Genetic Diseases Due to Single Gene Defects: Case Studies

APPROVED

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Why a lecture (or two) on Molecular Pathology

Paper from NEJM. An overweight patient shows up to your office with analysis of their entire genome sequenced. Pt will cite data about chances of a particular disease and will ask you, "what does this mean?" Your challenge will be to know how to respond.

Perspective
JANUARY 10, 2008

Letting the Genome out of the Bottle — Will We Get Our Wish?

David J. Hunter, M.B., B.S., Sc.D., M.P.H., Muin J. Khoury, M.D., Ph.D., and Jeffrey M. Drazen, M.D.

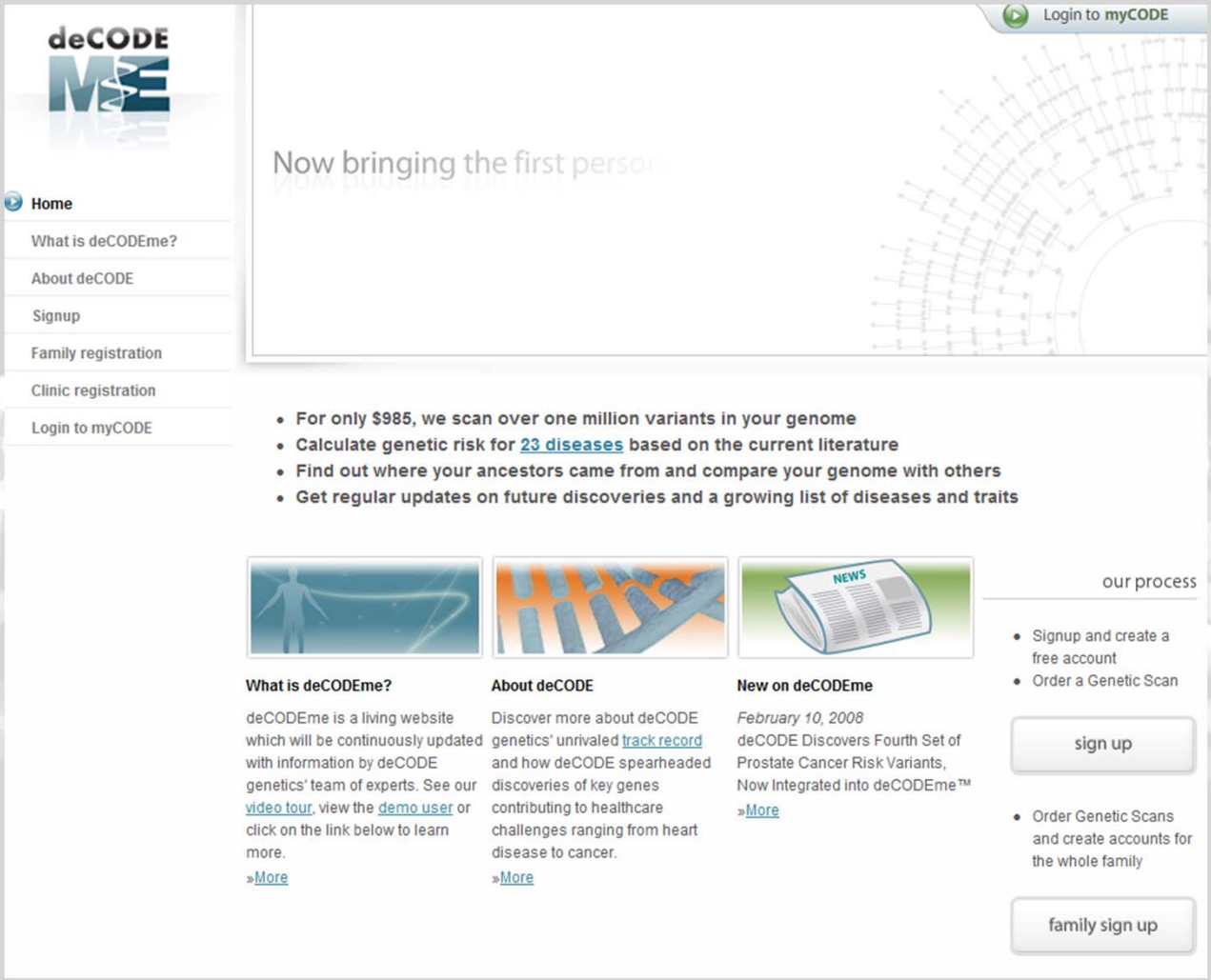
It may happen soon. A patient, perhaps one you have known for years, who is overweight and does not exercise regularly, shows up in your office with an analysis of his whole genome at multiple single-nucleotide polymorphisms (SNPs). His children, who were concerned about his health, spent $1,000 to give him the analysis as a holiday gift. The test report states that his genomic profile is

types. These studies rely on microarrays that can assess 300,000 or more SNPs in each DNA sample; researchers use these microarrays to examine interpersonal differences in inherited genetic

The test undergone by the patient described above is one of the products of this new knowledge.

As of November 2007, two companies have made available direct-to-consumer "personal genome services" (www.23andme.com) or "gene profiles" (www.decodeme.com) that rely on the same arrays of 500,000 to 1 million SNPs used in genomewide association studies. A third com-

Why a lecture (or two) on Molecular Pathology



Companies exist that will seq your genome. These companies don't provide genetic interpretation. That's your job.

Why a lecture (or two) on Molecular Pathology

Lecture Objective - Understand the fundamental concepts underlying the molecular nature of disease and the utility, practice and pitfalls of molecular diagnostic testing

(at least as well as your patients…)

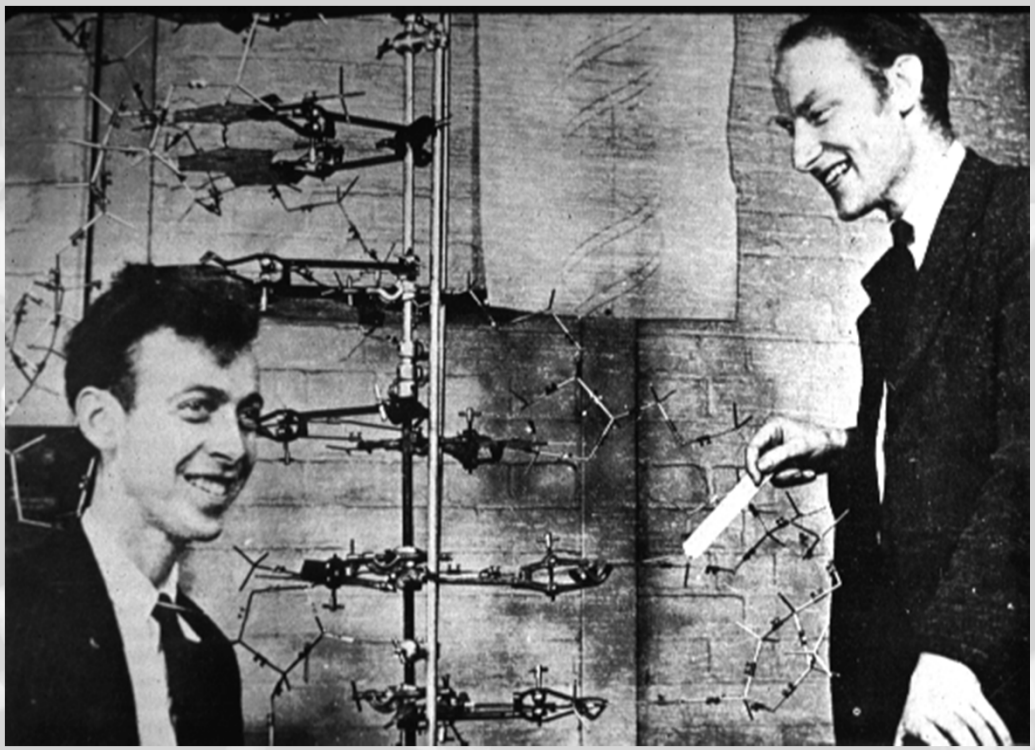
Read.

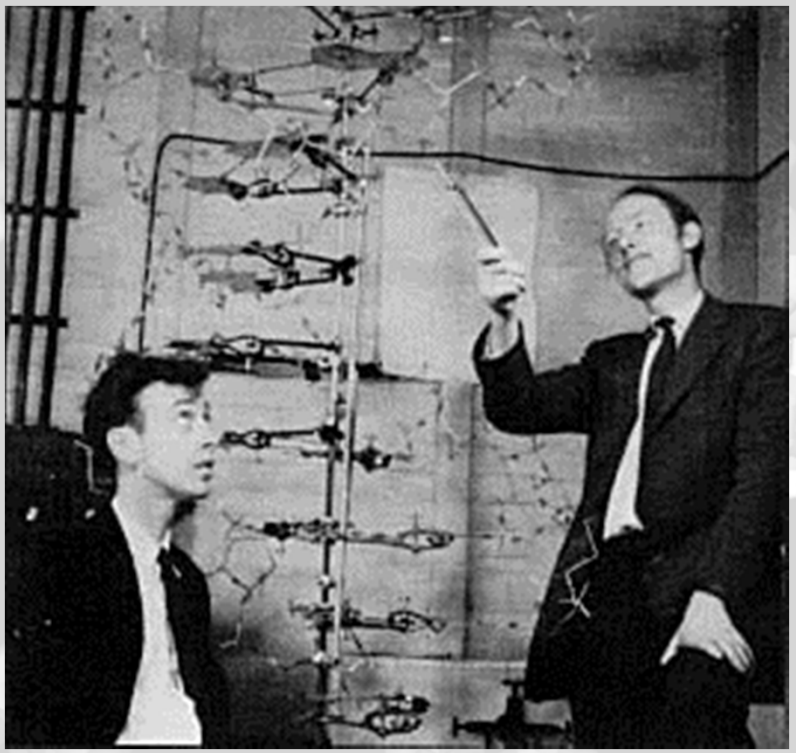
Resources

- www.GeneTests.org
- *www.ncbi.nlm.nih.gov/**Omim**/*
- Pathologic Basis of Disease. Robbins and Cotran 2005. Chapter 5

Resouces. Genetest.org is a great site.

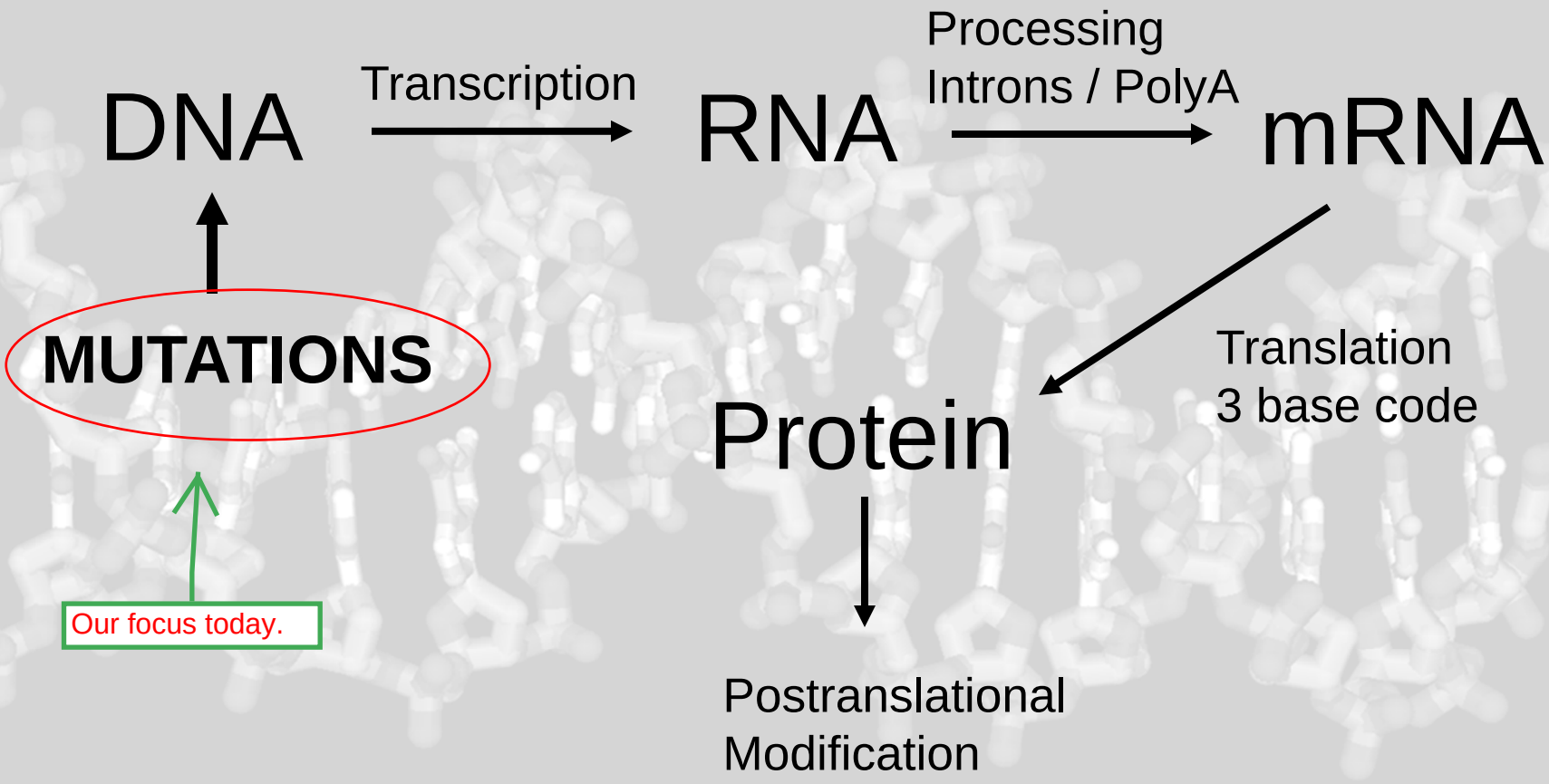
A Brief Word on the Chemical Nature and Structure of DNA





1962: Nobel Prize for the Discovery Of the Structure of DNA
James Watson, Francis Crick: DNA is a double helix composed of anti-parallel strands with bases paired on the inside and a phosphates backbone on the outside.

