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Prothrombin Thrombophilia

[*Prothrombin G20210A Thrombophilia*]

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Summary

Disease 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 thromophilia is variable; many individuals heterozygous or homozygous for the G20210A (20210G>A) allele never develop thrombosis, and while most G20210A 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 G20210A allele is two- to fourfold increased; in children, the relative risk for thrombosis is three- to fourfold increased. It is unclear whether G20210A heterozygosity increases the risk of recurrent VTE after a first episode. Although prothrombin thrombophilia may increase the risk of pregnancy loss and preeclampsia, its association with other complications of pregnancy such as fetal growth retardation and placental abruption remains controversial. Factors that predispose to thrombosis in G20210A heterozygotes include: the number of prothrombin G20210A alleles; presence of coexisting genetic abnormalities, such as factor V Leiden; and acquired thrombophilic disorders, such as hyperhomocysteinemia (plasma concentrations of homocysteine >12 µmol/L). Circumstantial risk factors for thrombosis include pregnancy and oral contraceptive use. Some evidence suggests that G20210A heterozygotes are more likely to develop VTE after travel.

Diagnosis/testing. The diagnosis of prothrombin thrombophilia requires DNA analysis of *F2*, the gene encoding prothrombin, to identify the common mutation, a G>A transition at nucleotide 20210A.

Management. The management of individuals with prothrombin thrombophilia depends on the clinical circumstances. The first acute thrombosis should be treated according to standard guidelines with a course of intravenous unfractionated heparin or low molecular-weight heparin. Oral administration of warfarin is started concurrently with heparin (except in pregnancy), and should be overlapped for at least five days. The international-normalized ratio (INR) is used to monitor anticoagulation. The duration of oral anticoagulation therapy should be tailored to the individual, based on an assessment of the risk of VTE recurrence and the risk of anticoagulant-related bleeding. Individuals with a spontanenous thrombosis with no identifiable provoking factors or persistent risk factors require a longer course of anticoagulation (at least six to 12 months or longer) than individuals with transient (reversible) risk factors, such as surgery. Graduated compression stockings should be worn for at least two years following the acute event. No consensus exists on the optimal management of prothrombin thrombophilia during pregnancy; guidelines are similar to those for individuals who are not pregnant. Heterozygous women with a history of VTE should avoid oral contraceptive use and hormone replacement therapy (HRT).

Genetic counseling. Prothrombin thrombophilia and an associated risk of thrombosis are inherited in an autosomal dominant manner. Homozygosity for the prothrombin gene mutation and a greater risk of thrombosis are inherited in an autosomal recessive manner. All individuals reported to date with prothrombin thrombophilia who are heterozygous for the prothrombin G20210A allele have had an affected parent. Because of the relatively high prevalence of this allele in the general population, occasionally one parent is homozygous or both parents are heterozygous for this allele. If one parent of a heterozygous proband is heterozygous, the sibs of the proband have a 50% risk of being heterozygous for a prothrombin G20210A allele. If one parent is homozygous, the sibs of the proband will be heterozygous for a prothrombin G20210A allele. Although technically possible, prenatal diagnosis for prothrombin thrombophilia is rarely requested as the disorder may never cause thrombosis and effective treatment is available.

Diagnosis

Clinical Diagnosis

No clinical features are specific for prothrombin thrombophilia. The diagnosis of prothrombin thrombophilia requires DNA analysis of *F2*, the gene encoding prothrombin, to identify the common mutation, a G>A transition at nucleotide 20210.

Prothrombin thrombophilia should be suspected in individuals with a history of venous thromboembolism (VTE) manifest as deep-vein thrombosis (DVT) or pulmonary embolism, especially those with a personal or family history of recurrent thrombosis at a young age.

The growing consensus is that **prothrombin G20210A testing should be performed** in the following individuals/circumstances [Manco-Johnson et al 2002, McGlennen & Key 2002, Bates et al 2004]:

- A first VTE before age 50 years
- A first unprovoked VTE at any age
- A history of recurrent VTE
- Venous thrombosis at unusual sites such as the cerebral, mesenteric, portal, or hepatic veins
- VTE during pregnancy or the puerperium
- VTE associated with the use of oral contraceptives or hormone replacement therapy (HRT)
- A first VTE at any age in an individual with a first-degree family member with a VTE before age 50 years
- Women with unexplained fetal loss after ten weeks' gestation

Prothrombin G20210A testing may be considered in the following individuals/ circumstances [McGlennen & Key 2002]:

- Selected women with unexplained early-onset severe preeclampsia, placental abruption, or significant intrauterine growth retardation
- A first VTE related to tamoxifen or other selective estrogen receptor modulators (SERM)
- Female smokers under age 50 years with a myocardial infarction

- Individuals older than age 50 years with a first provoked VTE in the absence of malignancy or an intravascular device
- Asymptomatic adult family members of probands with one or two known prothrombin G20210A alleles, especially those with a strong family history of VTE at a young age
- Asymptomatic female family members of probands with known prothrombin thrombophila who are pregnant or considering oral contraception or pregnancy
- Women with recurrent unexplained first-trimester losses with or without second- or third-trimester losses.
- Children with arterial thrombosis

Prothrombin G20210A testing is not recommended for the following:

- General population screening
- Routine initial testing during pregnancy
- Routine initial testing prior to the use of oral contraceptives, HRT, or SERMs
- Prenatal or newborn testing
- Routine testing in asymptomatic children
- Routine initial testing in adults with arterial thrombosis

Testing

Prothrombin level. Most G20210A heterozygotes have mildly elevated prothrombin levels; however, values vary widely among individuals [Poort et al 1996, Simioni et al 1998]. Because the range of prothrombin levels in G20210A heterozygotes overlaps significantly with the normal range, prothrombin levels are not reliable for diagnosis of prothrombin thrombophilia.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *F2*, the gene encoding prothrombin, is the only gene associated with prothrombin thrombophilia.

Molecular genetic testing: Clinical uses

- Diagnostic testing
- Prenatal diagnosis (technically available but rarely performed)
- Preimplantation genetic diagnosis (technically available but rarely performed)

Note: It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Molecular genetic testing: Clinical method

Targeted mutation analysis. Targeted mutation analysis for the 20210G>A mutation is performed by a variety of comparable methods (See ACMG guidelines).

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Prothrombin Thrombophilia

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis	*F2* G20210A allele	100%	Clinical Testing

Interpretation of test results. Molecular genetic test results are reliable in individuals on warfarin or heparin anticoagulation and independent of thrombotic episodes.

Test results on DNA extracted from peripheral blood leukocytes need to be interpreted with caution in the setting of liver transplantaion or hematopoetic stem cell transplantation (HSCT) because of hepatic synthesis of prothrombin and other clotting factors.

