



Prothrombin Thrombophilia

Synonym: Prothrombin G20210A Thrombophilia

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Summary

Clinical characteristics

Prothrombin thrombophilia is characterized by venous thromboembolism (VTE) manifest most commonly in adults as deep-vein thrombosis (DVT) in the legs or pulmonary embolism. The clinical expression of prothrombin thrombophilia is variable; many individuals heterozygous or homozygous for the 20210G>A *F2* variant never develop thrombosis, and while most heterozygotes who develop thrombotic complications remain asymptomatic until adulthood, some have recurrent thromboembolism before age 30 years. The relative risk for DVT in adults heterozygous for the 20210G>A variant is two- to fivefold increased; in children, the relative risk for thrombosis is three- to fourfold increased. Heterozygosity for 20210G>A has at most a modest effect on recurrence risk after a first episode. Although prothrombin thrombophilia may increase the risk for pregnancy loss, its association with preeclampsia and other complications of pregnancy such as intrauterine growth restriction and placental abruption remains controversial. Factors that predispose to thrombosis in prothrombin thrombophilia include: the number of 20210G>A alleles; presence of coexisting genetic abnormalities including factor V Leiden; and acquired thrombophilic disorders (e.g., antiphospholipid antibodies). Circumstantial risk factors for thrombosis include pregnancy and oral contraceptive use. Some evidence suggests that the risk for VTE in 20210G>A heterozygotes increases after air travel.

Diagnosis/testing

The diagnosis of prothrombin thrombophilia is established in a proband by identification of a heterozygous or homozygous 20210G>A variant (also known as c.*97G>A) in *F2*, the gene encoding prothrombin.

Management

Treatment of manifestations: Management depends on the clinical circumstances. The first acute thrombosis is treated according to standard guidelines. The duration of anticoagulation therapy is determined by assessment of the risks for VTE recurrence and anticoagulant-related bleeding. 20210G>A heterozygosity alone is not an indication for long-term anticoagulation in the absence of other risk factors.

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Surveillance: Individuals receiving long-term anticoagulation require periodic reevaluation to confirm that the benefits of anticoagulation continue to outweigh the risk of bleeding. 20210G>A heterozygotes who do not require long-term anticoagulation may benefit from evaluation prior to exposure to circumstantial risk factors such as surgery or pregnancy.

Agents/circumstances to avoid: Women heterozygous for 20210G>A with a history of VTE and women homozygous for 20210G>A with or without prior VTE should avoid estrogen-containing contraception and hormone replacement therapy (HRT).

Pregnancy management: No consensus exists on the optimal management of prothrombin thrombophilia during pregnancy; guidelines for treatment of VTE are derived from studies in non-pregnant individuals.

Genetic counseling

Prothrombin thrombophilia is inherited in an autosomal dominant manner: heterozygosity for the 20210G>A variant results in an increased risk for thrombosis; homozygosity for this variant confers a higher risk for thrombosis than heterozygosity. Occasionally (because of the relatively high frequency of the 20210G>A variant in the general population) one parent is homozygous for the 20210G>A variant or both parents are heterozygous for the 20210G>A variant. The genetic status of both parents and/or the reproductive partner of an affected individual needs to be evaluated before information regarding potential risks to sibs or offspring can be provided. If one parent of a heterozygous proband is heterozygous for the 20210G>A variant, the sibs of the proband are at 50% risk of being heterozygous; if one parent is homozygous, the sibs of the proband will be heterozygous. Once the 20210G>A variant has been identified in a family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

No clinical features are specific for prothrombin thrombophilia. The diagnosis **should be suspected** in individuals with at least one of the following more specific findings:

- A first unprovoked venous thromboembolism (VTE) before age 50 years
- A history of recurrent VTE
- Venous thrombosis at certain unusual sites such as the cerebral, mesenteric, portal, or hepatic veins
- VTE during pregnancy or the puerperium
- VTE associated with the use of estrogen-containing oral contraceptives or hormone replacement therapy (HRT)
- An unprovoked VTE at any age in an individual with a first-degree family member with a VTE before age 50 years

Prothrombin thrombophilia testing **may be considered** in individuals who have less specific findings, including the following:

- A history of unprovoked VTE considering discontinuation of anticoagulation
- A first VTE related to use of tamoxifen or other selective estrogen receptor modulators
- Age greater than 50 years with a first unprovoked VTE
- Neonates and children with non-catheter related idiopathic VTE or stroke

Molecular genetic testing for the *F2* 20210G>A variant is **not recommended** for the following:

- General population screening

- Routine initial testing prior to the use of estrogen-containing contraceptives, HRT, or selective estrogen receptor modulators
- Adults with VTE occurring in the setting of major transient risk factors (e.g., surgery, trauma)
- Routine initial testing in adults with arterial thrombosis
- Individuals with unprovoked VTE already receiving long-term anticoagulation treatment
- Routine initial testing during pregnancy
- Routine testing in women with recurrent fetal loss, placental abruption, fetal growth restriction, or preeclampsia
- Prenatal or newborn testing
- Neonates and children with asymptomatic central venous catheter-related thrombosis
- Routine testing in asymptomatic children
- Routine testing of unselected children with a first episode of VTE

Establishing the Diagnosis

The diagnosis of prothrombin thrombophilia is **established** in a proband with a heterozygous or homozygous pathogenic variant(s) 20210G>A in *F2* identified by molecular genetic testing (see Table 1).

Note: The range of plasma concentrations of prothrombin in heterozygotes overlaps with the normal range. Therefore, plasma prothrombin concentration is not reliable for diagnosis.