The Central Dogma



What Diseases Are Associated with Specific Mutations?

All inherited diseases

CF, HFE, GSD, ETC

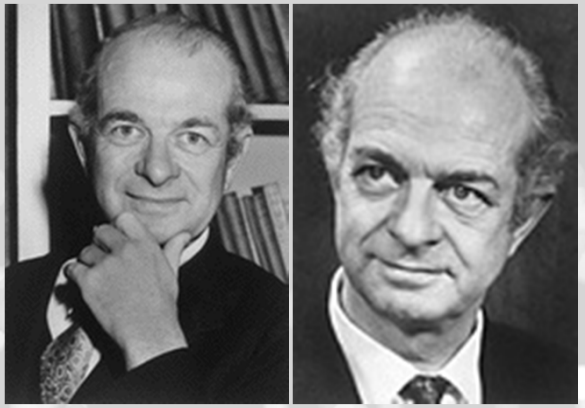
Tumor syndromes (FAP, HNPCC, ETC)

All Neoplasms

Associated with acquired mutations.

A lot of diseases that you wouldn't expect.

Type II diabetes, prostate cancer, risk of heart disease, any many others.



The birth of molecular diagnostics
Linus Pauling describes first molecular abnormality associated with a disease process.

Nobel prize in chemistry 1954
"for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances"
Nobel peace prize 1962

Pauling, ...949).

Molecular diagnostics and the molecular basis of disease was discovered before the discovery of DNA structure. Linus Pauling showed that hemoglobin from a person with sickle cell anemia and a normal person travelled differently under an electrical gradient. Furthermore, the trait was heritable. This linked heritability with molecular abnormality. It was a big deal.

What Diseases Are Associated with Specific Mutations?

- All inherited diseases
  - CF, HFE, GSD, ETC
  - Tumor syndromes (FAP, HNPCC, ETC)
- All Neoplasms
- A lot of diseases that you wouldn't expect.

  Type II diabetes, prostate cancer, risk of heart disease, any many others.

The Genetic Information Nondiscrimination Act of 2008 (GINA) was enacted on May 21, 2008 (Pub. L. 110-233). Title I of GINA amends the Employee Retirement Income Security Act of 1974 (ERISA), the Public Health Service Act (PHS Act), the Internal Revenue Code of 1986 (Code), and the Social Security Act (SSA) to prohibit discrimination in health coverage based on genetic information

Law passed in 2008. Basically says that you can't discriminate people based on their genetic information(like sex or race).

Read this slide. Basic knowledge.

How are Genes Mutated?

DNA damaging agents (UV, chemical)

Errors in replication or repair

Inherited (germ line) mutations

Point mutations: Mutation of a single base pair. (silent vs. missense vs. nonsense)

Deletions: loss of one or more base pairs from a gene sequence. (including frame-shift mutations)

Insertions: Insertion of one or more base pairs into a gene sequence. (including frame-shift mutations)

Repeat Expansions: multiplication of tri-nucleotide regions within gene regulatory regions.

Repeat sequences can become unstable during some disease processes.

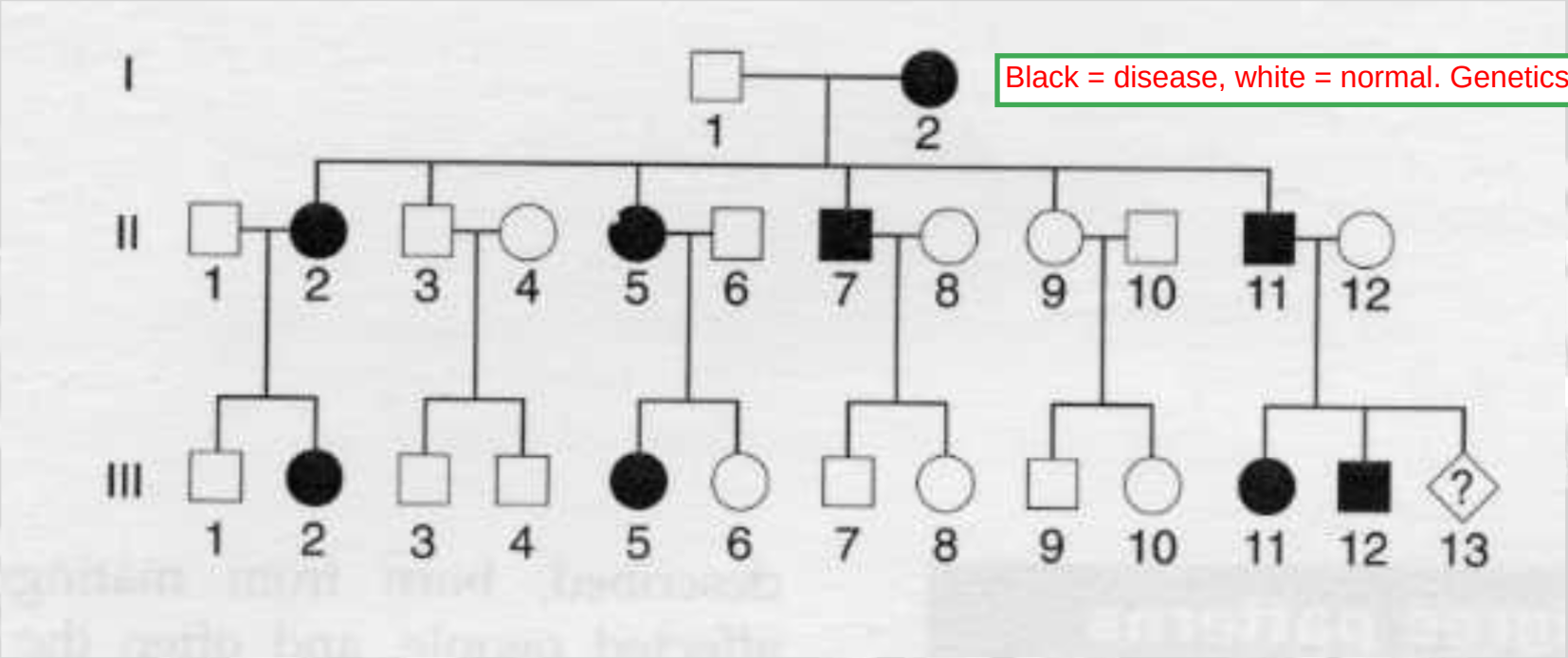
Inherited Mutations

- Autosomal Dominant
- Autosomal Recessive
- X-Linked
  - Recessive
  - Dominant
- Mitochondrial Mutations

Mutations can be any of these.

Autosomal dominant inheritance

Pop Quiz



Black = disease, white = normal. Genetics is racist.

Autosomal dominant inheritance.

50% of children are affect by disease

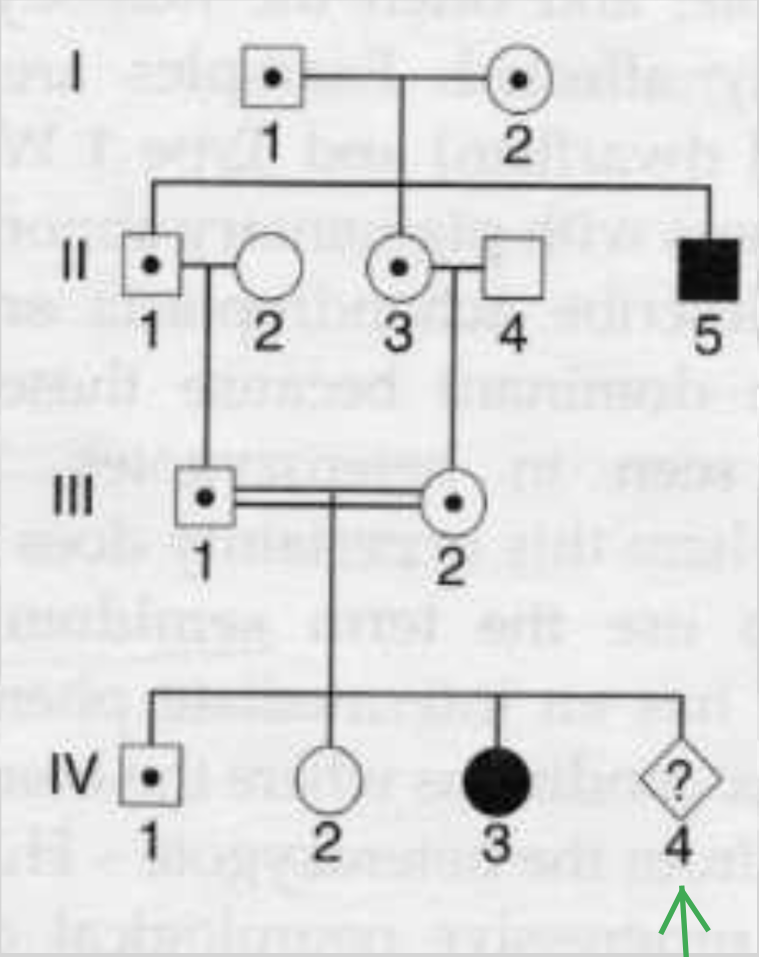
Common Autosomal Dominant Inherited Diseases

Familial Hypercholesterolemia	1 / 500
Adult Polycystic Kidney Disease	1 / 1,000
Hereditary Spherocytosis	1 / 5,000
Neurofibromatosis Type 1	1 / 3,500
Familial Adenomatous Polyposis	1 / 10,000
Ehlers-Danlos Syndrome	1 / 5,000
Marfan Syndrome	1 / 10,000
Huntington Disease	1 / 15,000
HNPCC	3% (of Colon Cancer)

Not enough time to talk about all autosomal dominant diseases. Expects you to read about these on your own.
Good idea, since Step 1 loves this stuff.

Autosomal recessive inheritance

Pop Quiz



Black dot = carriers.

25% of offspring are homozygotes (affected by disease)

50% are heterozygotes (carriers)

25% are normal

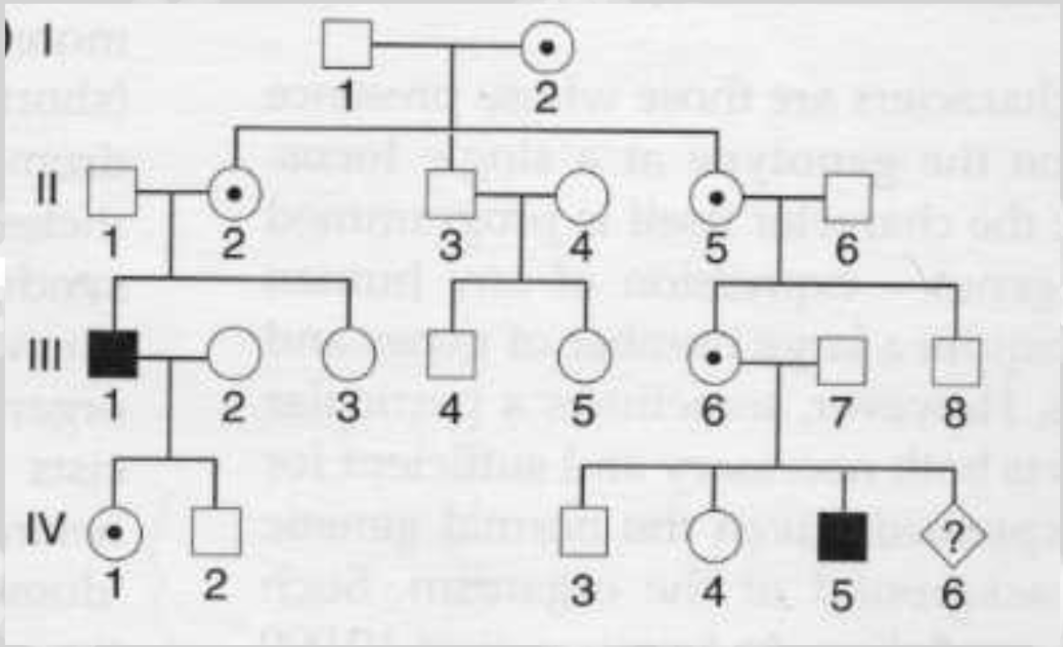
If disease is lethal what is probability that this person is a carrier? 66%. Why? Because those who are alive can only be heterozygotes (carriers) or normals. They have 50% and 25% distribution respectively and so this turns into 2/3 and 1/3 respectively.