- In a liver recipient with hepatic artery thrombosis, the G20210A allele was found in DNA obtained from donor liver, but not in DNA from recipient peripheral blood leukocytes [Mas et al 2003]. Therefore, diagnosis of prothrombin thrombophilia in the setting of liver transplantation requires molecular genetic testing of both donor liver and recipient leukocytes.
- HSCT from a donor with prothrombin thrombophilia should not increase the thrombotic risk in the recipient. Diagnosis of prothrombin thrombophilia in HSCT recipients requires molecular analysis of non-hematopoietic tissue in the recipient.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *F2*.

Clinical Description

Natural History

The clinical expression of prothrombin thrombophilia is variable. Many individuals who are heterozygous or homozygous for the G20210A mutation never develop thrombosis. While most G20210A heterozygotes who develop thrombotic complications remain asymptomatic until adulthood, some have recurrent thromboembolism before age 30 years.

Venous Thromboembolism (VTE)—The primary clinical manifestation of prothrombin G20210A thrombophilia is venous thromboembolism (VTE).

Deep-vein thrombosis (DVT) is the most common VTE. The most common site for deep-vein thrombosis is the legs. G20210A heterozygotes have been reported to have a three- to fivefold increased risk of upper extremity thrombosis in some studies [Bombeli et al 2002, Vaya et al 2003, Martinelli et al 2004], but not in others [Heron et al 2000].

- **Adults.** The relative risk for DVT in adults who are heterozygous for the G20210A allele is two- to fourfold increased. The relative risk in homozygotes is unknown.
- **Children.** In children, the relative risk for thrombosis is increased three- to fourfold. Although venous thrombosis is uncommon in children, the likelihood of identifying a known risk factor in a child with thrombosis is higher than in a corresponding adult population. An increased prevalence of G20210A heterozygosity in neonates and children with thrombosis is reported in some, but not all studies.
  - Several retrospective case control studies found one or two prothrombin G20210A alleles in 4-8% of children with a first VTE compared to 1-3% of

control children (a three- to fourfold increase in relative risk) [Junker et al 1999, Schobess et al 1999].

- Several studies of unselected children with a history of VTE found a low prevalence of G20210A heterozygosity, similar to that in controls or in the general population [Bonduel et al 2002, Revel-Vilk et al 2003].

Although prothrombin G20210A mutations increase the risk of spontaneous thrombosis, most episodes occur in children with other predisposing factors [Junker et al 1999]. In a retrospective review of 38 symptomatic children with prothrombin G20210A mutations, additional circumstantial risk factors were identified in 92%, suggesting that the risk of VTE is highest in those with concomitant risk factors [Young et al 2003].

- In a prospective study of family members of symptomatic probands, asymptomatic children who were G20210A heterozygotes and G20210A homozygotes had no thrombotic complications during an average follow-up period of five years [Tormene et al 2002]. Thus, it appears that asymptomatic healthy children who are G20210A heterozygotes or G20210A homozygotes are at low risk for thrombosis except in the setting of circumstantial risk factors [Rosendaal et al 1997; Nowak-Gottl, Kosch et al 2001].

Superficial venous thrombosis may also occur. In one study the risk was nearly fourfold increased in G20210A heterozygotes [Martinelli, Cattaneo et al 1999].

Thrombosis in unusual locations may also occur, but less commonly.

- **Cerebral vein thrombosis** risk in G20210A heterozygotes was found to be six- to tenfold increased in several case control studies [Martinelli et al 1998, Reuner et al 1998].

  Although most thromboses in children occur in the extremities, some evidence suggests that G20210A heterozygosity may predispose to CNS thrombosis. G20210A heterozygosity was found in 4-5% of children with cerebral vein thrombosis compared to 1-2% of controls, differences that did not achieve statistical significance because of the small number of cases [Bonduel et al 2003, Heller et al 2003]. In the largest reported series of G20210A heterozygous children, 37% of symptomatic children had a history of arterial or venous CNS thrombosis, accounting for 30% of thromboembolic episodes. Cerebral sinus thrombosis occurred in 13% of symptomatic children, all of whom were age two years or older [Young et al 2003].

- **Hepatic, portal, and retinal vein thrombosis** have also been reported [Chamouard et al 1999, Incorvaia et al 1999, Janssen et al 2000, Amitrano et al 2004].

Recurrent thrombosis

- **Heterozygous adults.** It is unclear whether G20210A heterozygosity increases the risk of recurrent VTE after a first episode. In several studies, G20210A heterozygotes had a two- to fivefold increased risk of recurrent thrombosis during follow-up periods of seven to ten years [Simioni et al 2000, Miles et al 2001]. However, three other studies found no significant difference in the rate of recurrence between those heterozygous for the G20210A allele and those without the mutation [Eichinger et al 1999, Lindmarker et al 1999, De Stefano et al 2001]. Individuals who are heterozygous for both the G20210G>A mutation and the factor V Leiden mutation have a three- to ninefold higher risk of recurrence than those with neither mutation, and a threefold higher risk than individuals heterozygous for factor V Leiden alone [De Stefano et al 1999, Margaglione et al 1999, Meinardi et al 2002].

- **Heterozygous children.** Recurrent thrombosis occurred in 18% of pediatric G20210A heterozygotes compared to 5% without the mutation during an average seven years of follow-up [Nowak-Gottl, Junker et al 2001].
- **Pregnant women.** Women with a prior history of VTE have a risk of recurrence during pregnancy ranging from zero to 15%, making it difficult to decide which women require prophylactic anticoagulation in subsequent pregnancies. One prospective study evaluated the safety of withholding anticoagulation during pregnancy in a large group of women with a history of a single VTE. In subgroup analysis, women with a previous spontaneous thromboembolic event and thrombophilia had the highest recurrence rate during pregnancy (20%, odds ratio of ten) [Brill-Edwards et al 2000]. Women with either thrombophilia or a prior unprovoked VTE (but not both) had recurrence of 13% and 7.7%, respectively.
- **Homozygotes.** The risk of recurrent VTE in G20210A homozygotes is unknown but presumed to be higher than in heterozygotes.

Pregnancy Complications —Prothrombin thrombophilia may increase the risk of pregnancy loss and other complications of pregnancy. The available data indicate that G20210A heterozygosity is associated with a two- to threefold increased relative risk of pregnancy loss, and possibly other complications; however, the precise risk is unknown and requires prospective longitudinal study. Overall, the probability of a successful pregnancy outcome is high.