Molecular genetic testing approaches can include **targeted analysis** for the *F2* 20210G>A variant (see Table 1) or a **multigene panel** that includes the analysis of the *F2* variant and other genes of interest (see Differential Diagnosis). Note: The genes included and sensitivity of multigene panels vary by laboratory and are likely to change over time. For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Note: The diagnosis of prothrombin thrombophilia in the setting of liver transplantation requires molecular genetic testing of donor liver, the site of prothrombin synthesis.

Table 1. Molecular Genetic Testing Used in Prothrombin Thrombophilia

Gene ¹	Method	Proportion of Probands with a Pathogenic Variant ² Detectable by Method
<i>F2</i>	Targeted analysis for 20210G>A ³	100%

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. The official designation of the pathogenic variant is c.*97G>A per varnomen.hgvs.org guidelines.

Clinical Characteristics

Clinical Description

The clinical expression of prothrombin thrombophilia is variable. Many individuals who are heterozygous or homozygous for the *F2* 20210G>A variant never develop thrombosis. While most individuals with prothrombin thrombophilia do not experience a first thrombotic event until adulthood, some have recurrent VTE before age 30 years.

Venous Thromboembolism (VTE)

The primary clinical manifestation of prothrombin thrombophilia is VTE. The relative risk for VTE is increased two- to fivefold in 20210G>A heterozygotes [Gohil et al 2009, Lijfering et al 2009, Rosendaal & Reitsma 2009]. Deep-vein thrombosis (DVT) and pulmonary embolism (PE) are the most common VTE. The most common site for DVT is the legs, but upper-extremity thrombosis also occurs.

Among individuals with DVT, 20210G>A heterozygotes had a significantly higher rate of PE (32%) than those with the factor V Leiden variant (19%) or those without thrombophilia (17%). 20210G>A heterozygotes are also at increased risk of developing isolated PE [Martinelli et al 2006] and may develop VTE at a younger age than individuals without the variant [Martinelli et al 2006].

Upper-extremity thrombosis. Heterozygosity for 20210G>A is associated with a three- to sixfold increased risk for upper-extremity thrombosis [Martinelli et al 2004, Blom et al 2005a, Linnemann et al 2008]. Women heterozygous for 20210G>A who were using oral contraceptives had a nine- to 14-fold increased risk for idiopathic upper-extremity thrombosis [Martinelli et al 2004, Blom et al 2005a].

Cerebral venous thrombosis. 20210G>A heterozygosity is associated with a six- to tenfold increased risk for cerebral venous thrombosis [Dentali et al 2006, Lauw et al 2013, Gonzalez et al 2016]. The combination with this variant and other acquired risk factors greatly increases this risk. Women heterozygous for 20210G>A who used oral contraceptives had an 80- to 150-fold increased relative risk for cerebral venous thrombosis [Martinelli et al 1998].

Hepatic thrombosis and portal vein thrombosis. 20210G>A heterozygosity was associated with a fourfold increased risk for both idiopathic and liver disease-associated portal vein thrombosis [Dentali et al 2008a]. In contrast, a meta-analysis found that 20210G>A heterozygosity did not significantly increase the risk for hepatic vein thrombosis (Budd Chiari Syndrome) [Zhang et al 2014].

Thrombosis in unusual locations. Retinal vein thrombosis and other ocular thrombotic events have been reported in 20210G>A heterozygotes [Glueck & Wang 2009], although the association is much weaker than with DVT and/or PE. The risk for superficial venous thrombosis was increased nearly fourfold in 20210G>A heterozygotes [Martinelli et al 1999a]. These events are much less common than DVT or PE, and there is no evidence that identification of a 20210G>A variant should alter management [Tait et al 2012].

Risk for VTE in children. VTE in children is multifactorial, and is caused by acquired clinical risk factors, underlying medical conditions, and inherited predisposition to thrombosis [Klaassen et al 2015, van Ommen & Nowak-Göttl 2017, Nowak-Göttl et al 2018]. The most common clinical risk factors for thrombosis in children are central venous catheters and malignancy. Additional risk factors are present at the time of VTE in 92% [Young et al 2003, Young et al 2008].

Asymptomatic healthy children heterozygous or homozygous for 20210G>A are at low risk for thrombosis. Heterozygous children were found to have a three- to fourfold increase in relative risk for VTE [Junker et al 1999, Schobess et al 1999]. The relative risk for VTE was increased more than ninefold in children with two or more inherited thrombophilic disorders [Young et al 2008]. Other studies also found a higher risk in children compound heterozygous for the 20210G>A and [factor V Leiden](#) variants or with the 20210G>A variant in combination with other inherited thrombophilic disorders [Junker et al 1999, Young et al 2003]. Other reported manifestations in children include cerebral venous thrombosis [Kenet et al 2010] and hepatic, portal, and retinal vein thromboses.

Recurrent thrombosis. Due to conflicting data it is unclear to what extent the 20210G>A variant increases the risk of recurrent VTE. If there is an increased risk of recurrent thrombosis after initial treatment of a first VTE, the magnitude of the increase is small [Kyrle et al 2010, Berg et al 2011]. In children inherited thrombophilia appears to have at most a modest effect on the risk of recurrence, similar to the findings in adults [Klaassen et al 2015]. A two- to threefold increase in recurrence risk has been reported [Young et al 2009].

During pregnancy women with a prior history of VTE have an increased recurrence risk ranging from 0% to 15% in published studies. The risk is higher in women with a prior unprovoked episode or an estrogen-related VTE, and in those with coexisting genetic or acquired risk factors [Brill-Edwards et al 2000]. No studies have specifically evaluated the risk for recurrent VTE in pregnant women with a 20210G>A variant.

Pregnancy complications. It is unlikely that 20210G>A heterozygosity is a major factor contributing to pregnancy loss and other adverse pregnancy outcomes (e.g., preeclampsia, fetal growth restriction, placental abruption). Although multiple retrospective studies have suggested a modest increased risk of fetal loss, most prospective studies have not confirmed an association. The available data suggest that 20210G>A heterozygosity is associated with at most a two- to threefold increased relative risk for pregnancy loss [Rey et al 2003, Robertson et al 2006]. The association with preeclampsia, fetal growth restriction, and placental abruption is more controversial. At most, a 20210G>A variant is one of multiple largely unknown genetic and environmental predisposing factors contributing to these complications.