Autosomal Recessive Inherited Diseases

Hemochromatosis	1 / 200
Cystic Fibrosis	1 / 2,500
Phenylketonuria	1 / 12,000
Gaucher disease	1 / 1,000 (Ashkenazi Jews)
Tay-Sachs disease	1 / 4,000 (Ashkenazi Jews)
Von Gierke disease	1 / 100,000
Galactosemia	1 / 18,000 to 1 / 100,000

Autosomal recessive mutations are quite common in populations. Hemochromatosis is very common. You should know these because you'll see it in practice.

X-linked recessive inheritance



In this pedigree: If male 50% chance, if female 50% carrier, 0% affected

X-linked recessive inheritance

Fragile X Syndrome	1 / 3,000
Hemophilia A	1 / 5,000
Hemophilia B	1 / 40,000
Duchenne Muscular Distrophy	1 / 5,000
Chronic Granulomatous Disease	1 / 200,000
Lesch-Nyham Syndrome	1 / 400,000
Wiskott-Aldrich Syndrome	1 / 1,000,000

Many of these. "Look them up on your own."

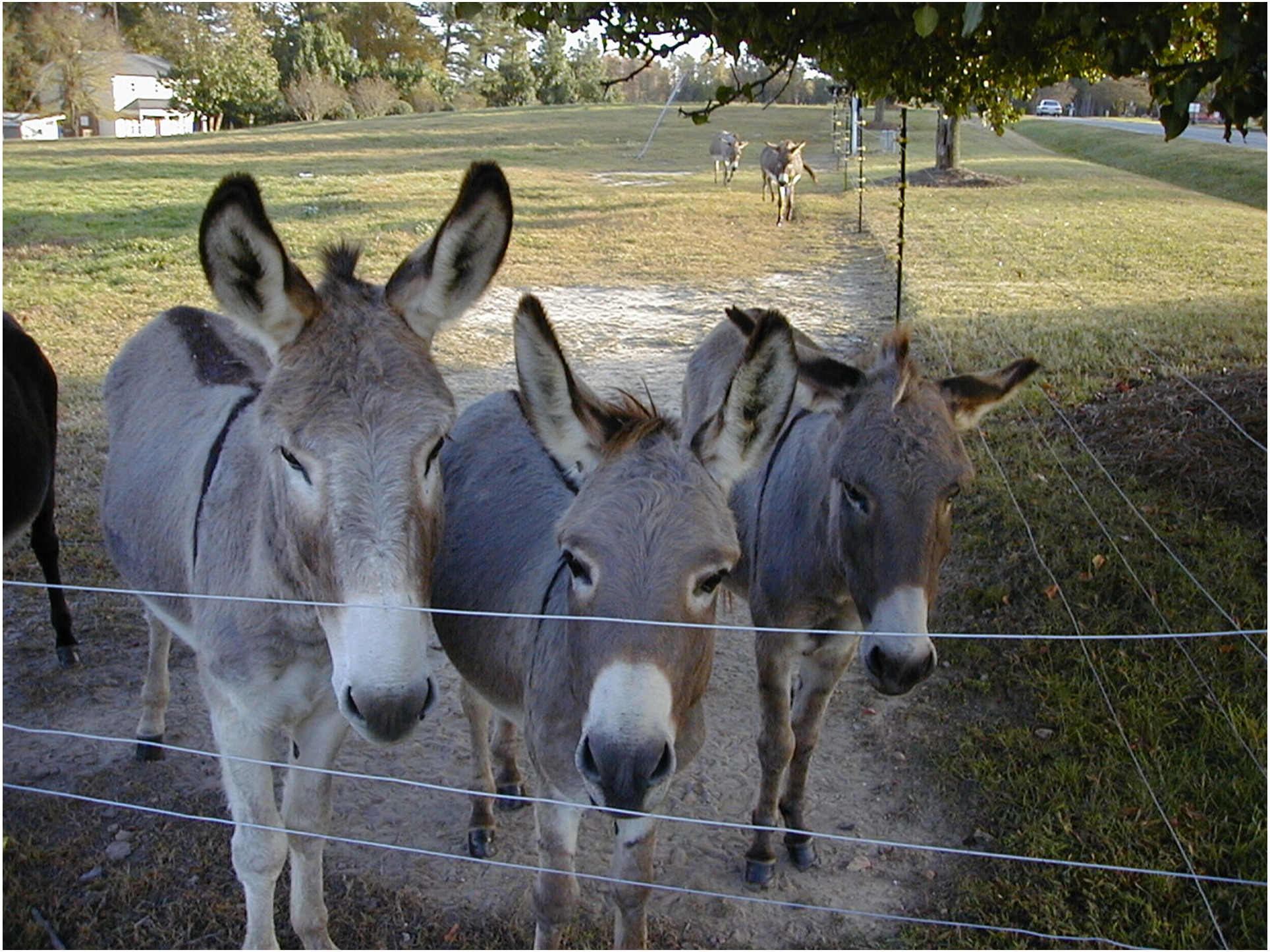
Single Nucleotide Polymorphisms

Single nucleotide changes in genes that subtly affect function.

Accounts for differences in individuals.

- Factor V leiden and clotting risk
- Compliment Factor H and AMD
- TCF7 polymorphisms and diabetes
- CYP2c9 polymorphisms and wafarin metabolism

While these don't cause overt disease, they affect our response to environment.



Medical Genetics: Case #1

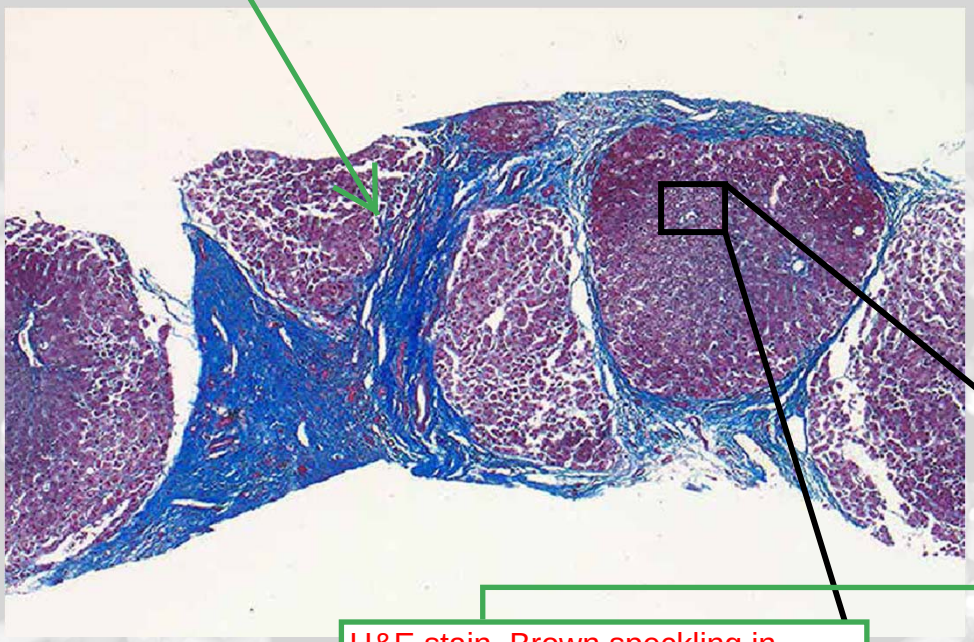
60 year old male with recent onset diabetes mellitus, hepatomegaly, skin pigmentation, cardiac arrhythmias, arthritis and loss of libido.

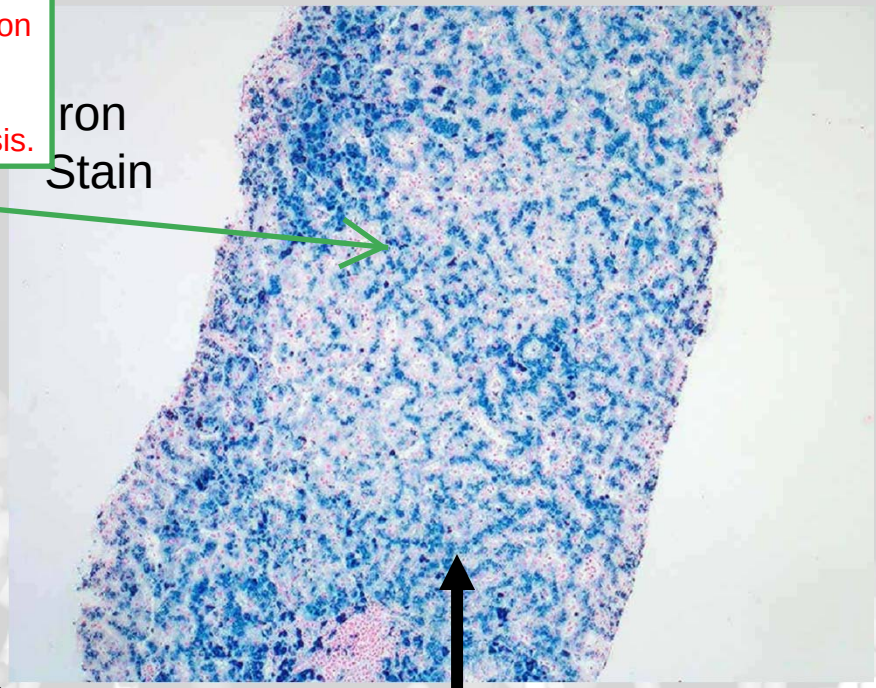
Liver CT concerning for cirrhosis, biopsy performed.

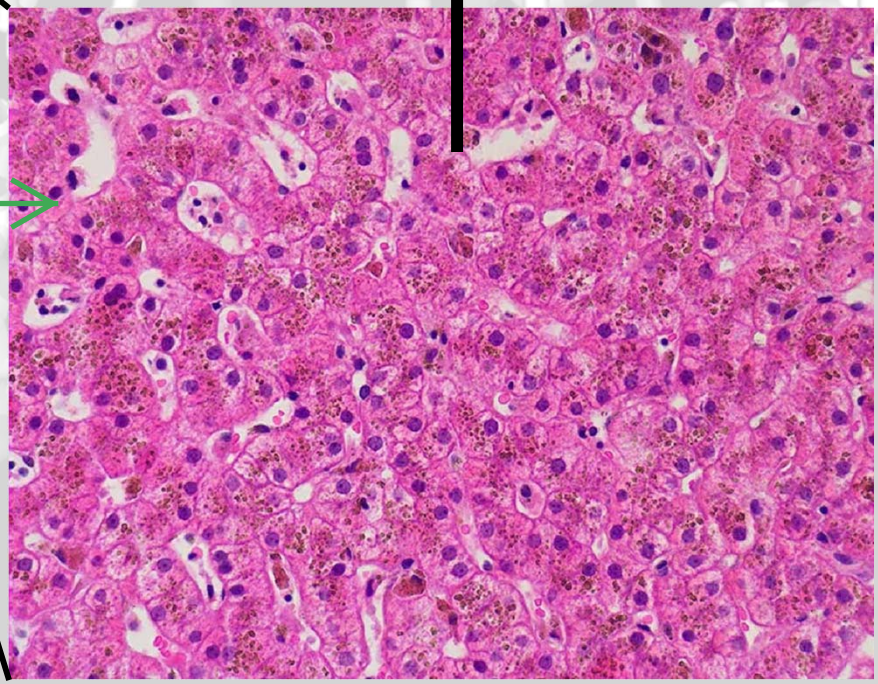
It's case studies from here on out.
He read this slide.

This is a liver biopsy using special stain that shows fibrous tissue (trichrome stain). You can see bands of fibrous tissue. This shows cirrhosis.

Colloidal iron stain (blue). Lots of iron in this liver --> diagnosis is hemachromatosis.







H&E stain. Brown speckling in hepatocytes and bile duct epithelium.

