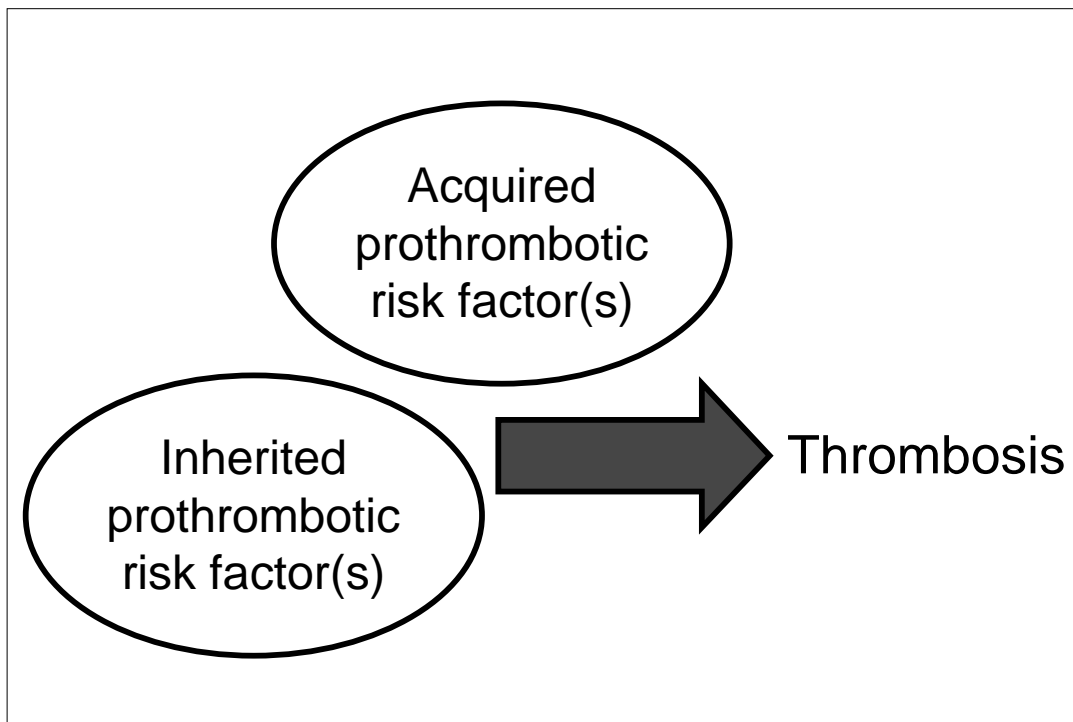


# Thrombophilia

Thomas L. Ortel, M.D., Ph.D.  
Duke University Medical Center  
29 September 2007

Thrombophilia: “the propensity to develop thrombosis (blood clots) due to an abnormality in the system of coagulation”.

*Wikipedia*, the Free Encyclopedia



## Acquired Prothrombotic Risk Factors

- Antiphospholipid antibodies.
- Malignancy.
- Myeloproliferative disorders/PNH.
- Pregnancy/postpartum.
- Therapy-related (HRT, OC, chemotherapy).
- Surgery/Immobilization.
- Travel.
- Trauma.

## Inherited Thrombophilia

- Who should be tested?

## Who should be considered for thrombophilia testing?

- Patients with unexplained, or 'idiopathic' thromboembolism, especially  $\leq 50$  years of age.
- Patients with thromboembolism that is unusually extensive, or in an unusual location (e.g., portal vein thrombosis).
- Patients with recurrent thrombosis.
- Patients with a strong family history for venous thromboembolism.

## Inherited Thrombophilia

- Who should be tested?
- What laboratory tests should be ordered?

## Screening Laboratory Evaluation

- APC resistance or factor V Leiden analysis.
- Prothrombin G20210A polymorphism analysis.
- Functional assays for antithrombin, protein C, and protein S.
- Lupus anticoagulant and enzyme-linked immunosorbent assays for anticardiolipin and/or anti- $\beta_2$ -glycoprotein I antibodies.
- Homocysteine level.

## Classification of Hereditary Thrombophilic Disorders

- Group 1 disorders: hereditary deficiencies of coagulation factor inhibitors. Many patients will have had a VTE prior to age 60 yrs. Uncommon.
- Group 2 disorders: hereditary disorders associated with increased levels or function of procoagulant coagulation factors. Most affected individuals will not have had a VTE prior to age 60 years. Common.