Homozygosity for 20210G>A variant. The risk of VTE is likely higher in individuals who are homozygous for the 20210G>A variant but the absolute risk has not been defined due to lack of data. 20210G>A homozygotes may develop thrombosis more frequently and at a younger age. The annual incidence of recurrent VTE was 12%/year in persons homozygous for 20210G>A, compared to 2.8% in those without a 20210G>A or factor V Leiden variant [González-Porrás et al 2006]. Numerous reports of asymptomatic 20210G>A homozygotes emphasize the contribution of other genetic and acquired risk factors to thrombosis [Ridker et al 1999].

Additional Factors that Predispose to Thrombosis

In addition to the number of variants, the clinical expression of prothrombin thrombophilia is influenced by: family history, coexisting genetic abnormalities, acquired thrombophilic disorders, and circumstantial risk factors.

Family History

A family history of thrombosis affecting at least one first-degree relative is an additional risk factor for VTE even in those with a known inherited thrombophilic disorder (including 20210A heterozygosity) [Bezemer et al 2009]. A family history of thrombosis is associated with a three- to fourfold increased risk for VTE among individuals with a 20210G>A variant [Noboa et al 2008, Rossi et al 2011]. The risk is higher when multiple members are affected and thrombosis occurs at a young age.

Coexisting Genetic Abnormalities

Another inherited thrombophilic disorder is present in 8%-14% of 20210G>A heterozygotes, creating an additive effect on overall thrombotic risk. Individuals with multiple thrombophilic disorders develop VTE at a younger age and are at higher risk for recurrent thrombosis than those with a single thrombophilic variant [Makris et al 1997].

- **Factor V Leiden.** Heterozygosity for a factor V Leiden variant occurs in 20%-40% of symptomatic 20210G>A heterozygotes [Poort et al 1996, Emmerich et al 2001]. The risk for VTE was reported to increase seven to 20-fold in individuals heterozygous for both variants [Emmerich et al 2001, Segal et al 2009]. Compound heterozygotes were at a three- to fourfold higher risk than those with a single thrombophilic variant and were more likely to develop thrombosis in unusual locations (e.g., hepatic, mesenteric, or cerebral veins) [De Stefano et al 1999]. A three- to ninefold higher risk of recurrent VTE was found compared to those with neither variant, and a threefold higher risk compared to individuals heterozygous for factor V Leiden alone [De Stefano et al 1999, Meinardi et al 2002, Segal et al 2009]. The annual incidence of recurrent VTE was 12%/year in compound heterozygotes, compared to 2.8% in those with neither thrombophilia-related variant [González-Porrás et al 2006].
- **Anticoagulant protein deficiency.** The combination of protein S deficiency and 20210G>A heterozygosity was associated with a nearly 13-fold increased risk for VTE, compared to a fourfold increased risk with 20210G>A heterozygosity alone [Tirado et al 2001]. In contrast, coinheritance of a 20210G>A variant did not increase the risk for thrombosis in a large kindred with protein C deficiency [Bovill et al 2000].

Other genetic factors (Note: Analysis of the following variants in *F8* and *SERPINE1* is not recommended in clinical practice.)

- ***F8*** (encoding factor XIII). The effect of *F8* Val34Leu has been extensively studied with conflicting results [Undas et al 2009, Berezky & Muszbek 2011]. Two meta-analyses found a slight overall protective effect of *F8* Val34Leu against VTE [Wells et al 2006, Gohil et al 2009]. Note: The *F8* variant in exon 2 (NM_000132.3:c.157G>T) encodes a normal protein variant officially designated NP_000123.1:p.Val53Leu (commonly known as Val34Leu, which does not count the 19 amino-acid signal sequence) [Kohler et al 1998].
- ***SERPINE1*** (encoding plasminogen activator inhibitor type 1). A polymorphism commonly referred to as 4G/5G is a missense substitution located at -675 (NG_013213.1: g.4328G>T;rs114094261) that results in four or five G nucleotides in a row. Heterozygosity for *SERPINE1* 4G in combination with 20210G>A heterozygosity was associated with a sixfold increased risk for VTE. Homozygosity for *SERPINE1* 4G in combination with 20210G>A heterozygosity was associated with a 13-fold increased risk for VTE [Barcellona et al 2003].

Acquired Thrombophilic Disorders

Acquired thrombophilic disorders include antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders, and increased levels of clotting factors.

Circumstantial Risk Factors for VTE

The 20210G>A variant interacts with multiple environmental risk factors to increase the risk for VTE. At least 50% of thrombotic episodes in individuals with the 20210G>A variant are provoked by additional risk factors, with pregnancy being the most common [Gerhardt et al 2000, Campello et al 2019].