Diagnosis ?

Medical Genetics: Case #1

HEMACHROMATOSIS

TRUE / FALSE ?

T 1. This disease has both an inherited form and an acquired form. You can acquire it by increased in intake of iron (usually from multiple tranfusions).

T 2. The inherited form of this disease usually become evident after the age of 40.

T 3. The inherited form has a male predominance (5:1).

T 4. The inherited form is an autosomal recessive disease.

T 5. The disease frequency (homozygotes) in individuals of Northern European descent is 1 in 200 (0.5%) with an allele frequency of 10%.

T 6. Carriers usually don't manifest symptoms.

T 7. Serum iron and ferritin are both elevated in this disease process.

T 8. Associated with a 200x increase in HCC HCC = hepatocellular carcinoma

People with hemachromatosis have increased iron uptake in gut, which leads to increased levels of serum iron and ferritin. Menses causes incidence to go down in women. Most people die without knowing they have the disease.

Medical Genetics: Case #1

TRUE / FALSE ?

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7. Serum iron and ferritin are both elevated in this disease process.
8. Associated with a 200x increase in HCC

Medical Genetics: Hemochromatosis

TRUE/FALSE

T 1. An autosomal recessive disease of iron metabolism resulting from a mutation of the HLA-H gene (HFE) (class I MHC like molecule) on chromosome 6.

T 2. A single genetic mutation accounts for > 95% of cases: Cysteine 282 - Tyrosine. Important because of residual risk

T 3. Can be diagnosed by a simple PCR-based test on peripheral blood. Because every cell in body has mutation.

T 4. The disease penetrance approaches 20% Penetrance = the likelihood of presenting with disease phenotype.

Medical Genetics: Hemochromatosis

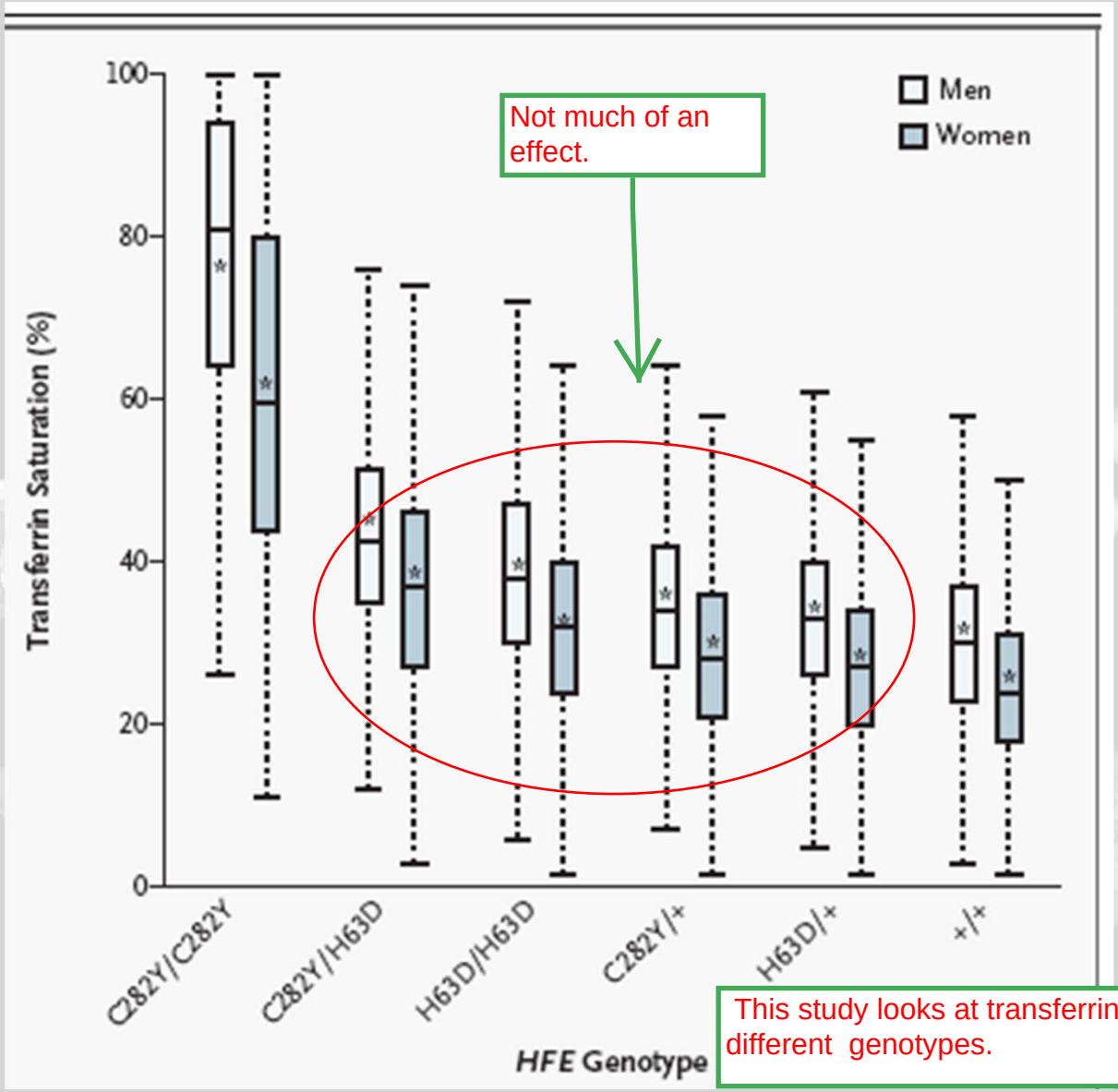
TRUE/FALSE

1. An autosomal recessive disease of iron metabolism resulting from a mutation of the HLA-H gene (H-E) (class I MHC like molecule) on chromosome 6.
2. A single genetic mutation accounts for > 95% of cases: Cysteine 282 - Tyrosine. (Also H63D and S65C in HF 9q13, and Hemojuvulin 1q21)
3. Can be diagnosed by a simple PCR-based test on peripheral blood.
4. The disease penetrance approaches 20%

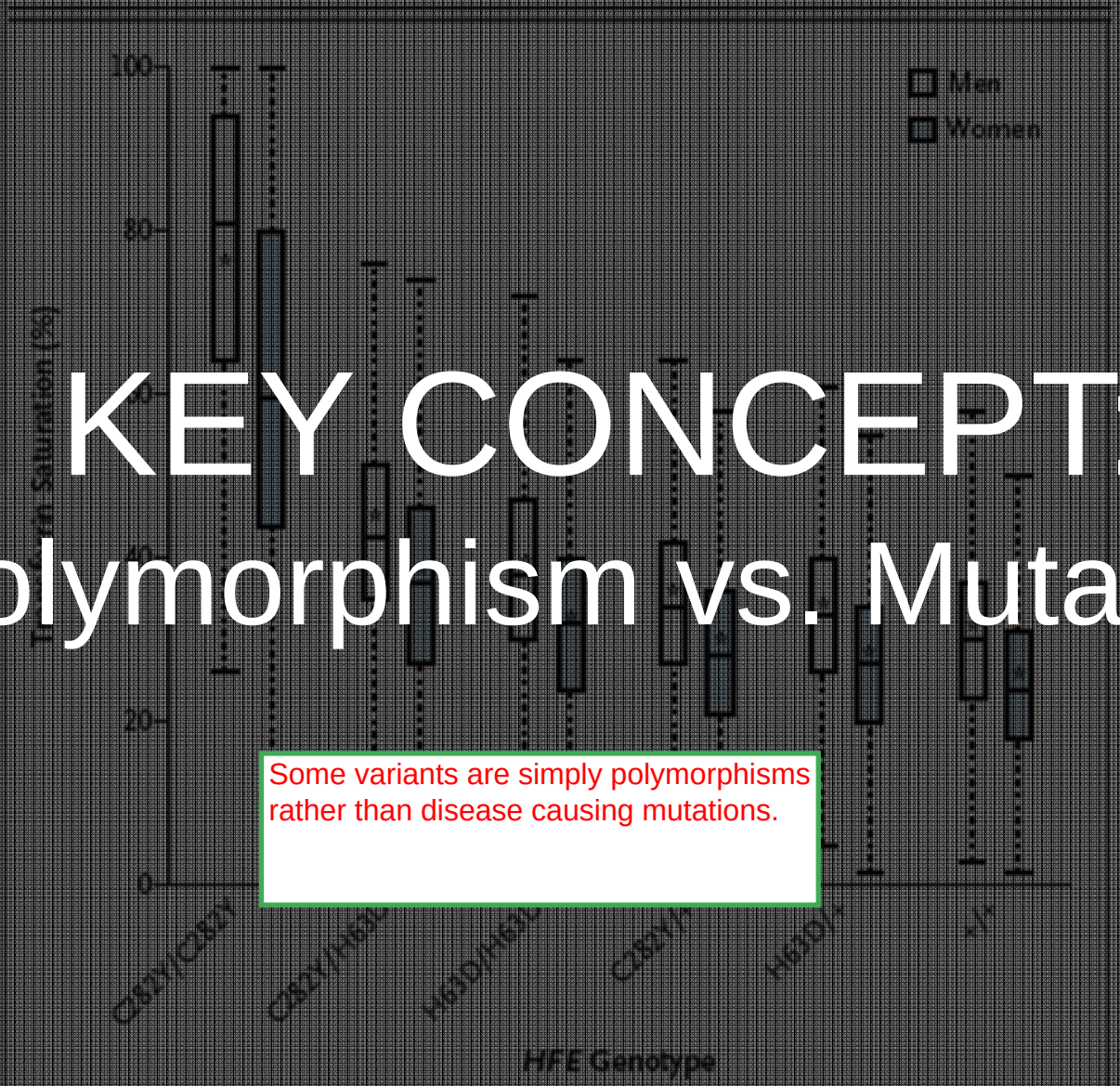
Not everybody with same genotype manifest the same disease phenotype = variable penetrance.

KEY CONCEPT:
Variable Penetrance Modifier Genes vs co-morbidity?

Medical Genetics: Hemochromatosis



This study looks at transferrin saturation of people with different genotypes.



KEY CONCEPT:
Polymorphism vs. Mutation

Some variants are simply polymorphisms rather than disease causing mutations.

Medical Genetics: Hemochromatosis

Table 1. Prevalence of *HFE* C282Y and H63D Genotypes According to Race or Ethnic Group.*

Race or Ethnic Group	Total No. of Participants	C282Y/C282Y		C282Y/H63D		H63D/H63D	
		No.	Prevalence (95% CI) %	No.	Prevalence (95% CI) %	No.	Prevalence (95% CI) %
White	44,082	281	0.44 (0.42–0.47)	908	2.0 (2.0–2.1)	1029	2.4 (2.3–2.4)
Native American	648	1	0.11 (0.061–0.20)	7	0.77 (0.56–1.1)	7	1.3 (0.98–1.8)
Hispanic	12,459	7	0.027 (0.022–0.032)	48	0.33 (0.30–0.37)	154	1.1 (0.98–1.1)
Black	27,124	4	0.014 (0.012–0.017)	35	0.071 (0.065–0.078)	30	0.089 (0.081–0.097)
Pacific Islander	698	0	0.012 (0.0043–0.032)	0	0.096 (0.055–0.17)	0	0.20 (0.12–0.32)
Asian	12,772	0	0.000039 (0.000015–0.00010)	0	0.0055 (0.0029–0.0093)	29	0.20 (0.17–0.22)
Multiple/unknown	1928	6	—	19	—	21	—
All	99,711	299	—	1017	—	1270	—

Low prevalence in non-whites.

Medical Genetics: Hemochromatosis

60 year old male with recent onset diabetes mellitus (75%), Cirrhosis (100%), skin pigmentation (75%), cardiac arrhythmias, arthritis and loss of libido.

Classic Triad

Diagnosis in stages

Elevated total serum iron and ferritin,

Liver biopsy with quantitative iron measurement (> 10,000 ug/gm).
Symptoms begin at 20 gm of storage iron.