- **Pregnancy loss.** In addition to the increased risk of venous thromboembolism during pregnancy, some evidence suggests that G20210A heterozygosity increases the risk of fetal loss [Kujovich 2004b]. G20210A heterozygosity was found in 4-9% of women with recurrent pregnancy loss (the majority in the first trimester), compared with 1-2% of those with uncomplicated pregnancies, with odds ratios ranging from two to nine [Souza et al 1999, Foka et al 2000, Pihusch et al 2001, Raziel et al 2001, Reznikoff-Etievan et al 2001]. Two other studies found G20210A heterozygosity in 9-13% of women with a first unexplained third-trimester loss, compared with 2-3% of controls, suggesting a two- to threefold increase in risk [Martinelli, Taioli et al 2000; Many et al 2002]. However, other studies found no significant association with fetal loss [Brenner et al 1999, Gris et al 1999]. A large meta-analysis concluded that G20210A heterozygosity was associated with a two- to threefold increased risk of all recurrent, early first-trimester recurrent, and late non-recurrent fetal loss [Rey et al 2003].
- **Preeclampsia.** G20210A heterozygosity was found in 7-11% of women with preeclampsia, compared with 1-4% of those with normal pregnancies, suggesting a two- to sevenfold increase in risk [Grandone et al 1998; Kupferminc, Fait et al 2000; Benedetto et al 2002]. In contrast, the majority of studies, including two meta-analyses, found no significant association [Kupferminc et al 1999, Alfirevic et al 2001, D'Elia et al 2002, Morrison et al 2002, Lin & August 2005].

  In one study, G20210A heterozygosity did not increase the risk of severe preeclampsia; however, women heterozygous for G20210A had a significantly earlier onset of preeclampsia [Gerhardt et al 2005]. The conflicting results reported may be in part the result of differences in the severity of preeclampsia. Some evidence suggests a stronger association with early and severe forms of the disease.
- **Fetal growth retardation.** The data on the risk of fetal growth retardation are limited and conflicting.

  G20210A heterozygosity was found in seven to 15% of women with pregnancies complicated by fetal growth retardation, compared with 2-4% of controls, with odds

ratios ranging from four to nine [Kupferminc et al 1999; Kupferminc, Peri et al 2000; Martinelli et al 2001; Kupferminc et al 2002]. A recent meta-analysis also found a significant two- to threefold increased risk [Howley et al 2005].

In contrast, a larger case-control study found no significant association between maternal or fetal thrombophilia and fetal growth retardation. Women heterozygous for the G20210A allele had no increase in risk of pregnancies complicated by fetal growth retardation compared with unaffected controls [Infante-Rivard et al 2002].

- **Placental abruption.** The data on the risk of placental abruption are limited and conflicting.

  G20210A heterozygosity was found in 18% to 20% of women with placental abruption compared with 2-3% of those with normal pregnancies, suggesting a six- to 12-fold increase in risk [Kupferminc et al 1999; Kupferminc, Peri et al 2000; Facchinetti et al 2003].

  Several other studies found no association [Alfirevic et al 2001, Camilleri et al 2004].

Thus, although G20210A heterozygosity may also increase the risk of preeclampsia, fetal growth retardation, and placental abruption, the association remains controversial. The inconsistent results may reflect varying definitions of these complications, different ethnic groups and selection criteria, and the small number of individuals studied. The majority of published studies are too small to yield statistically significant results. G20210A heterozygosity is more likely to be present in women with unexplained severe and/or recurrent adverse pregnancy outcomes.

Factors that Predispose to Thrombosis—The clinical expression of prothrombin thrombophilia is influenced by four factors:

1 **The number of prothrombin G20210A alleles**

   - **G20210A heterozygotes** have a relative risk of venous thrombosis that is approximately two- to fourfold increased [Poort et al 1996, Cumming et al 1997, Leroyer et al 1998].
   - **G20210A homozygotes** have a higher risk, although the magnitude is not well defined. Although G20210A homozygotes tend to develop thrombosis more frequently and at a younger age, the risk is much lower than that associated with homozygous protein C deficiency or homozygous protein S deficiency.

     G20210A homozygosity was reported in 1.8% to 4.5% of individuals with a history of VTE, compared to no controls in several studies [Margaglione et al 1999, Barcellona et al 2003]. In an analysis of pooled data from eight case control studies, G20210A homozygosity was found in 0.2% of individuals with a history of VTE, and in no controls [Emmerich et al 2001]. In most studies, however, no G20210A homozygotes were identified [Poort et al 1996, Brown et al 1997].

     Furthermore, numerous reports of asymptomatic G20210A homozygotes emphasize the contribution of other genetic and acquired risk factors to thrombosis [Ridker et al 1999, Souto et al 1999].

2 **Coexisting genetic abnormalities.** Eight to 14% of G20210A heterozygotes have other inherited thrombophilic disorders. The combination of G20210A heterozygosity and most thrombophilic disorders has a supra-additive effect on

overall thrombotic risk. Individuals with multiple prothrombotic (thrombophilic) disorders develop VTE at a younger age and are at higher risk for recurrent thrombosis than those with a single defect [Ferraresi et al 1997, Makris et al 1997]

- **Factor V Leiden**. G20210A heterozygosity is found in 6-12% of individuals heterozygous for factor V Leiden who have a history of VTE [Makris et al 1997, Emmerich et al 2001, Tirado et al 2001]. Conversely, factor V Leiden heterozygosity occurs in 20-40% of symptomatic individuals who are heterozygous for the prothrombin G20210A mutation [Poort et al 1996, Emmerich et al 2001]. Double heterozygosity (i.e., heterozygosity for factor V Leiden and for the G20210A mutation) was found in 1-5% of individuals with a history of VTE compared to 0-1% of control individuals in multiple studies [Margaglione et al 1998, Salomon et al 1999, Simioni et al 2000]. Double heterozygosity for the prothrombin G20210A mutation and factor V Leiden mutation was found in 2.5% of children with a history of VTE compared to none of controls [Junker et al 1999, Schobess et al 1999].

  Doubly heterozygous individuals have an estimated 20- to 60-fold increased relative risk of venous thrombosis [Salomon et al 1999, Emmerich et al 2001]. In a pooled analysis of eight case control studies, factor V Leiden heterozygosity alone and G20210A heterozygosity alone were associated with a fivefold and fourfold increased risk, respectively. However, the risk was increased 20-fold in individuals heterozygous for both mutations, suggesting a multiplicative effect on overall thrombotic risk [Emmerich et al 2001]. Doubly heterozygous individuals develop thrombotic complications at a significantly younger age and are more likely to develop thrombosis in unusual locations (e.g., hepatic, mesenteric, or cerebral veins) [Ehrenforth et al 1999, Emmerich et al 2001].

- **Protein S deficiency.** In one study of thrombophilic families, the combination of protein S deficiency and G20210A heterozygosity was associated with a nearly 13-fold increased risk of VTE, compared to a fourfold increased risk with G20210A heterozygosity alone [Tirado et al 2001]. However, coinheritance of a G20210A heterozygosity did not increase the risk of thrombosis in a large kindred with protein C deficient thrombophilia [Bovill et al 2000].

- **Other genetic factors.** A prothrombin G20210A allele may also interact with other genetic factors, such as the following two polymorphisms, which independently may not predispose to thrombosis.