Table 2. Circumstantial Risk Factors: Increased Risk for Thrombophilia in Persons with the 20210G>A Variant

Circumstance	Relative Risk for VTE	Comment	Reference
Pregnancy	<ul style="list-style-type: none"> • 3x-15x ↑ risk (heterozygotes) • 31x ↑ risk during pregnancy or postpartum • 26x ↑ risk (homozygotes) • 8-47x ↑ risk in compound heterozygotes (w/factor V Leiden) 	<p>Incidence:</p> <ul style="list-style-type: none"> • During pregnancy: 1:200 to 1:300 • Post partum: 1:66 (highest risk: 1st 6 wks post partum) • In homozygotes: 1:40 • In compound heterozygotes (w/factor V Leiden): 1:20 to 1:125 	Gerhardt et al [2000], Martinelli et al [2002], Gerhardt et al [2003], Robertson et al [2006], Martinelli et al [2008], Jacobsen et al [2010], Bates et al [2016], Gerhardt et al [2016]
Combined oral contraceptives	16x-59x ↑ risk (heterozygotes)	<ul style="list-style-type: none"> • Higher risk during 1st yr of use than subsequent yrs • Incidence 1/500/yr • Unopposed progestin is assoc w/↓ risk for thrombosis vs estrogen-containing contraception. 	Martinelli et al [1999b], Bloemenkamp et al [2000], Emmerich et al [2001], Wu et al [2005], Mohllajee et al [2006]
Other contraceptives (e.g., transdermal, vaginal ring)	VTE risk at least as high as risk w/ combined oral contraceptives; not specifically studied in women w/ 20210G>A		Cole et al [2007], Jick et al [2007], Dore et al [2010]

Table 2. continued from previous page.

Circumstance	Relative Risk for VTE	Comment	Reference
Oral HRT	<ul style="list-style-type: none"> • 3x ↑ risk (heterozygotes) vs women using HRT w/o 20210G>A variant • 8x-25x ↑ risk (heterozygotes) vs women w/o 20210G>A variant not using HRT 	5x ↑ risk w/conjugated equine estrogen use vs w/esterified estrogen	Straczek et al [2005], Smith et al [2006], Canonico et al [2008], Roach et al [2013]
Transdermal HRT	Preliminary data suggest may not ↑ risk.	Lower relative risk than oral HRT	Canonico et al [2010], ACOG [2013a]
SERMS	Risk uncertain but likely > risk assoc w/ SERMS alone		Abramson et al [2006]
Obesity	<ul style="list-style-type: none"> • 7x ↑ risk if BMI >30 kg/m² • 5x ↑ risk if BMI 25-30 kg/m² 	Risk ↑ w/↑ BMI	Pomp et al [2007]
Malignancy	<ul style="list-style-type: none"> • 17x ↑ risk of VTE • 20x ↑ risk of UE VTE • 5x ↑ risk of CVC thrombosis 		Blom et al [2005a], Blom et al [2005b], Dentali et al [2008b]
Air travel	17x ↑ risk		Martinelli et al [2003]
Minor leg injury	9x-30x ↑ risk		van Stralen et al [2008]
Organ transplantation	Data unclear		Ghisdal et al [2010], Pereboom et al [2011]
CVC	Data unclear; CVC is most common risk factor for UE thrombosis in children. Studies evaluating risk in children w/ 20210G>A were not identified.	Studies found no ↑ or 2x-3x ↑ risk.	Vayá et al [2003], Van Rooden et al [2004], Linnemann et al [2008]
Surgery	Data unclear; any excess risk likely small compared to risk assoc w/surgery	Studies found no ↑ or 10x-13x ↑ risk.	Wählander et al [2002], Blom et al [2005a], Joseph et al [2005], Ringwald et al [2009]
Antiphospholipid antibody syndrome	Data unclear	1 study found 4x ↑ risk (heterozygotes).	DeSancho et al [2010]

BMI = body mass index; CVC = central venous catheter; HRT = hormone replacement therapy; SERMS = selective estrogen receptor modulators; UE = upper-extremity; VTE = venous thromboembolism

Pregnancy. Women with thrombophilia are at higher risk for VTE during pregnancy. In several studies 20210G>A heterozygotes had a three- to 15-fold higher risk for pregnancy-associated VTE than pregnant women without inherited thrombophilia [Gerhardt et al 2000, Martinelli et al 2002, Robertson et al 2006]. Heterozygous women without a family history of VTE have a lower thrombotic risk than women with prothrombin thrombophilia and a family history of VTE. Although 20210G>A heterozygosity increases the relative risk for pregnancy-associated VTE, the absolute risk in asymptomatic heterozygotes is low in the absence of other predisposing factors with an estimated probability in the range of 1:200 to 1:300 pregnancies [Gerhardt et al 2000, Gerhardt et al 2003]. The highest risk occurs during the first six weeks post partum but the risk does not return to pre-pregnancy baseline until three months post partum.

Women homozygous for 20210G>A or compound heterozygous for 20210G>A and factor V Leiden have a higher relative risk for pregnancy-associated VTE, but the absolute risk is less well defined [Robertson et al 2006, van Vlijmen et al 2011]. The probability of VTE during pregnancy and the puerperium is lower in compound heterozygous women younger than age 35 years (5.5%) than in older women (8.2%) [Gerhardt et al 2016].

Combined oral contraceptive (COC) use substantially increases the relative risk for VTE in women heterozygous for 20210G>A [Bistervels et al 2019]. The additive effect of both a 20210G>A variant and COC use was confirmed in multiple studies in which the odds ratios for VTE in women with both risk factors ranged from 16 to 59 [Martinelli et al 1999b, Wu et al 2005]. For women who are compound heterozygous for a 20210G>A variant and factor V Leiden, the odds ratios for VTE ranged from 17 to 110 [Mohllajee et al 2006, van Vlijmen et al 2016]. Despite the marked increase in relative risk, the absolute incidence of VTE is low because of the low baseline risk in young healthy women [van Vlijmen et al 2011]. The incidence of VTE in COC users with either factor V Leiden or a 20210G>A variant ranged from 0.49 to 2.0 VTE/100 pill-years compared to 0.19 to 0 VTE/100 pill-years in COC users without these variants. The absolute VTE risk is substantially higher in women who are compound heterozygous for 20210G>A and factor V Leiden variants or homozygous for either variant (0.86 vs 0.19 VTE/100 pill-years) [van Vlijmen et al 2016].

Other newer forms of combined hormonal, transdermal, and vaginal ring contraception have not been studied in 20210G>A heterozygotes but the risk is likely at least as great as the risk associated with COC use.