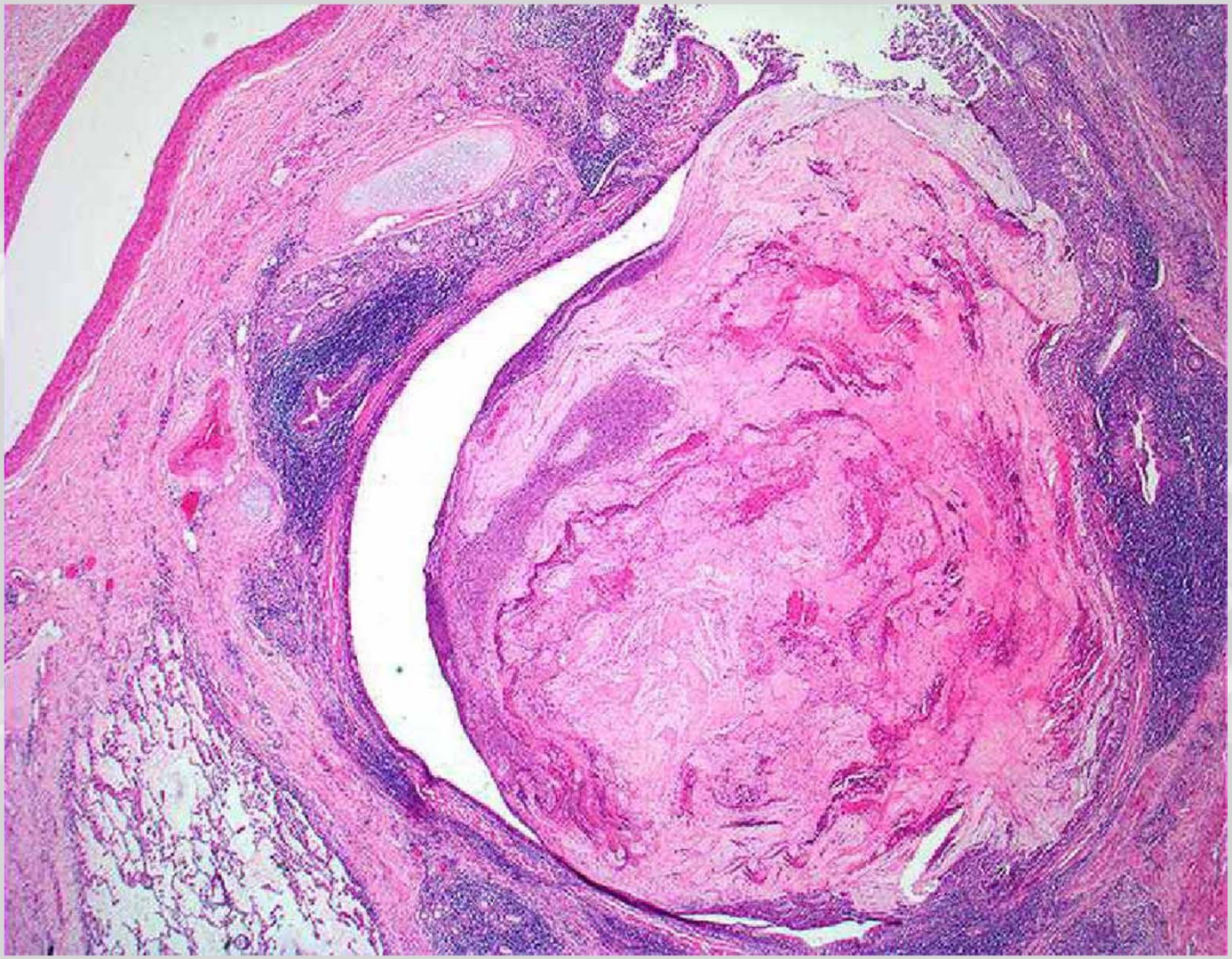
molecular analysis of HFE

Medical Genetics: Case #2

1 year old child with intestinal malabsorption, poor weight gain, recurrent and persistent lung infections. A chloride sweat test shows elevated sweat electrolyte concentrations.

Cystic fibrosis.

Medical Genetics: Case #2

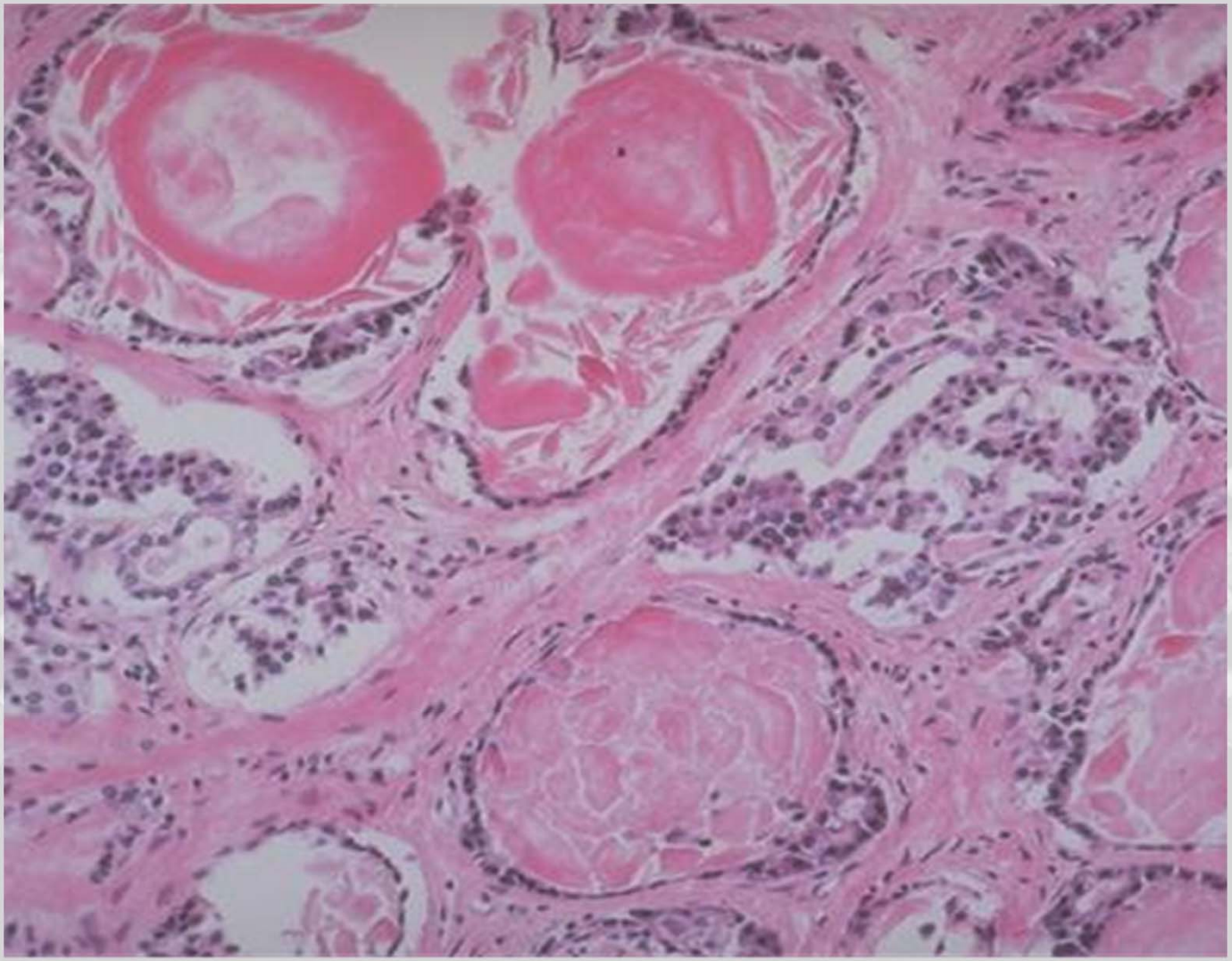


Tissue?

Finding?

Lung tissue. Abundant chronic inflammation. Big ball of mucous.

Medical Genetics: Case #2



Tissue?

Finding?

Diagnosis?

Pancreas. Islets of Langerhans are missing the acini. CF was initially described as cystic change and fibrosis of the pancreas.

Medical Genetics: Case #2

TRUE/FALSE ? All answers are true

1. Typical symptoms of this disease include bronchiectasis, pancreatic insufficiency, male infertility and hepatic biliary cirrhosis.
2. Results from mutations in the CFTR gene, a 24 exon, 1480 AA transmembrane chloride ion channel at 7q31
3. 10's to 100's of mutations accounts for 95% of affected individuals: delta F508 is the most common in European descent (but still ONLY 65%) Again example of residual risk. Testing F508 goes a long way.
4. The disease is inherited in an autosomal recessive fashion.
5. This is the most common lethal genetic disease in the US affecting 1:1500 to 1:4000 live births with a carrier frequency of 2 - 4%.
6. Carrier screening is recommended by the ACMG for all women who are pregnant or planning pregnancy

Medical Genetics: Cystic Fibrosis

TRUE/FALSE ?

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TABLE 2. Ideal Recommended CFTR Mutation Screening Panel for 2001 Neonatal Screening in the USA

Mutation	Location in *CFTR*[a]	Estimated percentage[b]	Reason for inclusion
ΔF508	Exon 10	68.6%	CFF registry, >1%, Pan-European
G542X	Exon 11	2.4%	CFF registry, >1%, Mediterranean
G551D	Exon 11	2.1%	CFF registry, >1%, Celtic
W1282X	Exon 20	1.4%	CFF registry, >1%, Ashkenazi Jew
N1303K	Exon 21	1.3%	CFF registry, >1%, Mediterranean
R553X	Exon 11	0.9%	CFF registry, >0.5%, Hispanic
621+1G→T	Intron 4	0.9%	CFF registry, >0.5%, multi-ethnic
1717-1G→A	Intron 10	0.7%	CFF registry, >0.5%, Italian
3849+10KbC→T	Intron 19	0.7%	CFF registry, >0.5%, Hispanic
R117H[c]	Exon 4	0.7%	CFF registry, >0.5%
1898+1G→T	Intron 12	0.4%	CFF registry, >0.1%, East Asian
ΔI507	Exon 10	0.3%	CFF registry, >0.1%, Hispanic
2789+5G→A	Intron 14b	0.3%	CFF registry, >0.1%
G85E	Exon 3	0.3%	CFF registry, >0.1%
R347P	Exon 7	0.2%	CFF registry, >0.1%
R334W	Exon 7	0.2%	CFF registry, >0.1%, multi-ethnic
R1162X	Exon 19	0.2%	CFF registry, >0.1%, multi-ethnic
R560T	Exon 11	0.2%	CFF registry, >0.1%
3659delC	Exon 19	0.2%	CFF registry, >0.1%
A455E	Exon 9	0.2%	CFF registry, >0.1%
2184delA	Exon 13	0.1%	CFF registry, >0.1%
S549N	Exon 11	0.1%	CFF registry, >0.1%, multi-ethnic
711+1G→T	Intron 5	0.1%	CFF registry, >0.1%
R75X	Exon 3	0.2%	Hispanic
406-1G→A	Intron 3	0.2%	Hispanic
I148T	Exon 4	0.2%	Hispanic, French
2055del9→A	Exon 13	0.1%	Hispanic
935delA	Exon 6b	0.1%	Hispanic
I506T	Exon 10	0.1%	Hispanic
3199del6	Exon 17a	0.1%	Hispanic
2183AA→G	Exon 13	0.1%	Hispanic
3120+1G→A	Intron 16	1.5%	African American, Arabian
2307insA	Exon 13	0.2%	African American
A559T	Exon 11	0.2%	African American
ΔF311	Exon 7	0.2%	African American
G480C	Exon 10	0.2%	African American
405+3A→C	Intron 3	0.2%	African American
S1255X	Exon 20	0.2%	African American
L1093P	Exon 17b	Undetermined	Native American
D648V	Exon 13	Undetermined	Native American
I1234V	Exon 19	Undetermined	Arabian linkage
S549R	Exon 11	Undetermined	Arabian linkage
1898+5G→T	Intron 12	Undetermined	East Asian linkage
CFTRdele2,3	Exons 2,3	Undetermined	Eastern European linkage (Slavic)
Y1092X	Exon 17b	Undetermined	French linkage
394delTT	Exon 3	Undetermined	Nordic linkage
Y569D	Exon 12	Undetermined	Pakistani linkage
3905insT	Exon 20	Undetermined	Swiss linkage (also: Amish, Acadian, Me
1898+1G→A	Intron 12	Undetermined	Welsh linkage
M1101k	Exon 17b	Undetermined	Hutterite ancestry

Cystic Fibrosis USA mutation frequencies

Bobadilla et al., (2002) Cystic Fibrosis: A Worldwide Analysis of CFTR Mutations – Correlation With Incidence Data and Application to Screening. Human Mutation 19: 575-606.

There are different classes of mutations (in red box).