  - **The factor XIII V34L polymorphism** in combination with G20210A heterozygosity was associated with a 12-fold increased risk of myocardial infarction (MI) [Butt et al 2003].
  - ***PAI1*.** Heterozygosity for the 4G polymorphism in the *PAI1* gene in combination with G20210A heterozygosity was associated with a sixfold increased risk of venous thrombosis. Homozygosity for the 4G polymorphism in the *PAI1* gene in combination with G20210A heterozygosity was associated with a 13-fold increased risk of venous thrombosis [Barcellona et al 2003]. (The risk for 4G/5G was not calculated in this study.)

3 Acquired thrombophilic disorders

- **Hyperhomocysteinemia** increases the thrombotic risk associated with G20210A heterozygosity. In one study, high plasma concentrations of homocysteine (>12 µmol/L) and G20210A heterozygosity conferred a 3.8- and 2.5-fold increased risk of VTE, respectively. However, the combination of both risk factors was associated with an estimated 50-fold increase in risk, indicating a multiplicative effect on overall thrombotic risk [De Stefano et al 2001].
- **Antiphospholipid antibodies (APLA).** G20210A heterozygosity did not increase the risk of thrombosis in individuals with antiphospholipid antibodies in the few studies evaluating this combination of risk factors [Galli et al 2000, Chopra et al 2002].

4 **Circumstantial risk factors.** At least 50% of thrombotic episodes in individuals with prothrombin thrombophilia are provoked by additional predisposing factors, with pregnancy being the most common [Gerhardt et al 2000].

- **Pregnancy.** Women with thrombophilia have a higher risk of VTE during pregnancy [Kujovich 2004a]. G20210A heterozygosity is identified in six to 26% of unselected women with a history of VTE during pregnancy or the puerperium. Women heterozygous for G20210A have a three- to 15-fold higher risk of pregnancy-associated VTE than women who do not have the G20210A mutation [Gerhardt et al 2000, Martinelli et al 2002, Meglic et al 2003].

  Although G20210A heterozygosity increases the relative risk of pregnancy-associated VTE, the absolute risk in asymptomatic G20210A heterozygotes is unknown. Several retrospective studies estimated the probability of VTE in the range of one in 200 to 300 pregnancies [Gerhardt et al 2000, Gerhardt et al 2003]. These estimates suggest that asymptomatic women heterozygous for the G20210A allele and no other predisposing factors have a relatively low absolute risk.

  Women with multiple thrombophilic defects have the highest risk of pregnancy-associated VTE. In one study, the risk of pregnancy-associated VTE was increased 15-fold in women heterozygous for the G20210A allele, ninefold in those heterozygous for Factor V Leiden, and greater than 100-fold in women who were double heterozygotes for both mutations [Gerhardt et al 2000]. For women doubly heterozygous for both mutations, the risk of VTE is 1/20 to 1/100 pregnancies [Gerhardt et al 2000, Gerhardt et al 2003]. In another study, VTE complicated 17.8% of pregnancies in women doubly heterozygous for both mutations, compared to 6.2% of those in women heterozygous for the G20210A allele alone, suggesting the combination confers a nearly threefold greater risk than heterozygosity for the G20210A allele alone [Samama et al 2003].
- **Oral contraceptive use.** Oral contraceptive use alone and G20210A heterozygosity alone are associated with a two- to fourfold and two- to threefold increased risk of VTE, respectively. However, the combination of G20210A heterozygosity and oral contraceptive use has a supra-additive effect increasing the risk of VTE to 16- to 59-fold [Martinelli, Taioli et al 1999; Legnani et al 2002]. In a retrospective study of families with prothrombin thrombophilia, VTE occurred in 49% of heterozygous oral contraceptive users compared to 25% of heterozygous non-users. Sixty percent of VTE episodes in heterozygous women were associated with oral contraceptive use [Santamaria et al 2001]. In another study, G20210A

heterozygosity alone and oral contraceptive use alone increased the risk of cerebral vein thrombosis by ten- and 20-fold, respectively; the risk was 150-fold higher in women with both risk factors. [Martinelli et al 1998].

Oral contraceptive users who are doubly heterozygous for G20210A and factor V Leiden have an estimated 17- to 86-fold increase in overall thrombotic risk, based on limited data [Emmerich et al 2001, Legnani et al 2002].

The risk associated with oral contraceptive use to women who are G20210A homozygotes is not well defined but predicted to be substantially higher than the risk to G20210A heterozygotes.

Women with inherited thrombophilic disorders who use oral contraceptives tend to develop thrombotic complications sooner than women without these disorders, with the highest risk occurring during the first year of oral contraceptive use [Bloemenkamp et al 2000].

Multiple studies have confirmed a two- to fourfold increase in relative risk of VTE in women on HRT, compared to those who are not [Daly et al 1996, Grodstein et al 1996, Hulley et al 1998, Rossouw et al 2002].

Limited data are available to estimate the increased risk of HRT in women known to have thrombophilia.

Although G20210A heterozygosity did not significantly increase the thrombotic risk associated with combined estrogen and progestin in a case control study of participants in the Women's Health Initiative trial [Cushman et al 2004], only a small number of G20210A heterozygous women on HRT were included. No other studies have evaluated the venous thrombotic risk associated with these two risk factors.

Preliminary data suggest that the combination of HRT and G20210A heterozygosity may increase the risk of myocardial infarction (MI) nearly 11-fold in hypertensive postmenopausal women [Psaty et al 2001].

Although some evidence suggests that the thrombotic risk from transdermal HRT is lower than the thrombotic risk from oral preparations in low-risk postmenopausal women, no data compare the risk in women known to be heterozygous for G20210A [Scarabin et al 2003].

- **Selective estrogen receptor modulators (SERMs).** The risk of VTE in women heterozygous for G20210A who use SERMs is unknown but likely higher than that associated with SERM use in the general population.
- **Organ transplantation**
  - **Renal transplantation.** The prevalence of G20210A heterozygosity in individuals undergoing renal transplantation is similar to that in the general population, suggesting that G20210A heterozygosity is not a risk factor for developing end-stage renal disease (ESRD) [Heidenreich et al 1998, Fischereder et al 2001]. However, evidence suggests that G20210A heterozygosity may contribute to thrombotic and other complications after renal transplantation [Kujovich 2004c]. In one retrospective study, renal transplant recipients heterozygous for the G20210A allele had a significantly reduced median graft survival time and a nearly threefold

increased risk of graft failure, compared to renal transplant recipients without the G20210A mutation [Fischereder et al 2001]. A prospective study found that a heterozygous G20210A mutation was associated with a 12-fold increased risk of acute rejection and a tenfold increased risk of graft loss within the first year after transplantation. Renal transplant recipients heterozygous for the G20210A allele had elevated levels of the prothrombin activation fragment F1+2, a marker of coagulation activation [Heidenreich et al 2003]. In both studies, graft failure resulted from arterial or venous thrombosis in the majority of individuals.