Oral hormone replacement therapy (HRT) is associated with a two- to fourfold increased relative risk for VTE in healthy postmenopausal users of HRT compared to non-users [Renoux et al 2010, Eisenberger & Westhoff 2014]. The risk of VTE in HRT users is threefold greater in postmenopausal women with a factor V Leiden or prothrombin 20210G>A variant than in HRT users without a thrombophilic variant [Roach et al 2013].

Transdermal HRT. Multiple observational studies consistently found that transdermal HRT did not increase the risk of VTE [Canonica et al 2010, Sweetland et al 2012, ACOG 2013a, Rovinski et al 2018]. There is also evidence that transdermal estrogen is associated with a lower thrombotic risk than oral estrogen in women with a thrombophilic variant including 20210G>A [Canonica et al 2010]. Women with a 20210G>A variant using transdermal estrogen had a risk of VTE similar to that of non-users with the variant [Straczek et al 2005]. However no prospective randomized trials have confirmed the safety of transdermal HRT in women with inherited thrombophilia.

Selective estrogen receptor modulators (SERMs). Limited data suggest that SERMs (e.g., tamoxifen, raloxifene) are associated with a twofold increased risk for VTE, similar to the risk associated with HRT [Barrett-Connor et al 2006]. The risk for VTE in 20210G>A heterozygotes who use SERMs is uncertain but likely higher than that associated with SERM use alone.

Arterial Thrombosis: NOT Convincingly Associated with Prothrombin Thrombophilia

The available evidence indicates that the 20210G>A variant is not a major risk factor for arterial thrombosis of any sort including myocardial infarction and stroke in fetuses, children, and adults.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified for other *F2* variants.

Nomenclature

Prothrombin thrombophilia may also be referred to as *F2*-related thrombophilia, factor II-related thrombophilia, or prothrombin 20210G>A thrombophilia.

Prevalence

F2 20210G>A heterozygosity is the second most common inherited thrombophilia, after **factor V Leiden**. The prevalence varies by population. Heterozygosity for 20210G>A occurs in 1.7%-3% of the general US and European populations. The highest heterozygosity rate is found in Europe; the variant is extremely rare in Asian,

African, and Native American populations. Within Europe, prevalence varies from 3% in southern Europe to 1.7% in northern countries [Rosendaal et al 1998]. In the US, the 20210G>A variant is present in 2%-5% of Americans of European origin, 2.2% of Hispanic Americans, and 0%-0.6% of African Americans [Dowling et al 2003, Chang et al 2009].

The 20210G>A variant is present in:

- 8.2% of Americans of European origin with VTE;
- 1.1% of African Americans with VTE;
- 6%-14% of adults with a first VTE;
- 18%-21% of adults with VTE and a personal or family history of recurrent VTE [Poort et al 1996, Tosetto et al 1999];
- 3.7% of children with a first spontaneous VTE [Nowak-Göttl et al 2001].

The frequency of homozygosity for the 20210G>A variant is 1:10,000. 20210G>A homozygosity is found in 1.8%-4.5% of individuals with VTE [Margaglione et al 1999, Barcellona et al 2003].

Genetically Related (Allelic) Disorders

Prothrombin deficiency (OMIM 613679), including hypoprothrombinemia and dysprothrombinemia, results from biallelic *F2* missense, nonsense, and splicing variants and deletions that inactivate or decrease prothrombin levels. Prothrombin deficiency is a rare bleeding disorder associated with easy bruising and hematoma formation, epistaxis, heavy menstrual bleeding, and bleeding after trauma and surgery.

Differential Diagnosis

The differential diagnosis of venous thromboembolism (VTE) includes several other inherited thrombophilic disorders (discussed here) and acquired thrombophilic disorders (outside of the scope of this GeneReview).

Factor V Leiden refers to the specific G-to-A substitution in *F5* that predicts a single amino-acid replacement (Arg506Gln) that destroys a cleavage site for activated protein C. Factor V Leiden thrombophilia (the most common inherited form of thrombophilia) is characterized by a poor anticoagulant response to activated protein C and an increased risk for VTE. Deep vein thrombosis (DVT) is the most common VTE, with the legs being the most common site. Factor V Leiden heterozygosity is found in 3%-8% of the general US and European population; the Leiden variant is present in approximately 15%-20% of individuals with a first DVT and up to 50% of individuals with recurrent VTE or an estrogen-related thrombosis.

Inherited deficiencies of the natural anticoagulant proteins C, S, and antithrombin are approximately tenfold less common than *F2* 20210G>A heterozygosity with a combined prevalence of less than 1%-2% of the population. Anticoagulant protein deficiencies are found in 1%-3% of individuals with a first VTE.

Hereditary dysfibrinogenemias (OMIM 616004) are rare and infrequently cause thrombophilia and thrombosis.

See [Thrombophilia: OMIM Phenotypic Series](#), to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To assess the risk for venous thromboembolism (VTE) in an individual found to have the *F2* 20210G>A variant, the following are recommended:

- An activated protein C resistance or DNA assay for [factor V Leiden](#)
- Serologic assays for anticardiolipin antibodies and anti-beta₂ glycoprotein 1 antibodies
- Multiple phospholipid-dependent coagulation assays for a lupus inhibitor

For high-risk individuals (e.g., those with a history of recurrent VTE, especially at a young age, or those with strong family history of VTE at a young age), evaluation should also include assays of the following:

- Protein C activity
- Antithrombin activity
- Protein S activity or free protein S antigen

Note: Measurement of the following is NOT recommended:

- Plasma concentration of homocysteine, since no data support a change in duration of anticoagulation or the use of vitamin supplementation in individuals with hyperhomocysteinemia and a history of VTE
- *MTHFR* variants, as no clinical rationale for this testing exists
- Factor VIII and other clotting factor levels [Moll 2015]

Treatment of Manifestations

Treatment of VTE in Adults

The management of thrombosis in individuals with prothrombin thrombophilia depends on the clinical circumstances.