CFTR – Classes of Mutations

- 1. Absence of mRNA synthesis
- 2. Defective protein maturation / folding
- 3. Disordered regulation (ATP hydrolysis)
- 4. Defective chloride conductance
- 5. Defective splicing or reduced expression
- 6. Increased turnover

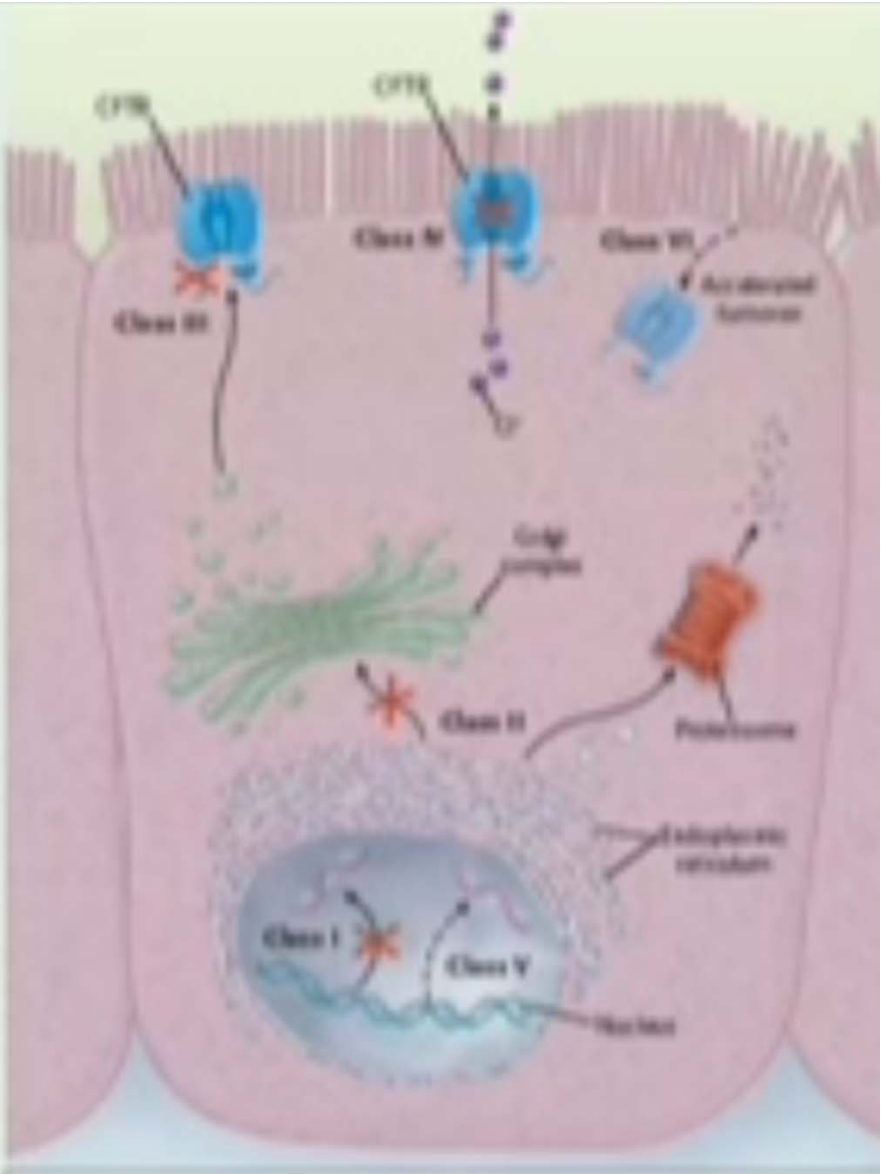

Figure 1. Categories of CFTR Mutations.
Classes of defects in the *CFTR* gene include the absence of synthesis (class I); defective protein maturation and premature degradation (class II); disordered regulation, such as diminished ATP binding and hydrolysis (class III); defective chloride conductance or channel gating (class IV); a reduced number of CFTR transcripts due to a promoter or splicing abnormality (class V); and accelerated turnover from the cell surface (class VI).[8]

CFTR – Classes of Mutations

- 1. Absence of mRNA synthesis
- 2. Defective protein maturation and trafficking
- 3. Disordered regulation (ATP hydrolysis)
- 4. Defective chloride conductance
- 5. Defective splicing or reduced expression
- 6. Increased turnover

KEY CONCEPT:

The Severity of Disease Can Vary Depending on the Type of Mutation

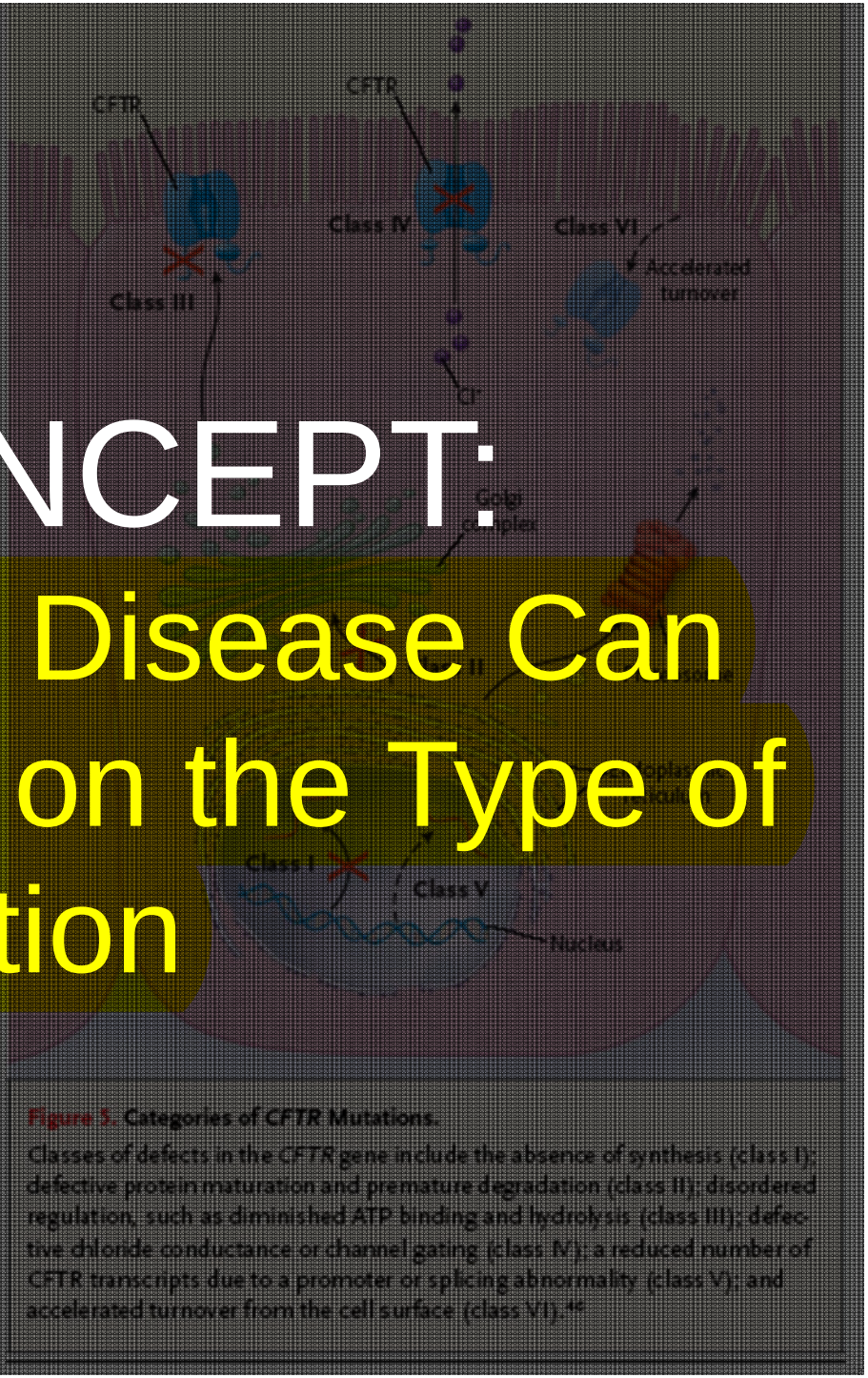

Figure 5. Categories of *CFTR* Mutations.

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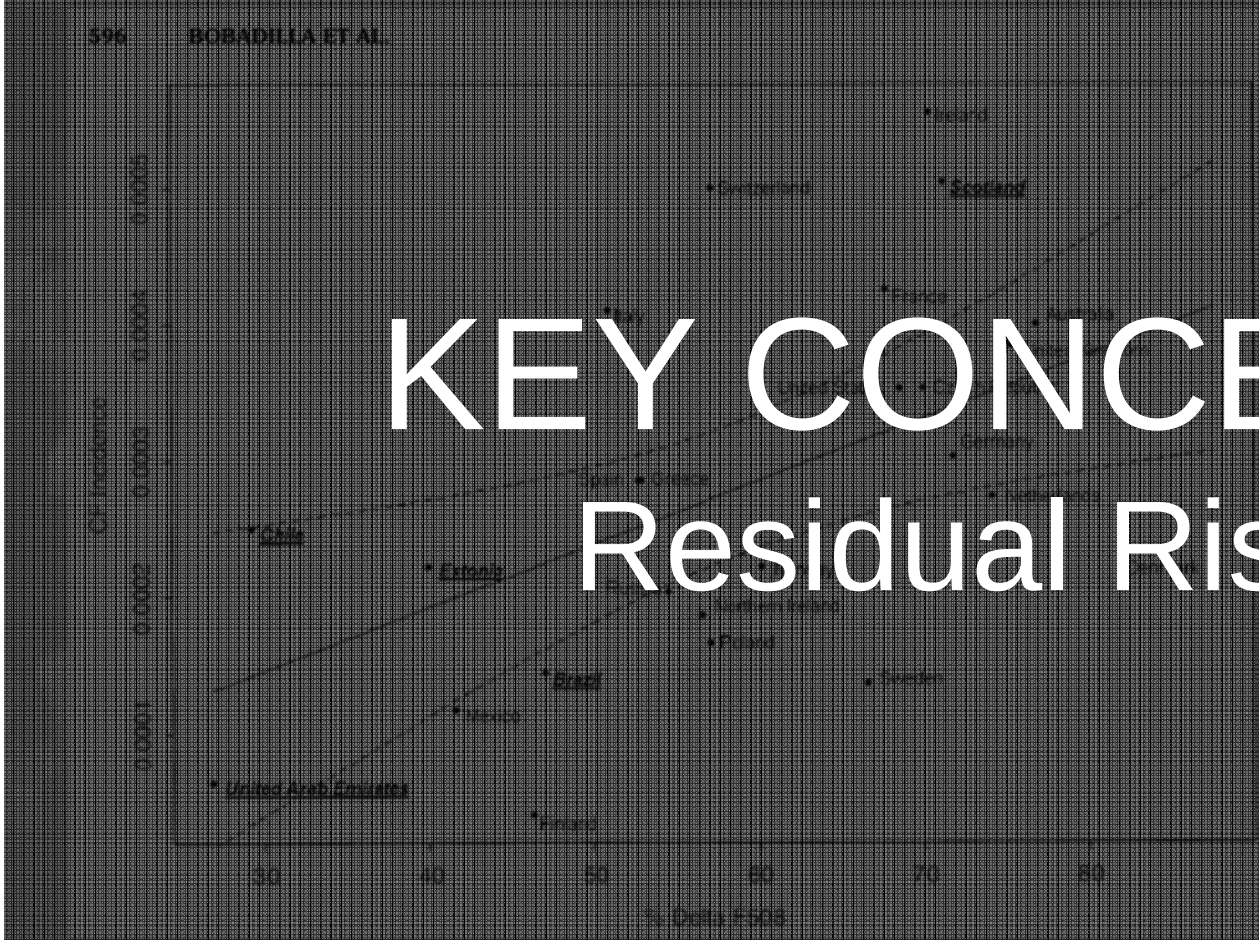
Rowe et al. NEJM 2005



