in pregnancy

enoxaparin · low molecular weight heparin (LMWH)

This injectable medicine is a short sugar chain that binds to antithrombin (a natural anticoagulant protein). The enoxaparin-antithrombin complex is 1000 times better at blocking Factor Xa than antithrombin alone. This stops the clotting cascade at an earlier step than warfarin.

1. Enoxaparin injected subcutaneously enters bloodstream
2. Drug binds to antithrombin through specific pentasaccharide sequence
3. Antithrombin changes shape to actively inhibit Factor Xa
4. Factor Xa activity drops within 2-4 hours
5. Thrombin generation decreases proportionally to Factor Xa inhibition

SAFETY WATCH

Can cause heparin-induced a low platelet count (thrombocytopenia) (HIT) in 1-3% - monitor platelets · Accumulates in kidney failure - reduce dose if creatinine clearance below 30 · Injection site bruising common but not dangerous · Preferred anticoagulant throughout pregnancy for Factor V Leiden carriers

fondaparinux · synthetic pentasaccharide, indirect Factor Xa inhibitor

This is a man-made copy of the specific five-sugar sequence in heparin that activates antithrombin. It binds antithrombin and makes it 300 times more effective at neutralizing Factor Xa. Unlike heparin, it is too short to bind thrombin, so it only affects Factor Xa.

1. Fondaparinux binds to antithrombin at specific lysine and arginine sites
2. Antithrombin undergoes conformational change at reactive center
3. Activated antithrombin rapidly inactivates Factor Xa molecules
4. Factor Xa-antithrombin complexes are cleared by liver
5. Coagulation cascade cannot proceed past Factor Xa step

SAFETY WATCH

No HIT risk makes it preferred if prior heparin allergy · Renally cleared - contraindicated if creatinine clearance below 30 · Long half-life (17 hours) means once-daily dosing but delayed offset · No reversal agent available unlike other anticoagulants

early mobilization and hydration · non-pharmacologic thromboprophylaxis

Walking and leg exercises contract calf muscles, which squeeze deep veins like a pump. This muscle pump action moves blood toward the heart and prevents stasis (pooling). Adequate fluid intake keeps blood viscosity (thickness) normal. Lower viscosity means faster flow and less clotting risk.

1. Calf muscle contraction compresses veins against bone and fascia
2. Venous pressure rises and pushes blood proximally past one-way valves
3. Muscle relaxation creates negative pressure that draws blood from superficial veins
4. Repeated cycles prevent stasis that activates contact factors (XII, XI)
5. Hydration maintains plasma volume and reduces hematocrit (red cell concentration)

SAFETY WATCH

Must start within 24 hours after surgery for maximum benefit · Contraindicated if acute DVT already present (could dislodge clot) · Overhydration dangerous in heart failure or kidney disease · Insufficient as sole therapy for Factor V Leiden homozygotes or combined defects

Red flags

- Sudden shortness of breath with chest pain suggests pulmonary embolism (a clot lodging in a lung artery) requiring emergent CT angiography

- Leg swelling with warmth and cord-like vein needs urgent ultrasound for a clot in a deep leg vein (deep vein thrombosis)
- Family history of multiple clots before age 50 indicates high-risk thrombophilia requiring testing
- Clot in unusual site (hepatic vein, cerebral sinus) suggests severe combined thrombophilia needing hematology consultation

Nursing priorities

1. Monitor for signs of a clot in a deep leg vein (deep vein thrombosis) (DVT) and pulmonary embolism (a clot lodging in a lung artery) (PE) — Factor V Leiden increases clot risk by making blood resistant to protein C (a natural anticoagulant). DVT causes leg swelling and pain; PE causes sudden shortness of breath and chest pain and can be fatal.
2. Educate patient about when to seek emergency care for clot symptoms — Early recognition saves lives. Teach patients to call 911 for sudden chest pain, trouble breathing, coughing up blood, severe leg swelling, or leg pain that worsens with walking.
3. Review all medications and supplements that increase clot risk — Birth control pills and hormone therapy containing estrogen dramatically raise clot risk in Factor V Leiden patients. Smoking also multiplies risk. These must be avoided or alternatives found.
4. Assess patient understanding of lifelong condition and inheritance pattern — Factor V Leiden is inherited (passed from parents to children). Each child has a 50% chance if one parent has it. Patients need genetic counseling so family members can be tested if they have clot history.
5. Ensure proper anticoagulation therapy during high-risk periods — Pregnancy, surgery, long flights, and hospitalization greatly increase clot risk. Preventive (Prophylactic) (preventive) anticoagulation with heparin or low-molecular-weight heparin (LMWH) is often needed during these times.
6. Teach prevention strategies like mobility and compression stockings — Movement prevents blood from pooling in leg veins. During long travel or bed rest, ankle pumps, walking every 2 hours, staying hydrated, and wearing graduated compression stockings reduce clot formation.
7. Monitor for bleeding if patient is on anticoagulant therapy — Warfarin, rivaroxaban, apixaban, or other anticoagulants (blood thinners) are used long-term after clots. Bleeding risk includes easy bruising, blood in urine or stool, nosebleeds, and gum bleeding.
8. Coordinate care between hematology, obstetrics, and primary care providers — Management changes with life stages. Pregnant women need specialist monitoring because clot risk peaks postpartum. Surgery requires bridging anticoagulation plans. Team communication prevents gaps in care.

Sources

- American Society of Hematology (ASH) 2020 guidelines on venous thromboembolism: diagnosis, treatment, and prevention in adults
- American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines on Antithrombotic Therapy and Prevention of Thrombosis, 9th edition (2012, reaffirmed 2019)
- American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 197: Inherited Thrombophilias in Pregnancy (2018, reaffirmed 2022)
- National Institute for Health and Care Excellence (NICE) Clinical Guideline NG89: Venous thromboembolism in adults – reducing the risk in hospital and after discharge (2018, updated 2019)

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