The first acute thrombosis should be treated according to standard guidelines [Kearon et al 2012, Kearon et al 2016, Ortel et al 2020]. For initial treatment of VTE, current guidelines suggest a direct oral anticoagulant (dabigatran, edoxaban, rivaroxaban, or apixaban) over warfarin because of a lower bleeding risk and greater convenience [Kearon et al 2016, Ortel et al 2020]. Of note, low molecular-weight heparin (LMWH) is given before dabigatran and edoxaban but not before rivaroxaban or apixaban. Instead, a higher dose is administered for the first three weeks of therapy with rivaroxaban and for the first week of treatment with apixaban. The recommendation for a direct oral anticoagulant may not apply to certain subgroups such as individuals with severe renal insufficiency, antiphospholipid antibody syndrome, or extremes of body weight [Ortel et al 2020].

For individuals not treated with one of the direct oral anticoagulants, administration of warfarin is started concurrently with LMWH or fonadaparinux, a pentasaccharide (except during pregnancy), and monitored with the international-normalized ratio (INR). A target INR of 2.5 (therapeutic range: 2.0-3.0) provides effective anticoagulation, even in *F2 20210G>A* homozygotes [Tzoran et al 2017]. LMWH and warfarin therapy should be overlapped for at least five days, and until the INR has been within therapeutic range for 24 hours, at which time LMWH is stopped [Witt et al 2018].

Note: LMWH and warfarin are both safe in women who are breast-feeding (see Pregnancy Management for issues with anticoagulants).

The duration of oral anticoagulation therapy should be based on an individualized assessment of the risks for VTE recurrence and anticoagulant-related bleeding. Recurrence risk is determined by the clinical circumstances of the first event (provoked or unprovoked), adequacy of early treatment, and individual risk factors.

- 20210G>A heterozygosity alone is not an indication for long-term anticoagulation in the absence of other risk factors according to American College of Chest Physicians guidelines on antithrombotic therapy and American Society of Hematology guidelines for management of venous thromboembolism (see Published Guidelines / Consensus Statements).
- Anticoagulation for at least three months is recommended for persons with DVT and/or PE associated with a transient (reversible) risk factor [Kearon et al 2012, Kearon et al 2016, Ortel et al 2020].

Indefinite anticoagulation is recommended for individuals with a first or recurrent unprovoked (i.e., idiopathic) proximal DVT of the leg or pulmonary embolism who have a low or moderate bleeding risk [Kearon et al 2012, Kearon et al 2016, Ortel et al 2020]. The decision should be based on an assessment of potential risks and benefits regardless of 20210G>A status [Berg et al 2011]. Long-term anticoagulation is occasionally considered in selected individuals homozygous for 20210G>A or with multiple thrombophilic disorders particularly in the presence of additional risk factors [De Stefano & Rossi 2013], as the potential benefits of long-term anticoagulation may outweigh the bleeding risks.

Treatment of VTE in Children

Treatment recommendations for children with VTE are largely adapted from studies in adults. There is no evidence that identification of a 20210G>A variant should influence decisions about the intensity or duration of anticoagulation in children [Heleen van Ommen & Middeldorp 2011, Monagle et al 2012].

Children with a first VTE should receive initial treatment with either unfractionated heparin or LMWH for at least five days. American Society of Hematology guidelines suggest using either LMWH or warfarin in children with symptomatic DVT or PE. The decision on anticoagulant should be individualized based on preference of the affected individual, underlying condition, comorbidities, and other medications [Monagle et al 2018]. LMWH is often favored over warfarin for continued therapy, especially in very young children and those with complex medical problems [Monagle & Newall 2018]. Recommendations on the duration of antithrombotic therapy are based on the nature of the thrombotic event (e.g., spontaneous or provoked) [Monagle et al 2012]; see Published Guidelines / Consensus Statements.

Anticoagulation is recommended:

- For three months following a VTE provoked by a clinical risk factor that has resolved;
- At least three months and until the risk factor has resolved in children with ongoing but potentially reversible risk factor;
- For 6-12 months after a first unprovoked VTE.

Consensus guidelines and expert opinion emphasize the importance of a careful risk/benefit assessment in each individual.

Prevention of Primary Manifestations

In the absence of a history of thrombosis, long-term anticoagulation is not recommended for asymptomatic 20210G>A heterozygotes because the 1%-3%/year risk for major bleeding from anticoagulation is greater than the estimated less than 1%/year risk for thrombosis [Berg et al 2011].

Prophylactic anticoagulation may be considered in high-risk clinical settings such as surgery, pregnancy, or prolonged immobilization, although currently no evidence confirms the benefit of primary prophylaxis for asymptomatic 20210G>A heterozygotes. Factors that may influence decisions about the indication for and duration of anticoagulation include age, family history, and other coexisting risk factors. Recommendations for prophylaxis at the time of surgery and other high-risk situations are available in the American College of Chest Physicians and American Society of Hematology consensus guidelines [Guyatt et al 2012] ([full text](#)) [Anderson et al 2019, Schünemann et al 2018].

Surveillance

Individuals receiving long-term anticoagulation require periodic reevaluation to confirm that the benefits of anticoagulation continue to outweigh the risk of bleeding.

20210G>A heterozygotes who do not require long-term anticoagulation may benefit from evaluation prior to exposure to circumstantial risk factors such as surgery or pregnancy (see Prevention of Primary Manifestations).

Agents/Circumstances to Avoid

Women with a history of VTE who are heterozygous for 20210G>A should avoid estrogen-containing contraception and hormone replacement therapy (HRT).