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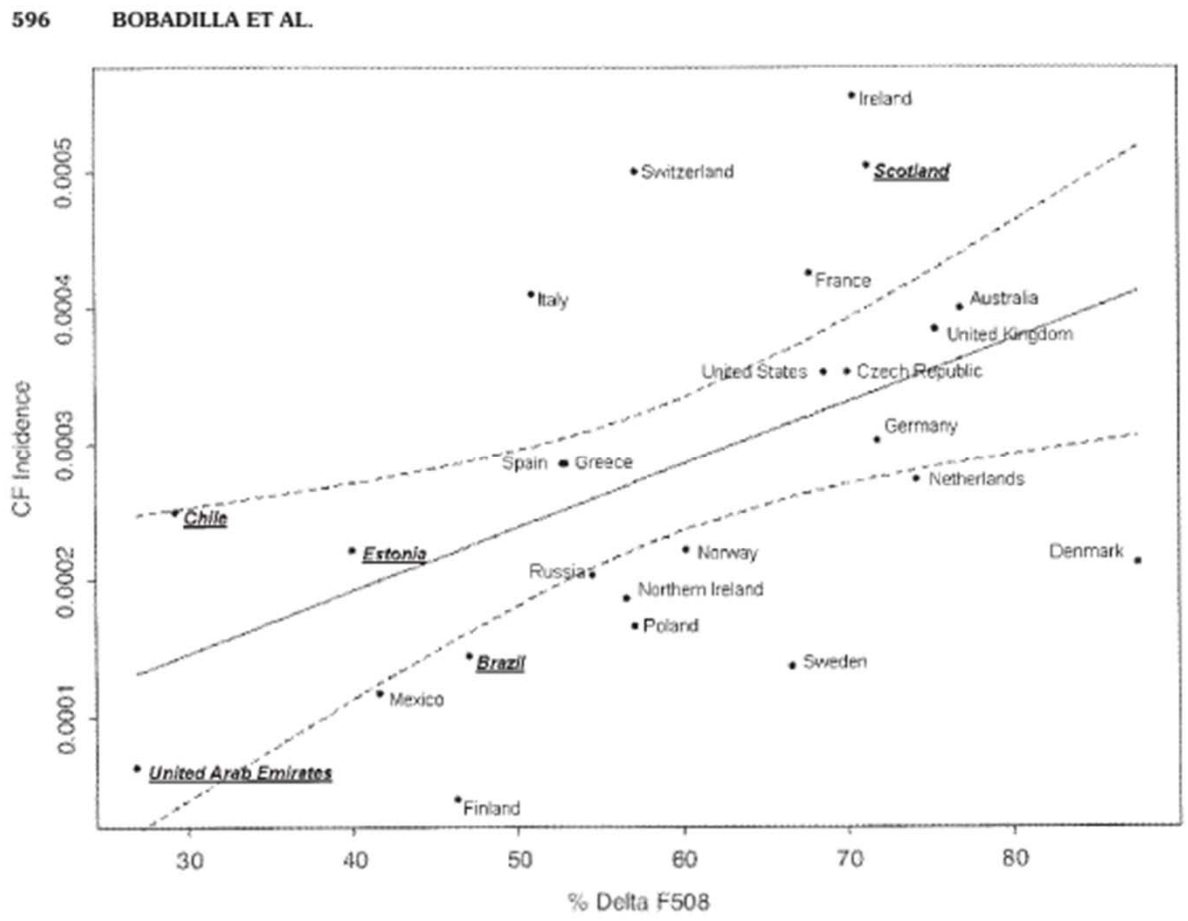
KEY CONCEPT:
Residual Risk

Cystic Fibrosis USA mutation frequencies

Bobadilla et al., (2002)
Cystic Fibrosis: A Worldwide Analysis of CFTR Mutations – Correlation With Incidence Data and Application to Screening. Human Mutation 19: 575-606.



Ethnic background dictates residual risk. You must test mutations appropriate for the target population (ethnic group). Not to do so would be a disservice to your patient.

Coagulation: Case #3

- 25 year old female with right lower extremity pain and swelling. Imaging studies reveal a deep vein thrombosis. She is otherwise healthy and her only risk factor for thrombosis is oral contraception.

Factor V mutation.

Coagulation: Case #3

TRUE/FALSE ?

1. A mutation in Factor V can be found in approximately 20% of patients with this clinical picture. (Glu 506 Arg)
2. The population (European descent) frequency of this allele is 3-4%.
3. Hypercoagulability due to Factor V mutations is autosomal dominant.
4. This mutation inhibits the ability of protein C to inactivate factor V.
5. This mutation increases the risk of spontaneous thrombosis 2-4 fold. 1% chance / year after 60.
6. A mutation in Prothrombin (G20210A, 3'UTR) can be found in 4-8% of these patients.

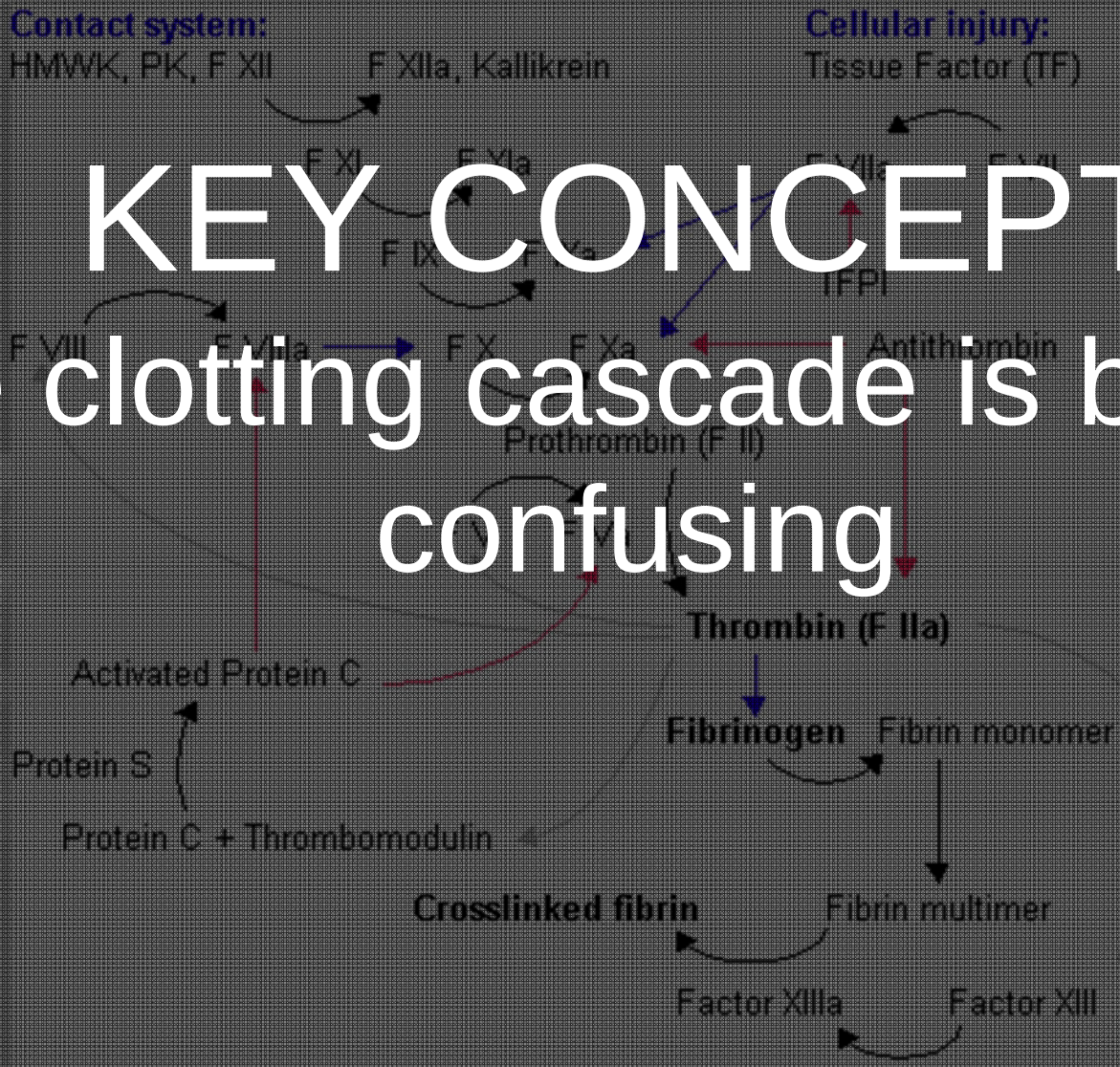
All are true. Half of you factor V is relatively resistant to the actions of protein C. A mutation in UTR of prothrombin can affect the stability of the mRNA.

Coagulation: Factor V Leiden

TRUE/FALSE ?

1. A mutation in Factor V can be found in approximately 20% of patients with this clinical picture. (Glu 506 Arg)
2. The population (European descent) frequency of this allele is 3-4%.
3. Hypercoagulability due to Factor V mutations is autosomal dominant. Homozygotes have further increased risk.
4. This mutation inhibits the ability of protein C to inactivate factor V.
5. This mutation increases the risk of spontaneous thrombosis 2-4 fold. 1% chance / year after 60.
6. A mutation in Prothrombin (G20210A, 3'UTR) can be found in 4-8% of patients with this clinical picture.

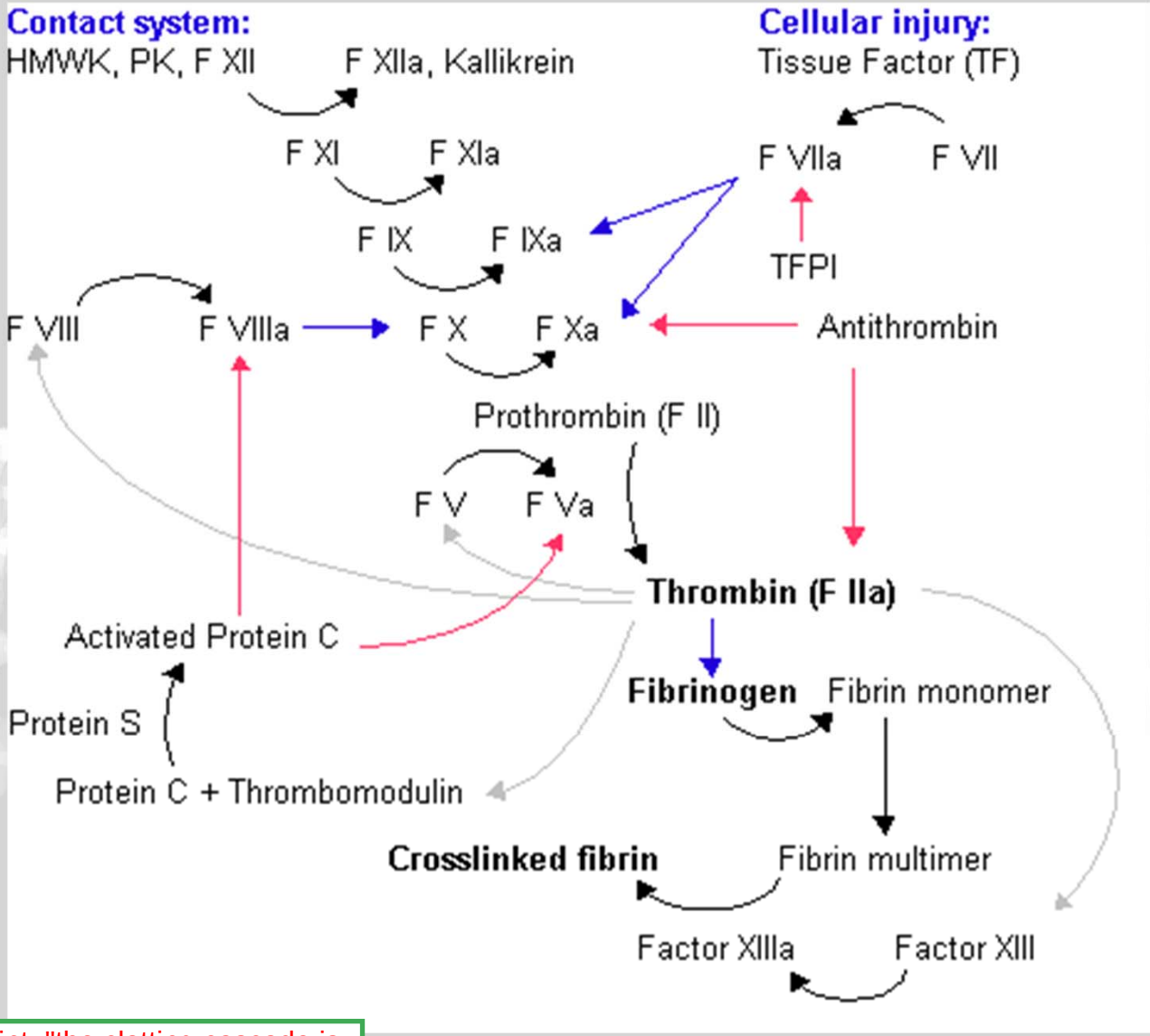
Coagulation: Factor V Leiden



KEY CONCEPT:

The clotting cascade is big and confusing

Coagulation: Factor V Leiden



Clotting cascade. The point: "the clotting cascade is big and confusing." Mutations in a lot of these proteins can cause problems (Hemophilia for example)

An Aside: Coagulation + Pharmacogenomics: Warfarin Metabolism

- Warfarin - background
  - blocks vitamin K dependent clotting enzymes by inhibiting vitamin K epoxide reductase VKORC1.
    - Gama-glutamylcarboxylastion of II, VII, IX and X (assay therapeutic effects through changes in INR)
  - Very commonly used drug for long term anticoagulation to prevent thrombo-embolic events
    - 20 million prescriptions / year to 1 million patients.
    - 1-2% chance of a major bleed
    - Estimated 0.1% mortality

Read this.