- **Liver transplantation.** The contribution of G20210A heterozygosity to thrombotic complications after other types of organ transplantation is not well defined. Hepatic artery thrombosis was reported in individuals who acquired prothrombin thrombophilia after liver transplantation. G20210A heterozygosity was identified in 14% of allografts complicated by hepatic artery thrombosis, but not in recipient peripheral blood leukocytes [Mas et al 2003]. However, it is unknown whether G20210A heterozygosity predisposes to this particular transplant complication.

- **Central venous catheter-associated thrombosis.** Preliminary data suggest that G20210A heterozygosity increases the risk of central venous catheter-associated thrombosis two- to threefold in individuals with malignancy or other medical conditions [Van Rooden et al 2004].

- **VTE after travel.** Some evidence suggests that G20210A heterozygotes are more likely to develop VTE after travel. G20210A heterozygosity was identified in 12% of individuals with VTE within 30 days after air travel [McQuillan et al 2003]. Another study of 35 G20210A heterozygotes found that air travel was a mild risk factor for a first VTE (OR=2). However, the combination of air travel and any type of thrombophilia was associated with a 17-fold increase in risk, indicating a multiplicative interaction between these two risk factors [Martinelli et al 2003].

- **In children.** In several studies 62% to 97% of children with VTE had coexisting circumstantial risk factors with central venous catheters, malignancy, and congenital heart disease among the most frequently reported [Junker et al 1999, Revel-Vilk et al 2003, Young et al 2003].

Thrombosis NOT Convincingly Associated with Prothrombin Thrombophilia—
Arterial thrombosis in adults. The prothrombin gene mutation is not a major risk factor for arterial thrombosis. Most studies of unselected adult populations found no significant association between presence of one or two prothrombin G20210A alleles and myocardial infarction or stroke [Corral et al 1997, Redondo et al 1999, Ridker et al 1999]. In a meta-analysis of 25 studies, G20210A heterozygosity did not increase the risk of MI, stroke, or peripheral vascular disease; however, a modestly increased risk was observed when these three forms of arterial disease were analyzed collectively, especially in individuals younger than age 55 years.

- **Myocardial infarction (MI).** The contribution of prothrombin gene mutations to ischemic heart disease is controversial, with conflicting results from different studies. An analysis of pooled data from four case control studies found no association of

G20210A heterozygosity with MI [Boekholdt et al 2001]. However, data suggest that the mutation may contribute to the risk of MI in selected populations:

- G20210A heterozygosity increased the risk of MI in individuals with major cardiovascular risk factors in several studies [Rosendaal et al 1997, Doggen et al 1998, Franco et al 1999]. In a study of women younger than age 50 years, G20210A heterozygosity increased the risk of MI 43-fold in those with traditional cardiovascular risk factors, particularly smoking [Rosendaal et al 1997].
- In another study, the combination of G20210A heterozygosity and HRT increased the risk of MI in hypertensive post-menopausal women 11-fold over women who were not on HRT and did not have a G20210A mutation [Psaty et al 2001].
- Other evidence suggests that G20210A heterozygosity increases the risk of MI primarily in individuals without major cardiovascular risk factors or significant coronary artery disease [Van de Water et al 2000, Burzotta et al 2002].

- **Stroke.** G20210A heterozygosity conferred a fivefold increased risk of stroke in young individuals without traditional cardiovascular risk factors [De Stefano et al 1998].

  One study found a high prevalence of G20210A heterozygosity or factor V Leiden heterozygosity in individuals with cryptogentic stroke and a patent foramen ovale, suggesting the possibility of paradoxical thromboembolism [Karttunen et al 2003].

  G20210A heterozygosity increased the risk of systemic embolism in individuals with atrial fibrilliation in one study [Pengo et al 2002], but not in another [Poli et al 2003].

- **Peripheral vascular disease.** The few studies evaluating the association of G20210A heterozygosity and peripheral vascular disease reported conflicting results. Reny et al (2004) found a significantly increased risk of peripheral vascular disease, particularly in smokers, whereas Renner et al (2000) found no association.

Arterial thrombosis in children. Symptomatic children younger than age two years with prothrombin thrombophilia have a significantly higher rate of arterial thrombosis, in contrast to older children in whom venous thrombosis is far more common [Young et al 2003]. The data on the risk of ischemic stroke is conflicting, with an increased risk reported in several but not all studies. G20210A heterozygosity was found in 6-9% of children with ischemic stroke compared to 1% of controls, suggesting a nearly fivefold increase in risk [Nowak-Gottl et al 1999; Barreirinho et al 2003]. However, several other smaller studies found a low prevalence of G20210A heterozygosity in children with ischemic stroke, similar to that found in normal controls or the general population [Zenz et al 1998, Kenet et al 2000, Bonduel et al 2003].

Genotype-Phenotype Correlations

G20210A homozygotes have a greater risk of thrombosis than G20210A heterozygotes, although the magnitude of risk is not well defined.

An acute thrombotic episode in G20210A homozygotes is not more severe or resistant to anticoagulation than in G20210A heterozygotes.

Penetrance

No prospective studies define the absolute risk of VTE in asymptomatic heterozygous family members.

In several retrospective studies of relatives of symptomatic probands heterozygous for the G20210A allele, the absolute incidence of VTE was 0.12%/year to 0.13%/year, compared to 0.04%/year to 0.06%/year in family members without the mutation.

The incidence of VTE was 0.4%/year to 0.5%/year in family members doubly heterozygous for the G20210A allele and factor V Leiden mutation [Faioni et al 1999; Martinelli, Bucciarelli et al 2000].

In one study, the probability of remaining free of thrombosis at age 50 was 95% for G20210A heterozygotes, compared to 97% for family members with a normal genotype [Martinelli, Bucciarelli et al 2000]. At least 50% of thrombotic events were associated with other risk factors, especially pregnancy.

Anticipation

Anticipation is not observed.

Prevalence

G20210A heterozygosity is the second most common inherited thrombophilia after factor V Leiden.

The prevalence of G20210A heterozygosity varies by population.

- The highest prevalence is in Europe, where it ranges between 3% in southern Europe and 1.7% in northern countries [Rosendaal et al 1998].
- In the US, the prevalence is 2-5% in Caucasian Americans, and zero to 0.3% in African Americans, reflecting the world distribution of the mutation [Dilley et al 1998, Dowling et al 2003].
- G20210A heterozygosity is extremely rare in Asian, African, and Native American populations [Rosendaal et al 1998].

Among adults with VTE, G20210A heterozygosity is present in six to 14% of those with a first VTE, and 18% to 21% of those with a personal or family history of recurrent VTE [Poort et al 1996, Margaglione et al 1998, Tosetto et al 1999]. A prospective study identified G20210A heterozygosity in 3.7% of children with a first spontaneous VTE [Nowak-Gottl, Junker et al 2001].

The prevalence of G20210A homozygosity is approximately one in 10,000.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The differential diagnosis of venous thromboembolism (VTE) includes several other inherited and acquired thrombophilic disorders. Because these disorders are not clinically distinguishable, laboratory testing is required for diagnosis in each case. (See also Evaluations at Initial Diagnosis to Establish the Extent of Disease.)