Women homozygous for 20210G>A with or without prior VTE should avoid estrogen-containing contraception and HRT.

Asymptomatic women heterozygous for 20210G>A:

- Should be counseled on the risks of estrogen-containing contraception and HRT use and should be encouraged to consider alternative forms of contraception and control of menopausal symptoms;
- Electing to use oral contraceptives should avoid third-generation and other progestins with a higher thrombotic risk;
- Electing short-term hormone replacement therapy for severe menopausal symptoms should use a low-dose transdermal preparation, which has a lower thrombotic risk than oral formulations [Renoux et al 2010].

Evaluation of Relatives at Risk

The genetic status of apparently asymptomatic at-risk family members can be established using molecular genetic testing for the 20210G>A variant.

Note: The indications for family testing are unresolved.

- In the absence of evidence that early identification of the 20210G>A variant reduces morbidity or mortality, decisions regarding testing should be made on an individual basis.
- Clarification of 20210G>A variant status may be useful in at-risk female relatives considering hormonal contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age if the results are likely to affect management.

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

Pregnancy Management

No consensus exists on the optimal management of prothrombin thrombophilia during pregnancy; guidelines are derived from studies in non-pregnant individuals [Bates et al 2012, ACOG 2013b, Bates et al 2018]; see Published Guidelines / Consensus Statements. All women with inherited thrombophilia should undergo individualized risk assessment. Decisions about anticoagulation should be based on the number and type of thrombophilic defects, coexisting risk factors, and personal and family history of thrombosis.

LMWH is the preferred antithrombotic agent for prophylaxis during pregnancy. The oral direct thrombin inhibitor, dabigatran, and the direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) are contraindicated during pregnancy and breastfeeding because of (1) absence of data on fetal and neonatal safety and (2) animal studies that showed reproductive toxicity [Ageno et al 2012, Bates et al 2018].

Prophylactic anticoagulation during pregnancy **is recommended** for all women:

- With a history of unprovoked VTE, including those heterozygous for 20210G>A. LMWH should be given during pregnancy followed by six weeks of postpartum anticoagulation [ACOG 2013b, Bates et al 2018].

- Heterozygous for 20210G>A with a prior pregnancy or estrogen-related thrombosis who are also at an increased risk for recurrence [ACOG 2013b, Bates et al 2018].

Prophylactic anticoagulation during pregnancy **may be considered** for asymptomatic women who:

- Are homozygous for 20210G>A and have a family history of thrombosis [ACOG 2013b, Bates et al 2018].
- Are compound heterozygotes for 20210G>A and factor V Leiden, especially those with coexisting circumstantial risk factors (obesity, immobilization, multiple gestation) [ACOG 2013b, Bates et al 2018].

Prophylactic anticoagulation during pregnancy **is not routinely recommended** in asymptomatic women heterozygous for 20210G>A with no history of thrombosis. All women heterozygous for 20210G>A should be warned about potential thrombotic complications and counseled regarding the risks and benefits of anticoagulation during pregnancy [ACOG 2013b, Bates et al 2018].

Prevention of Thrombosis During the Postpartum Period

A **six-week course of postpartum prophylaxis anticoagulation** is recommended for:

- All women heterozygous for 20210G>A women with a prior history of VTE;
- All asymptomatic homozygous women and those with combined thrombophilia;

Postpartum prophylaxis may be considered in asymptomatic women heterozygous for 20210G>A with a positive family history of VTE, although consensus guideline suggestions differ for this group [Bates et al 2012, ACOG 2013b, Bates et al 2018].

Other

Unexplained pregnancy loss. Current consensus guidelines and expert opinion recommend against the use of antithrombotic therapy outside of clinical trials in women with inherited thrombophilia and unexplained pregnancy loss because of the absence of high-quality evidence confirming benefit [Bates et al 2012, ACOG 2013b, Skeith et al 2016].

Pregnancy complications. Current guidelines recommend against antithrombotic prophylaxis for women with inherited thrombophilia and a history of other pregnancy complications such as preeclampsia or placental abruption [Bates et al 2012, ACOG 2013b].

Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

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

Prothrombin thrombophilia (i.e., predisposition to the development of venous thrombosis) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- All individuals reported to date with prothrombin thrombophilia have had a parent who is heterozygous or homozygous for the *F2* 20210G>A variant.
- Prothrombin thrombophilia as the result of a *de novo* pathogenic variant has not been reported.
- Occasionally (because of the relatively high prevalence of the 20210G>A variant in the general population) one parent is homozygous for the 20210G>A variant or both parents are heterozygous for the 20210G>A variant.
- The family history of some individuals diagnosed with prothrombin thrombophilia may appear to be negative because no other family members developed thrombosis or because of failure to recognize prothrombin thrombophilia in affected family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing for the 20210G>A variant has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If one parent is heterozygous for the 20210G>A variant, each sib of the proband is at a 50% risk of being heterozygous for the 20210G>A variant.
- If one parent is homozygous for the 20210G>A variant, each sib of the proband has a 100% chance of being heterozygous for the 20210G>A variant.
- If both parents are heterozygous for the 20210G>A variant, each sib of the proband has a 25% chance of being homozygous for the 20210G>A variant, a 50% chance of being heterozygous for the 20210G>A variant, and a 25% chance of inheriting both normal *F2* alleles.

Offspring of a heterozygous proband

- Each child has a 50% chance of inheriting the 20210G>A variant.
- If the proband's reproductive partner is also heterozygous for the 20210G>A variant, each of their children has a 25% chance of inheriting two 20210G>A variants, a 50% chance of inheriting one 20210G>A variant, and a 25% chance of inheriting neither 20210G>A variant.