Crowther, M.A., and Kelton, J.G., *Ann Intern Med* 2003;138: 128-34

### Group 1 Thrombophilic Disorders

Disorder	Prevalence in Normals	Frequency in VTE Patients	RR for first VTE
Antithrombin deficiency	0.02-0.2%	0.5-7.5%	20*
Protein C deficiency	0.2-0.4%	2.5-6%	6.5
Protein S deficiency	0.003%	1.3-5.0%	5.0

\* Clinical phenotype depends on type of mutation.

## Group 2 Thrombophilic Disorders

Disorder*	Prevalence in Normals	Frequency in VTE Patients	Risk for first VTE
Factor V Leiden	-	18.8%	3-8 fold increase
-Caucasian	4.8%		
-African American	1.2%		
-Asian American	0.45%		
Prothrombin G20210A	2-3%	6-7%	2-3 fold increase

\* Information provided is for the heterozygous state for these two polymorphisms.

## Group 2 Thrombophilic Disorders

- Additional Group 2 thrombophilic disorders include:
  - Elevated factor VIII.
  - Elevated factor IX.
  - Elevated factor XI.
  - Elevated lipoprotein(a) levels.
  - Dysfibrinogenemia.

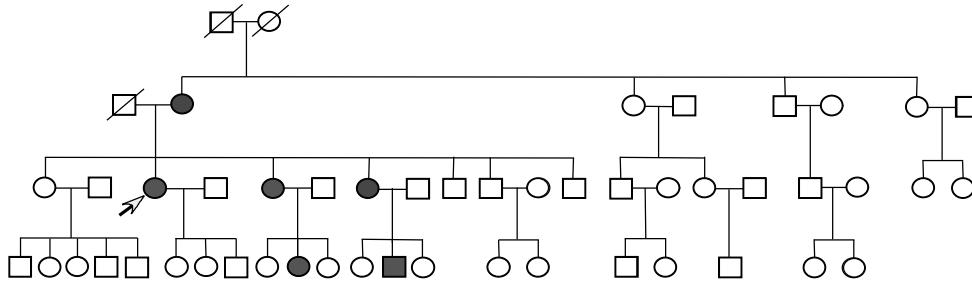
## Other Hereditary Prothrombotic Conditions

- Hyperhomocysteinemia.
- Fibrinolytic defects.
- Increased levels of thrombin-activatable fibrinolysis inhibitor (TAFI).
- Elevated lipoprotein(a) levels.
- Factor V HR2 haplotype (possibly only in association with factor V Leiden)...

## Antiphospholipid Antibodies

- Generally *not* considered an inherited disorder, but typically included in hypercoagulable workups.
- Frequency of antiphospholipid antibodies in patients with VTE is ~8-14%.
- Testing includes functional assays (lupus anticoagulant) and immunologic assays (anti-cardiolipin and anti- $\beta_2$ glycoprotein I antibodies).

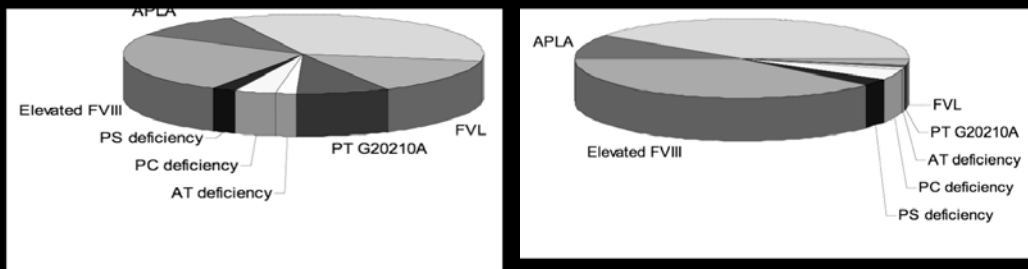
# Familial Antiphospholipid Syndrome



Pedigree 1500 from Goel, *et al.*, *Arthritis Rheum.*, 1999; 42: 318.