Inherited

Factor V Leiden refers to the specific G-to-A substitution at nucleotide 1691 in the *F5* gene that predicts a single amino acid replacement (G506Q) that destroys a cleavage site for activated protein C. The resulting impaired anticoagulant response to activated protein C results in increased thrombin generation and a prothrombotic state. Factor V Leiden heterozygosity is found in 3-8% of the general population, 15-20% of individuals with a first VTE, and up to 50% of individuals with recurrent VTE or an estrogen-related thrombosis. Coinheritance of both factor V Leiden and G20210A heterozygosity occurs in approximately one in 1000 in the general population and 1-5% of individuals with venous thromboembolism [Margaglione et al 1998, De Stefano et al 1999, Simioni et al 2000, Emmerich et al 2001]. Factor V Leiden heterozygosity is identified in 29-40% of individuals heterozygous for the G20210A allele [Poort et al 1996, Leroyer et al 1998].

A specific point mutation (C677T) in the gene *MTHFR*, encoding methylenetetrahydrofolate reductase results in a variant thermolabile enzyme with reduced activity for the remethylation of homocysteine. Homozygosity for C677T predisposes to mild hyperhomocysteinemia, usually in the setting of suboptimal serum concentration of folate. Homozygosity for C677T occurs in ten to 20% of the general population.

Inherited deficiencies of the natural anticoagulant proteins C, S, and antithrombin are approximately tenfold less common than G20210A 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.

Elevated levels of lipoprotein(a) are associated with premature atherosclerosis and may also be a risk factor for venous thrombosis.

Hereditary dysfibrinogenemias are rare and infrequently cause thrombophilia and thrombosis.

Acquired

High plasma concentration of homocysteine occurs in 10% of individuals with a first VTE and is associated with a two- to threefold increase in relative risk [den Heijer et al 1996]. The plasma concentration of homocysteine reflects genetic as well as environmental factors and is more directly associated with thrombotic risk than molecular genetic testing of the *MTHFR* gene.

Antiphospholipid antibodies comprise a heterogeneous group of autoantibodies directed against proteins bound to phospholipid. Anticardiolipin antibodies and the related anti-beta2 glycoprotein 1 antibodies are detected by solid phase immunoassays. Lupus inhibitors are autoantibodies that interfere with phospholipid-dependent clotting assays. High titer IgG anticardiolipin antibodies and persistent lupus inhibitors are most strongly associated with arterial and venous thromboembolism [Galli et al 2003]. Testing for antiphospholipid antibodies should include assays for both anticardiolipin antibodies and lupus inhibitors, since only 50% of individuals with the antiphospholipid antibody syndrome have both types of antibodies.

A factor VIII level greater than 150% of normal is a common independent risk factor for VTE, conferring a four- to fivefold increase in risk in several studies [Koster et al 1995]. High factor VIII levels also significantly increase the risk of recurrent thrombosis [Kyrle et al 2000]. A familial form of high factor VIII levels has also been reported.

Elevated plasma levels of factor IX and factor XI are associated with a twofold increased risk of VTE.

Elevated plasma levels of both factor VIII and factor IX are associated with an eightfold increased risk of VTE [Meijers et al 2000, van Hylckama Vlieg et al 2000]

High plasma prothrombin concentrations are an independent risk factor for VTE, in the absence of G20210A heterozygosity. Prothrombin concentrations greater than 110% to 115% of normal conferred a twofold increased thrombotic risk and also increased the thrombotic risk of oral contraceptives [Poort et al 1996, Legnani et al 2002].

The combination of high levels of prothrombin and factor V or factor XI and oral contraceptives had a supra-additive effect on thrombotic risk, with odds ratios ranging from ten to 13 [van Hylckama Vlieg & Rosendaal 2003].

Other

Although thrombosis has been reported in individuals with defects or deficiencies of other coagulation and fibrinolytic proteins, such as heparin cofactor II and PAI-1, a causal association has not been established.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

Individuals heterozygous for the G20210A allele should be tested for other inherited and acquired thrombophilic disorders. The following are indicated:

- An activated protein C resistance or DNA assay for factor V Leiden
- Measurement of total plasma concentration of homocysteine
- An immunologic assay for anticardiolipin antibodies (and in some cases anti-beta 2 glycoprotein 1 antibodies)
- Multiple phospholipid-dependent coagulation assays for a lupus inhibitor

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

- Protein C activity
- Antithrombin activity
- Protein S activity (or a free protein S antigen)

Although routine measurement of factor VIII levels is not recommended, testing may be useful in selected cases [Chandler et al 2002]. It is still unclear whether assessment of clotting factor concentrations should be included in a thrombophilia evaluation [Chandler et al 2002].

Treatment of Manifestations

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

The first acute thrombosis should be treated according to standard guidelines with a course of intravenous unfractionated heparin or low molecular-weight heparin [Buller et al 2004]. Oral administration of warfarin is started concurrently with heparin (except in 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 G20210A homozygotes. Heparin and warfarin therapy should be overlapped for at least five days, and until the INR has been within the therapeutic range on two consecutive measurements over two days. The use of warfarin is safe in breast-feeding women.

The duration of oral anticoagulation therapy should be tailored to the individual, based on an assessment of the risks of VTE recurrence and anticoagulant-related bleeding. Approximately 30% of individuals with an incident VTE experience recurrent thrombosis within the subsequent ten years [Prandoni et al 1996]. However, because individuals remain at risk for recurrence even after ten years, VTE is now considered a chronic disease. The optimal duration of anticoagulation for G20210A heterozygotes is debated. Individuals with a spontanenous thrombosis and no identifiable provoking factors or persistent risk factors require a longer course of anticoagulation (≥6-12 months). In contrast, individuals with transient (reversible) risk factors, such as surgery, require a shorter course of oral anticoagulation [Schulman et al 1995, Buller et al 2004].

Long-term anticoagulation should be considered in individuals with recurrent VTE, multiple thrombophilic disorders, or other coexistent circumstantial risk factors, and in G20210A homozygotes. In these individuals at high risk for recurrence, the potential benefits of long-term warfarin may outweigh the bleeding risks.

Although unfractionated and low molecular-weight heparin and warfarin are still the primary antithrombotic agents in use, new antithrombotic agents are available for prophylaxis and treatment of arterial and venous thromboembolism. A pentasaccharide and several direct thrombin inhibitors are approved for use in specific circumstances.

Graduated compression stockings should be worn for at least two years following the acute event.

Prevention of Primary Manifestations

In the absence of a history of thrombosis, long-term primary antithrombotic therapy is not routinely recommended for asymptomatic G20210A heterozygotes, since the 1-3% yearly risk of major bleeding from warfarin is greater than the estimated less than 1% yearly risk of thrombosis [Faioni et al 1999; Martinelli, Bucciarelli et al 2000].

Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment in each individual case. Factors that may influence decisions about the indication for and duration of anticoagulation include age, family history, and other coexisting risk factors.