Offspring of a homozygous proband

- A proband homozygous for the 20210G>A variant will transmit the 20210G>A variant to all offspring.
- If the proband's reproductive partner is heterozygous for the 20210G>A variant, each of their children has a 50% chance of inheriting two 20210G>A variants and a 50% chance of inheriting one 20210G>A variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: the family members of a person who is heterozygous or homozygous for 20210G>A variant are at risk.

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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the F2 20210G>A variant has been identified in a family member, prenatal testing for a pregnancy at increased risk for prothrombin thrombophilia and preimplantation genetic testing 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](#).

- **National Blood Clot Alliance**
Phone: 703-935-8845
Email: info@stoptheclot.org
www.stoptheclot.org
- **Thrombosis UK**
 United Kingdom
Phone: 0300 772 9603
Email: admin@thrombosisuk.org
www.thrombosisuk.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. Prothrombin Thrombophilia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
F2	11p11.2	Prothrombin	F2 database	F2	F2

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 Prothrombin Thrombophilia ([View All in OMIM](#))

176930	COAGULATION FACTOR II; F2
188050	THROMBOPHILIA DUE TO THROMBIN DEFECT; THPH1

Molecular Pathogenesis

The 20210G>A variant is associated with elevated plasma levels of prothrombin [Poort et al 1996, Kyrle et al 1998, Simioni et al 1998, Soria et al 2000]. Experimental evidence suggests that the G>A transition increases the efficiency and accuracy of processing of the 3' end of the mRNA, resulting in an accumulation of mRNA and increased synthesis of the protein prothrombin. The observation that elevated prothrombin levels independently increase the risk for thrombosis suggests that the allele may act through this mechanism [Poort et al 1996, Legnani et al 2003]. The results of several experimental and clinical studies suggest that elevated prothrombin

levels contribute to increased thrombin generation and a prothrombotic state, although other mechanisms may also be involved [Kyrlé et al 1998, Lavigne-Lissalde et al 2010].

Most 20210G>A heterozygotes have a mildly elevated plasma concentration of prothrombin that is approximately 30% higher than in healthy controls [Poort et al 1996, Soria et al 2000]. However, because the range of prothrombin concentrations in heterozygotes varies widely and overlaps significantly with the normal range, the plasma concentration of prothrombin is not reliable for diagnosis of prothrombin thrombophilia.

Individuals with one or two 20210G>A alleles often have elevated plasma levels of the prothrombin fragment F1+2, and other coagulation activation markers, reflecting the resulting mild hypercoagulable state [Eikelboom et al 1999, Gouin-Thibault et al 2002].

Mechanism of disease causation. Gain of function

Table 3. Notable *F2* Variants

Reference Sequences	DNA Nucleotide Change		Predicted Protein Change	Comment [Reference]
	Legacy ¹	Standard Nomenclature		
NM_000506.5 NP_000497.1		c.1621C>T	p.Arg541Trp	Uncertain significance [Mulder et al 2020]
		c.1787G>T	p.Arg596Leu	Uncertain significance
	20209C>T	c.*96C>T ²	None	
	20210G>A	c.*97G>A ²	None	Pathogenic; assoc w/↑ plasma levels of prothrombin

Variants listed in the table have been provided by the author. *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. * indicates that the variant is in the 3' untranslated region of *F2*; **96** indicates that the variant is the 96th nucleotide 3' of the translation stop codon. (Nucleotides are numbered *1, *2, ...)

Pathogenic variant. The 20210G>A pathogenic variant is located in the 3' untranslated region of *F2* where it increases the efficiency and accuracy of processing of the 3' end of the mRNA.

Haplotype analysis of *F2* strongly suggests that the 20210G>A variant was a single event that occurred 20,000 to 30,000 years ago, after the evolutionary separation of individuals of European ancestry from Asians and Africans [Zivelin et al 1998]. A more recent analysis of single-nucleotide polymorphisms and microsatellites flanking *F2* suggests that the variant arose 21,000-24,000 years ago in whites toward the end of the last glaciation [Zivelin et al 2006].

Although the high prevalence of the 20210G>A allele among individuals of European ancestry suggests a balanced nucleotide variant with some type of survival advantage associated with the heterozygous state, no such advantage has been confirmed. Some investigators speculate that the mild hypercoagulable state conferred by the allele may have had a beneficial effect in reducing mortality from bleeding associated with childbirth or trauma in premodern times [Corral et al 2001, Zivelin et al 2006].

Variants of uncertain significance. Three allelic variants have uncertain clinical significance. Larger studies are needed to determine if they increase the risk for thrombosis in individuals with and without inherited thrombophilic disorders. Genetic testing for these variants is not routinely recommended.

- c.1621C>T, a novel missense variant in exon 12 resulting in increased thrombin potential and resistance to heparin was identified in a Dutch family with unexplained thrombosis [Mulder et al 2020].
- c.1787G>T, a novel missense variant in exon 14 (prothrombin Yukuhashi) results in resistance to antithrombin and a prothrombotic state. Prothrombin Yukuhashi (p.Arg596Leu) was identified in a Japanese family in which five members developed thrombosis at a very young age [Miyawaki et al 2012]. Several other missense variants involving Arg596 and resulting in resistance to antithrombin were identified in thrombophilic individuals (e.g., prothrombin Belgrade and prothrombin Amrita p.Arg596Gln, prothrombin Padua 2 p.Arg596Trp) [Djordjevic et al 2013, Sivasundar et al 2013, Bulato et al 2016].
- 20209C>T in the 3' untranslated region of the gene is a rare variant of unclear significance reported primarily in individuals of African descent with a history of thrombosis or obstetric complications. Data as to whether this variant is an independent risk factor for thrombosis are conflicting [Itakura et al 2005, Danckwardt et al 2006, Hooper et al 2006, Warshawsky et al 2009].

Chapter Notes

Revision History

- 4 February 2021 (sw) Comprehensive update posted live
- 14 August 2014 (me) Comprehensive update posted live
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