Genetics of Antiphospholipid Syndrome  
 P.I.: Thomas L. Ortel, MD, PhD  
 Clinicaltrials.gov #NCT00482794

# Thrombophilic states and race



Dowling, *et al.*, *J.Thromb.Haemost.*, 2003; Patel, *et al.*, *Thromb.Haemost.*, 2003

## Sickle Cell Trait and VTE

Hb S genotype	VTE Cases	Controls	OR	95% CI
AA	451	520	1.0	-
AS	56	35	1.8	1.2-2.9
SS	8	0	$\infty$	2.5

Austin H. *et al.* Blood 2007; 110:908-912.

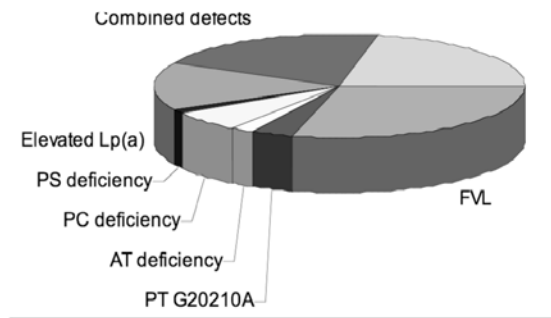
## Sickle Cell Trait and VTE Type

Type of VTE	Hb AS	Hb AA	OR	95% CI
Controls	35 (6.3)	520	1.0	-
DVT only	23 (7.0)	307	1.1	0.65-1.9
PE only	24 (21.9)	91	3.9	2.2-6.9
DVT/PE	9 (14.5)	53	2.5	1.2-5.5

Austin H. *et al.* Blood 2007; 110:908-912.

## Thrombophilia in the pediatric patient

- Many studies include children with central venous lines and other acquired disorders.
- Elevated factor VIII and D-dimer is also associated with recurrent thrombosis



Age: neonate to 18 yrs

Nowak-Göttl, *et al.*, *Blood*, 2001; Revel-Vilk, *et al.*, *J.Thromb.Haemost.*, 2003; Goldenberg, *et al.*, *NEJM*, 2004.

## Inherited Thrombophilia

- Who should be tested?
- What tests should be ordered?
- When should the tests be ordered?

## Variables Affecting Test Results

- Acute thromboembolic event:
  - May transiently decrease antithrombin, protein C, and/or protein S levels.
  - May transiently increase factor VIII, fibrinogen levels.
  - May make interpretation of antiphospholipid antibody results difficult.

## Variables Affecting Test Results

- Comorbid conditions:
  - Severe liver disease will affect many of the functional assays.
- Pregnancy:
  - Factor VIII and fibrinogen levels increased.
  - Functional protein S level decreased.
  - Increased frequency of elevated antiphospholipid antibody levels.

## Variables Affecting Test Results

- Heparin/low molecular weight heparin therapy:
  - May transiently decrease antithrombin level.
  - May interfere with interpretation of lupus anticoagulant results.
- Vitamin K antagonist therapy:
  - Typically decreases protein C and protein S levels.
  - May interfere with interpretation of lupus anticoagulant results.

## Inherited Thrombophilia

- Who should be tested?
- What tests should be ordered?
- When should the tests be ordered?
- What should be done with the information that is obtained?

## Reasons for Thrombophilia Testing

Reasons for testing	%
Patients with venous thromboembolism	41.7%
Patients with arterial cardiovascular event	23.2%
Pregnancy-related vascular events	17.0%
Asymptomatic individuals with a familial predisposition	16.0%
Reason not remembered	2.0%

Coppens, M. *et al.* J Thromb Haemost 2007;5:1979-81

## Management Consequences

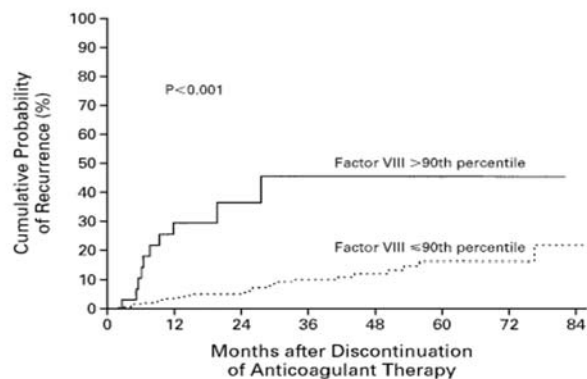
- Patient management influenced by tests (71%).
  - Management implications present in this patient (23%).
  - Management implications only if thrombophilia was present (48%).
- No influence on patient management (24%).
- Uncertain (5%).