Since the initial thrombosis occurs in association with other circumstantial risk factors in at least 50% of individuals, prophylactic anticoagulation should be considered in high-risk clinical settings such as surgery, prolonged immobilization, or pregnancy.

Pregnancy. No consensus on the optimal management of prothrombin thrombophilia during pregnancy exists; guidelines are similar to those for individuals who are not pregnant [Bates et al 2004, Kujovich 2004a]. Until more specific guidelines are defined by prospective trials, decisions about anticoagulation should be individualized based on the thrombophilic defects, coexisting risk factors, and personal and family history of thrombosis.

Prophylactic anticoagulation during pregnancy:

- **Is not routinely recommended** in asymptomatic heterozygous women with no history of thrombosis. These women should be warned about potential thrombotic complications, counseled about the risks and benefits of anticoagulation during

pregnancy, and offered a four to six week course of anticoagulation after delivery, as the greatest thrombotic risk is in the initial postpartum period.

- **Is recommended** for heterozygous women with a history of unprovoked VTE. Unfractionated or low molecular-weight heparin should be given during pregnancy and for four to six weeks postpartum.
- **Should be considered** in heterozygous women with a prior estrogen-related thrombosis, although no data are available to define the risk of recurrence in this group.
- **Can be offered** to asymptomatic homozygous women based on the markedly increased thrombotic risk associated with high estrogen states.
- **May be justified** in women doubly heterozygous for the G20210A allele and factor V Leiden, or with other combined thrombophilic defects, especially those with circumstantial risk factors [Bates et al 2004].

Prevention of Secondary Complications

Prevention of pregnancy loss. The current data on antithrombotic therapy in women with inherited thrombophilia and recurrent pregnancy loss is limited to several small case series, a cohort study, and two randomized trials.

- In one study, 50 thrombophilic women with recurrent pregnancy loss received enoxaparin throughout 61 subsequent pregnancies. The live birth rate was 75% with enoxaparin prophylaxis, compared to 20% in prior untreated pregnancies [Brenner et al 2000].
- Another study reported a similar live birth rate of 70% with enoxaparin prophyaxis compared to 44% in untreated historical control women [Carp et al 2003].
- A recent prospective randomized trial compared prophylactic dose enoxaparin and low-dose aspirin in women heterozygous for G20210A, factor V Leiden, or protein S deficiency who had had a single unexplained fetal loss. Enoxaparin prophylaxis was associated with a significantly higher live birth rate of 86% compared to 29% with aspirin, with an odds ratio of 15. In the subgroup of women heterozygous for the G20210A allele, the live birth rate was 80% with enoxaparin prophylaxis, compared to 33% with aspirin, suggesting an eightfold higher likelihood of a successful pregnancy outcome [Gris et al 2004].
- A recent multicenter prospective randomized trial compared two different prophylactic doses of enoxaparin in thrombophilic women (including 19 heterozygous for the G20210A allele) with a history of recurrent pregnancy loss. No significant difference was observed in pregnancy outcome between the two treatment arms. The high live birth rates of 84% and 78%, respectively reported with both doses (40 and 80 mg/day) support the use of antithrombotic therapy in this setting [Brenner et al 2005].

No prospective randomized trials including an untreated control group and confirming the benefit of low molecular-weight heparin in preventing pregnancy loss in thrombophilic women have been performed. However, the concordant results of the studies cited above strongly suggest that anticoagulation may improve pregnancy outcome in thrombophilic women.

The evolving consensus in favor of prophylactic anticoagulation is reflected by the recent recommendations of the Seventh American College of Chest Physicians Conference (AACP) on Antithrombotic Therapy [Bates et al 2004]. AACP guidelines suggest prophylactic-dose

low molecular-weight or standard heparin and low-dose aspirin for women with inherited thrombophilia and either recurrent pregnancy loss or a single second- or third-trimester loss.

Much less data support the benefit of antithrombotic therapy in thrombophilic women with other pregnancy complications. ACCP guidelines suggest low-dose aspirin and prophylactic low molecular-weight or unfractionated heparin for thrombophilic women with a history of severe or recurrent preeclampsia or placental abruption [Bates et al 2004].

Additional studies are needed to define the thrombophilic profiles and pattern of pregnancy loss most predictive of an improved outcome with antithrombotic therapy. Until these studies are completed, antithrombotic prophylaxis should be considered in selected cases of unexplained recurrent pregnancy loss in women with prothrombin thrombophilia, after an informed discussion of the risks and the data suggesting benefit [Kujovich 2005]. Assessment of the maternal risk of VTE should be incorporated into the decision regarding prophylactic anticoagulation. Because of the increased risk of thrombosis, anticoagulation should continue for six weeks postpartum.

Surveillance

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

Selected G20210A 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

Heterozygous women with a history of VTE should avoid oral contraceptive use and HRT.

Asymptomatic G20210A heterozygotes should be counseled on the risks of oral contraceptive use and HRT and should be encouraged to consider alternative forms of contraception and control of menopausal symptoms.

Asymptomatic heterozygous woman electing to use oral contraceptives should avoid third generation formulations due to their higher thrombotic risk.

For heterozygous women who require short-term hormone replacement therapy for severe menopausal symptoms, low-dose transdermal preparations may have a lower thrombotic risk [Scarabin et al 2003].

Testing of Relatives at Risk

The genetic status of asymptomatic at-risk family members can be established using molecular genetic testing; however, the indications for family testing are unresolved. In the absence of evidence that early diagnosis of G20210A heterozygosity reduces morbidity or mortality, decisions regarding testing should be made on an individual basis.

Clarification of prothrombin 20210 allele status may be useful in women considering hormonal contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age.

Asymptomatic G20210A heterozygotes should be aware of the signs and symptoms of venous thromboembolism that require immediate medical attention and the potential need for prophylactic anticoagulation in high-risk circumstances. They should be informed that

although G20210A heterozygosity is an established risk factor, it does not predict thrombosis with certainty because the clinical course is variable, even within the same family.

Therapies Under Investigation

Novel inhibitors of the initiation of coagulation and fibrin formation are still investigational at various stages of development [Weitz et al 2004]. None of these new antithrombotic agents are specific for either the prothrombin gene mutation or thrombophilia in general.

Search ClinicalTrials.gov 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Prothrombin thrombophilia and an associated risk of thrombosis are inherited in an autosomal dominant manner. Homozygosity for the prothrombin gene mutation and a greater risk of thrombosis are inherited in an autosomal recessive manner.

Risk to Family Members — Proband Heterozygous for the Prothrombin Gene Mutation

Parents of a proband

- All individuals reported to date with prothrombin thrombophilia have had an affected parent.
- Prothrombin thrombophilia as the result of a *de novo* gene mutation has not been reported.
- Because of the relatively high prevalence of this allele in the general population, occasionally one parent is homozygous or both parents are heterozygous for this allele.