Coagulation + Pharmacogenomics: Warfarin Metabolism

- Warfarin - background
  - Metabolized by a hepatic microsomal enzyme
    - CYP2C9 (p450 enzyme)
    - Two common polymorphisms are present in CYP2C9
      - CYP2C9*1 – wt allele
      - CYP2C9*2 – R144C – 30% decrease in activity, 11% population frequency
      - CYP2C9*3 – I359L – 80% decrease in activity, 7% population frequency.

3 types of alleles for CYP2C9. If you have CYP2C9*3 then you need lower dose of warfarin because you metabolize it slower.

Coagulation + Pharmacogenomics: Warfarin Metabolism

- Warfarin - background
  - Inhibits VKORVC1

Vitamin K Epoxide Reductase --> the target of warfarin

    - Two common Genomic variants of VKORC1
      - -1639 G>A (promoter polymorphism)
        - » GG 25%, GA 56%, AA 19%
      - 1173 C>T (Intron 1 polymorphism)
        - » C allele frequency is 58%
      - Both vary significantly in different populations

Alleles that cause higher expression of gene require higher doses.

Coagulation + Pharmacogenomics: Warfarin Metabolism

- Warfarin – the data

Table 3. Prescribed Daily Dose of Warfarin in Relation to CYP2C9 Genotype*

	Genotype					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
No.	127	28	18	4	3	5
Daily maintenance warfarin dose, mg						
Mean (SD)	5.63 (2.56)	4.88 (2.57)	3.32 (0.94)	4.07 (1.48)†	2.34 (0.35)	1.60 (0.81)
Median (IQR)	5.27 (3.93-7.14)	4.64 (3.61-5.29)	2.92 (2.50-3.93)	3.86 (2.50-4.00)	2.32 (2.00-2.70)	1.61 (1.14-1.96)

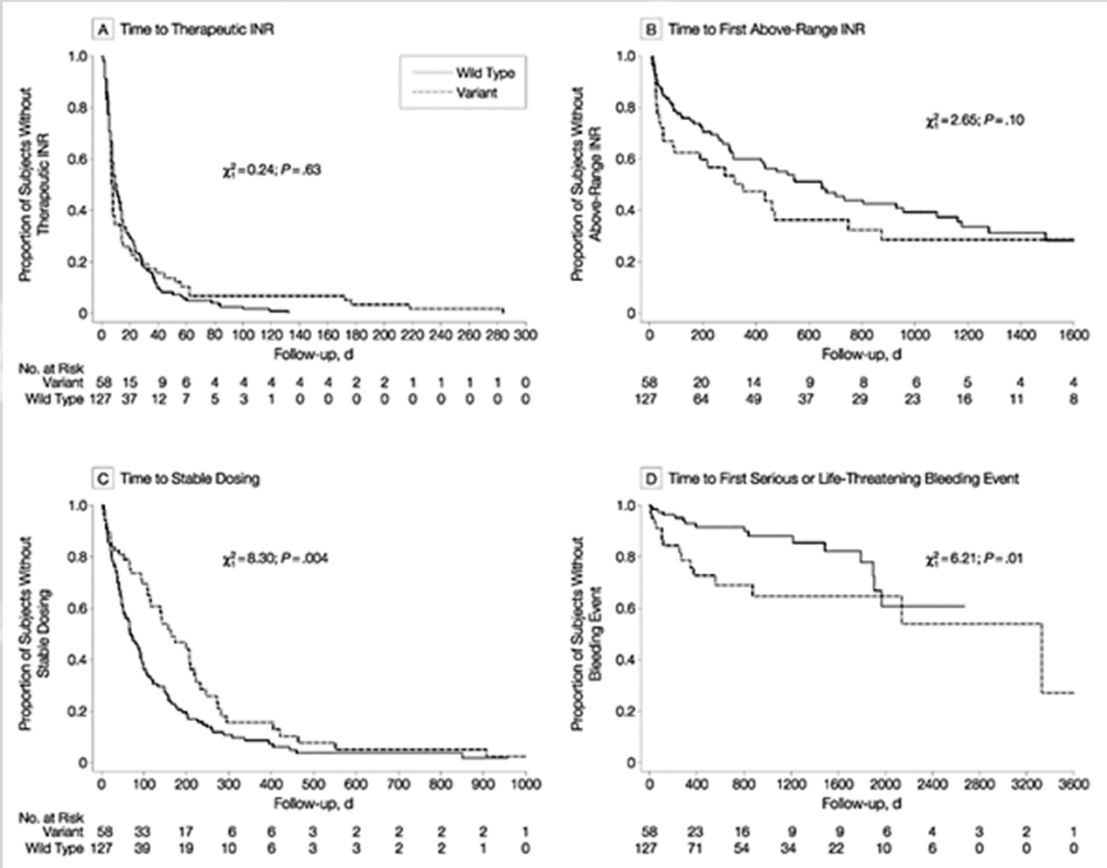
*Kruskal-Wallis $\chi^2_5 = 37.348$; $P<.001$. IQR indicates interquartile range.
†Mean doses (mg) for the 4 patients were 2.50, 3.71, 4.00, and 6.07. The mean of these is 4.07; however, the 75th percentile is 4.00. The patient with the mean daily dose of 6.07 had a prosthetic valve and experienced a serious bleeding event. This reflects the potential skewness that data from patients with prosthetic valves can introduce to small samples and reflects the range of maintenance doses that can occur in a clinical setting. An analysis was performed in which 12 patients having prosthetic valves with a higher target international normalized ratio range (2.5-3.5) were excluded; the effect on hazard ratio estimates was trivial (see text).

Just the numbers. The doses required for different alleles.

Higashi et al., (2002) JAMA

Coagulation + Pharmacogenomics: Warfarin Metabolism

- Warfarin – the data

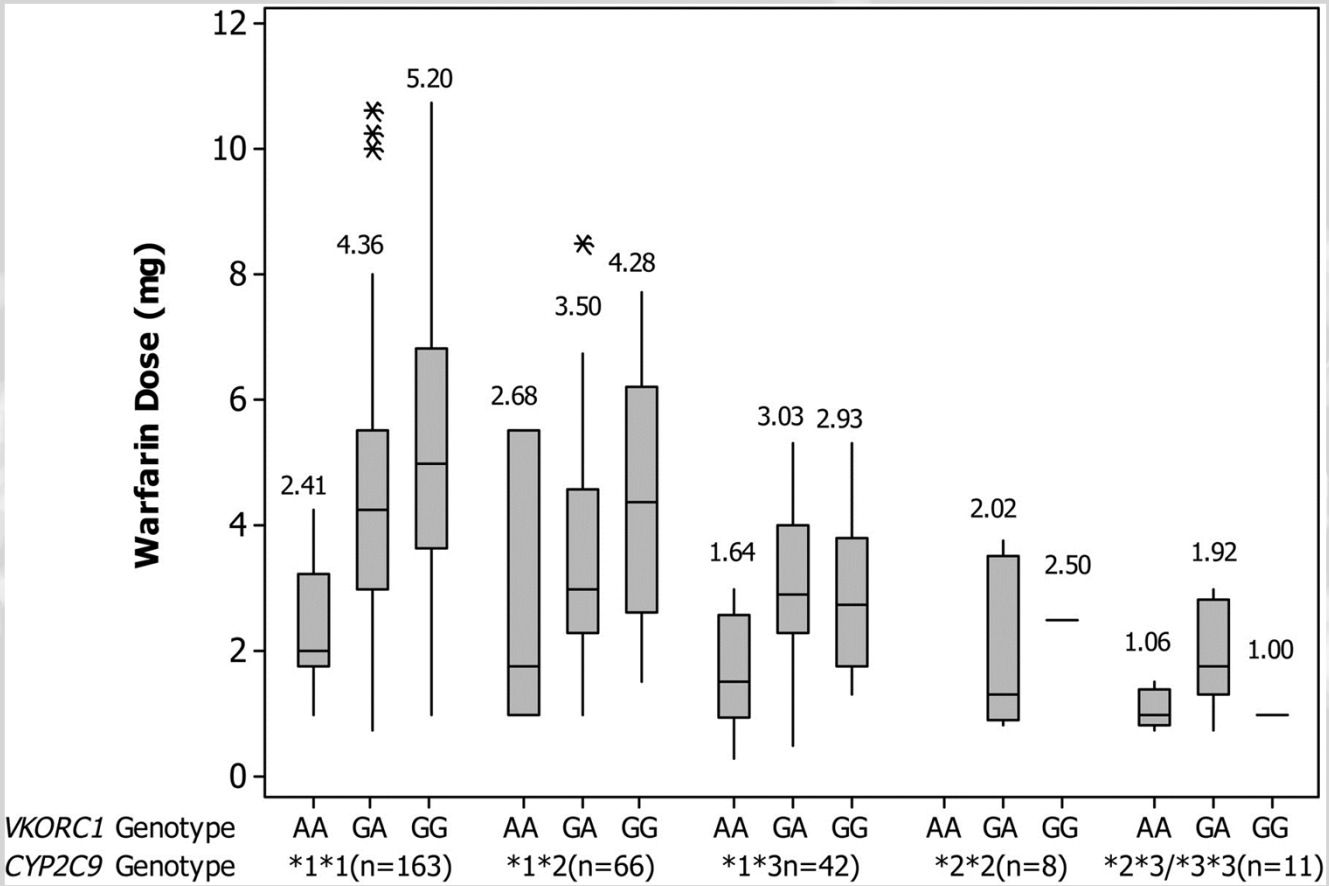


I'm going to quote him verbatim: "If we look at the time to therapeutic INR. The WT allele gets to a therapeutic INR faster than the mutant allele. And you can see that the time to the first above range INR is sooner for the mutant than the WT allele. So they require a smaller dose and they also have more life threatening bleeding events. **If you have *3 allele you have more life threatening bleeding events than if you have the *1 allele.**

Higashi et al., (2002) JAMA

Coagulation + Pharmacogenomics: Warfarin Metabolism

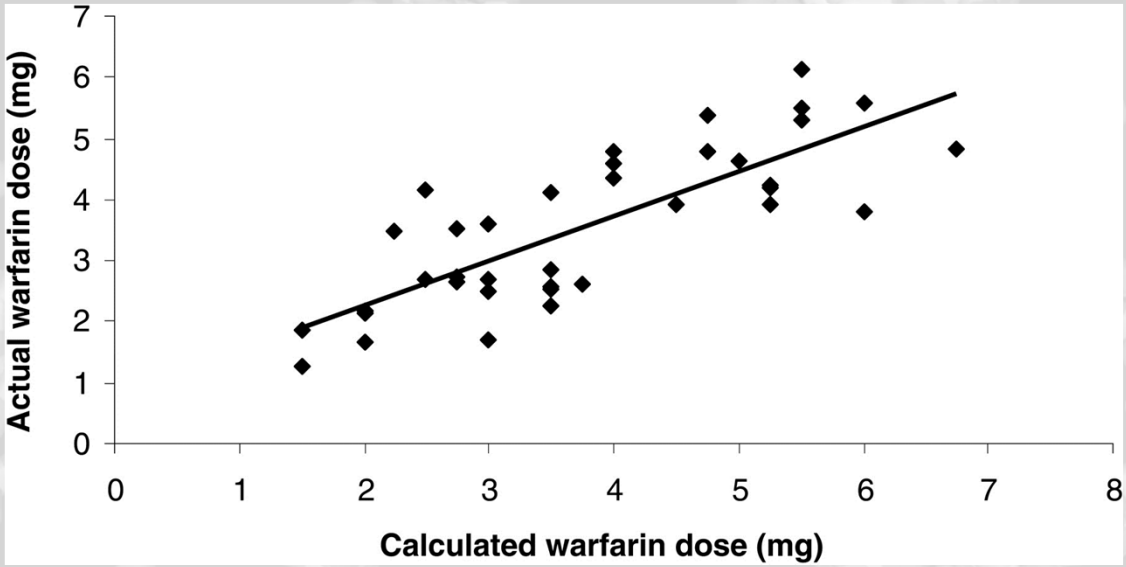
- Warfarin – the data



Sconce et al., (2005) Blood

Coagulation + Pharmacogenomics: Warfarin Metabolism

- Warfarin – the Question: Should everyone starting Warfarin be tested?



Regression Analysis to get:

Dose = 0.628 – 0.0135 (Age) – 0.240 (CYP*2) – 0.370 (CYP*3) – 0.241(VKOR) + 0.0162 (Height)

(VKOR = 1 for GG, 2 for GA and 3 for AA)

Sconce et al., (2005) Blood

This equation allows you to calculate proper dosage for patients. Genotype and then plug in values for alleles.

So should you genotype patients? Instructions of warfarin packet says you should but there isn't any data that shows that if you dose based on genotype, patients won't undergo adverse outcomes. Rarely done.

Medical Genetics: Case #4

4 year old boy who is behind in his developmental milestones, has a long face, large mandible, large everted ears. Similar findings in his older brother. His older sisters are apparently normal.

1. Probable Diagnosis?