Coppens, M. *et al.* J Thromb Haemost 2007;5:1979-81

# Reasons for Thrombophilia Testing

- Patients with VTE.
  - To provide an explanation for VTE.
  - To assess risk for recurrence of VTE and determine the optimal duration of anticoagulation.
  - To develop optimal prevention strategies for those patients who discontinue anticoagulation.
  - To potentially identify asymptomatic relatives at risk for VTE.

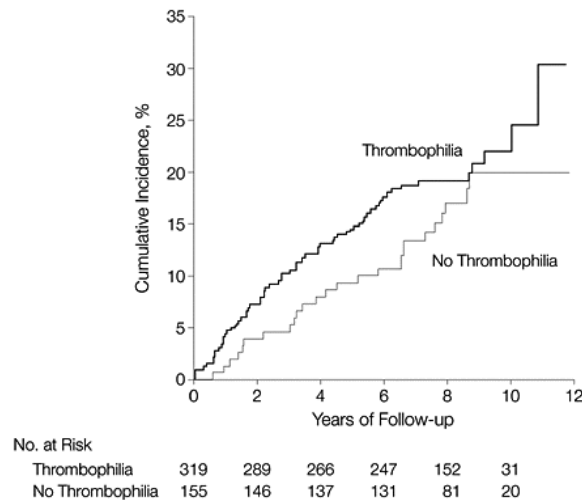
## Elevated Factor VIII and Recurrent VTE



NO. OF PATIENTS AT RISK								
Factor VIII >90th percentile	35	19	7	4	4	2	1	0
Factor VIII ≤90th percentile	325	258	181	112	78	50	22	3

Kyrle, P. A. *et al.* N Engl J Med 2000;343:457-462

# Thrombophilia and Recurrent VTE



Christiansen SC, et al. JAMA 2005; 293: 2352-2361

## ACCP Guidelines

2.1.4. For patients with first episode DVT and:

- Antiphospholipid antibodies;
- 2 or more thrombophilic conditions;  
→ therapy for 12 months (1C+) or indefinite (2C).

2.1.5. For patients with first episode DVT and:

- Antithrombin, protein C or protein S deficiency;
- Factor V Leiden or prothrombin G20210A;
- Elevated homocysteine or factor VIII levels  
→ therapy for 6-12 months (1A) or indefinite (2C).

Büller, et al., Chest, 2004

## Pregnancy Related Vascular Events

- For thrombophilia in the absence of thrombosis: close observation during pregnancy.
- For thrombophilia and prior poor pregnancy outcomes: low-dose anticoagulation.
- For antithrombin deficiency, or homozygosity of factor V Leiden or prothrombin G20210A: moderate or full-dose anticoagulation.
- For APS with prior VTE: full-dose anticoagulation.

James AH, et al., Clin Adv Hematol Oncol, 2002; 3: 187-197

## What general concepts should be discussed with the *asymptomatic* individual with thrombophilia?

- What is the risk of thrombosis to the individual and to his/her family members?
- What are the signs and symptoms of venous thromboembolism (or other manifestations)?
- What are the risks and benefits of thromboprophylaxis in high-risk situations?

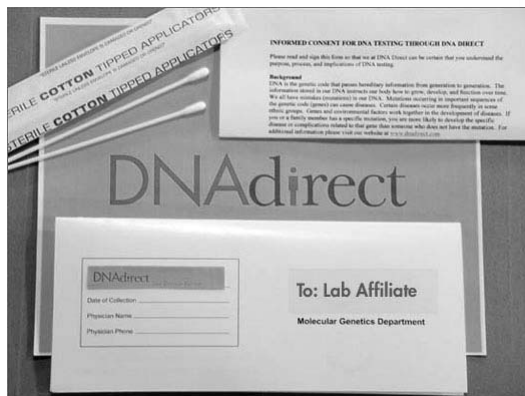
Olson, Arch.Pathol.Lab.Med., 2002

# Where can patients (and providers) find more information about thrombophilia?

- National Alliance for Thrombosis and Thrombophilia (NATT): a nationwide, community-based, volunteer health organization formed in August 2003.
- Located at: <http://www.nattinfo.org>



## And where can they get their thrombophilia testing done?



<http://www.dnadirect.com/>