Note: Although most individuals diagnosed with prothrombin thrombophilia have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or reduced penetrance.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If one parent of a heterozygous proband is heterozygous, each sib of the proband has a 50% chance of being heterozygous for a prothrombin G20210A allele.
- If one parent is homozygous, the sibs of the proband will be heterozygous for a prothrombin G20210A allele.

- If both parents are heterozygous, each sib of the proband has a 25% chance of being homozygous for the prothrombin G20210A allele, a 50% chance of being heterozygous, and a 25% chance of inheriting both normal prothrombin alleles.

Offspring of a proband

- Each child of an individual heterozygous for a prothrombin G20210A allele has a 50% chance of inheriting the mutation.
- If the proband's reproductive partner is heterozygous, each offspring has a 25% chance of being homozygous for the prothrombin G20210A mutation, a 50% chance of being heterozygous for the prothrombin G20210A allele, and a 25% chance of inheriting both normal prothrombin alleles.

Risk to Family Members — Proband Homozygous for the Prothrombin Gene Mutation

Parents of a proband

- In most cases, both parents of an individual homozygous for the prothrombin G20210A allele are heterozygous for the mutation.
- Because of the relatively high prevalence of this allele in the general population, occasionally one parent is homozygous and the other parent is heterozygous.

Sibs of a proband

- The risk to the sibs of a proband who is homozygous for a prothrombin G20210A allele depends upon the genetic status of the proband's parents.
- If the parents of the proband are heterozygotes, each sib of the proband has a 25% chance of being homozygous, a 50% chance of being heterozygous, and a 25% chance of inheriting both normal prothrombin alleles.
- If one parent is homozygous for the prothrombin G202010A allele and the other parent is heterozygous, each sib of the proband has a 50% chance of being homozygous and a 50% chance of being heterozygous for the prothrombin G20210A allele.

Offspring of a proband

- Each offspring of a proband homozygous for prothrombin thrombophilia will inherit one prothrombin G20210A allele.
- If the affected individual's reproductive partner is heterozygous, each offspring has a 50% chance of inheriting two prothrombin G20210A alleles and a 50% chance of inheriting one prothrombin G20210A allele.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. The family members of a person found to be heterozygous or homozygous for prothrombin thrombophilia are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation, possible non-medical explanations include alternate paternity or undisclosed adoption.

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for prothrombin thrombophilia is available using the same techniques described in Molecular Genetic Testing. This testing is not useful in predicting age of onset, severity, or type of thrombotic complications in asymptomatic individuals.

Testing for the disease-causing mutation in the absence of definite symptoms of the disease is predictive testing. Testing of asymptomatic at-risk adult family members should take into account the individual's knowledge of prothrombin thrombophilia, motives for requesting the test, and possible impact of a positive test result. Specific informed consent is not generally required for prothrombin thrombophilia genetic testing. However, individuals seeking testing should be counseled about possible problems with insurance coverage and implications for the at-risk status of other family members.

Testing of at-risk individuals during childhood. Currently no consensus exists on the indications for testing individuals younger than age 18 years for prothrombin thrombophlia. Asymptomatic at-risk individuals younger than age 18 years are not usually tested because thrombosis rarely occurs before young adulthood, even in homozygous individuals. Earlier testing may be considered in families with other known thrombophilic disorders or a strong history of thrombosis at a young age. Testing is also appropriate in children with a history of thrombosis [Manco-Johnson et al 2002]. (See also the National Society of Genetic Counselors resolution on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.)

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. A prothrombin G20210A allele should be identified in an affected family member before prenatal testing is performed. Although technically possible, prenatal diagnosis for prothrombin thrombophilia is rarely requested as the disorder may never cause thrombosis and effective treatment is available.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing. Although technically possible, PGD for prothrombin thrombophilia is rarely requested as the disorder may never cause thrombosis and effective treatment is available.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Prothrombin Thrombophilia

Gene Symbol	Chromosomal Locus	Protein Name
F2	11p11-q12	Prothrombin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Prothrombin Thrombophilia

176930	COAGULATION FACTOR II; F2
188050	THROMBOPHILIA

Table C. Genomic Databases for Prothrombin Thrombophilia

Gene Symbol	Entrez Gene	HGMD
F2	2147 (MIM No. 176930)	F2

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

The relatively high prevalence of prothrombin thrombophilia among Caucasians suggests a balanced polymorphism with some type of survival advantage associated with the heterozygous state. Some investigators speculate that the mild hypercoagulable state conferred by the mutation may have had a beneficial effect in reducing mortality from bleeding in premodern times [Corral et al 2001, McGlennen & Key 2002]. One case control study found a lower prevalence of a prothrombin G20210A allele in individuals with spontaneous intracranial hemorrhage (1.5%) compared to controls (3%), although the difference was not statistically significant because of the small number of individuals with prothrombin thrombophlia included [Corral et al 2001].

Normal allelic variants: Haplotype analysis of *F2* strongly suggests that the mutation at nucleotide 20210 was a single event that occurred 20,000 to 30,000 years ago, after the evolutionary separation of Caucasians from Asians and Africans [Zivelin et al 1998].

Pathologic allelic variants: The prothrombin gene mutation refers to a G>A transition at position 20210 in the 3' untranslated region of the prothrombin gene.

Normal gene product: Coagulation factor II (prothrombin)

Abnormal gene product: G20210A mutation is associated with elevated plasma levels of prothrombin [Poort et al 1996, Kyrle et al 1998, Simioni et al 1998]. 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 prothrombin protein synthesis. The observation that elevated prothrombin levels independently increase the risk of thrombosis suggests that the mutation may act through this mechanism [Poort et al 1996, Legnani et al 2002]. The results of several experimental and clinical studies suggest that elevated prothrombin levels result in increased thrombin generation and a prothrombotic state [Kyrle et al 1998, Butenas et al 1999]. High prothrombin levels may also inhibit activated protein C mediated inactivation of activated factor Va, further enhancing thrombin generation [Smirnov et al 1999]. Individuals with one or two prothrombin G20210A 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, Franco et al 1999, Gouin-Thibault 2002]. Impaired fibrinolysis resulting from enhanced activation of thrombin-activatable fibrinolysis inhibitor (TAFI) may be an additional mechanism contributing to the increased thrombotic risk [Colucci et al 2004].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Lifeblood: The Thrombosis Charity
PO Box 1050
Spalding PE12 6YF
United Kingdom
Phone: (+44) 01406 381017
Email: information@thrombosis-charity.org.uk
www.thrombosis-charity.org.uk

The National Alliance for Thrombosis and Thrombophilia
PO Box 66018
Washington DC 20035-6018
Email: nattinfo@yahoo.com
www.nattinfo.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American College of Medical Genetics. Technical standards and guidelines: Venous thromboembolism (factor V Leiden and prothrombin 20210G>A testing): A disease-specific supplement to the standards and guidelines for clinical genetics laboratories . 2005

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Chapter Notes

Revision History

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