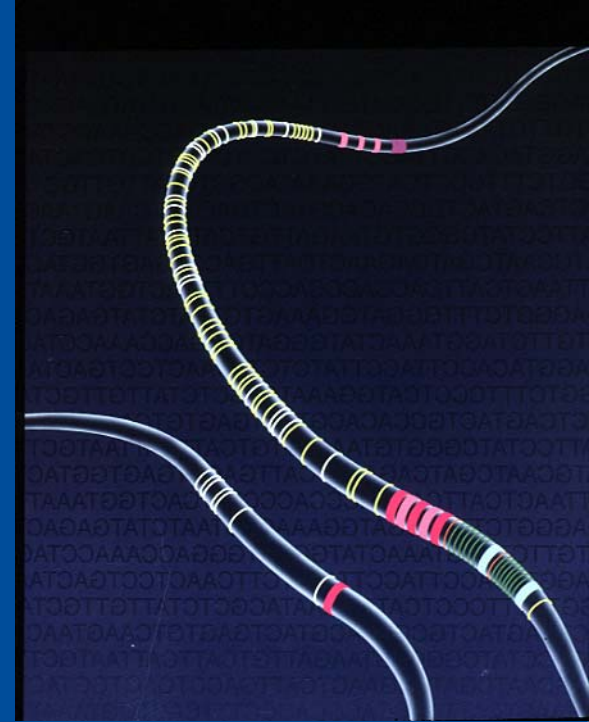
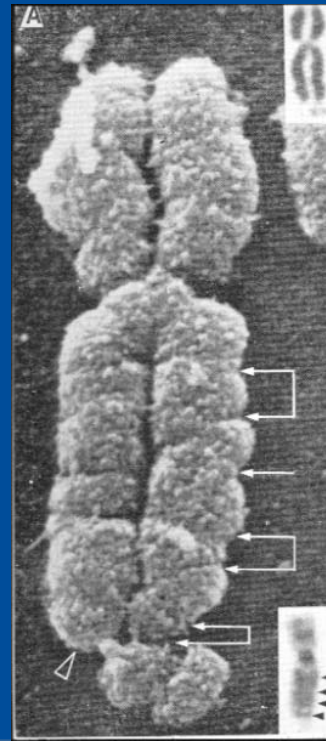
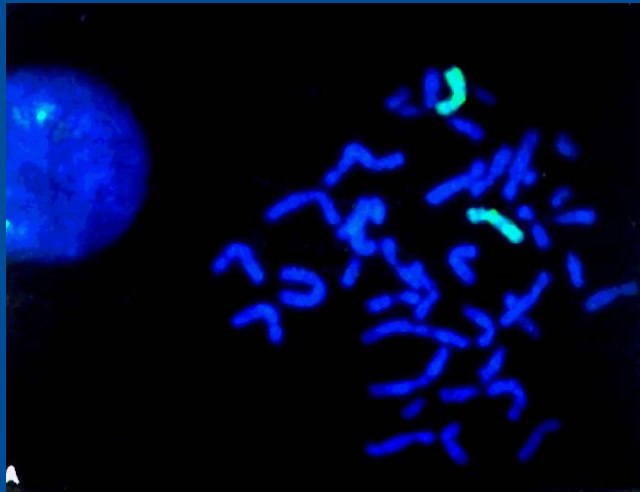
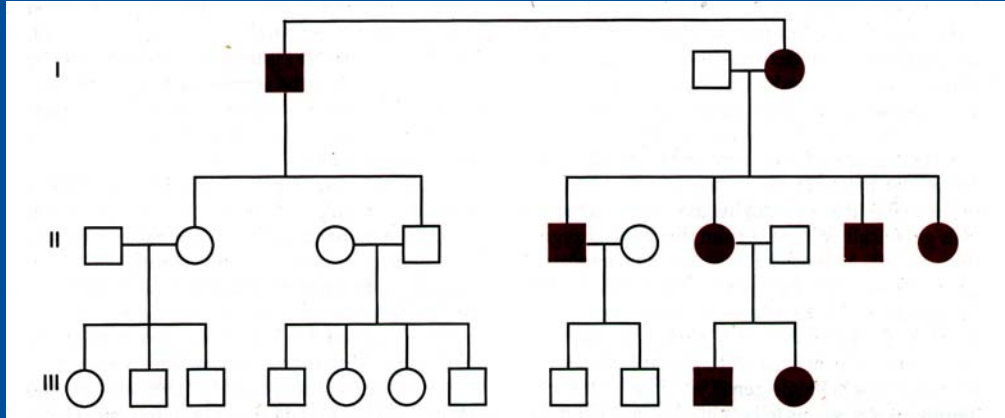
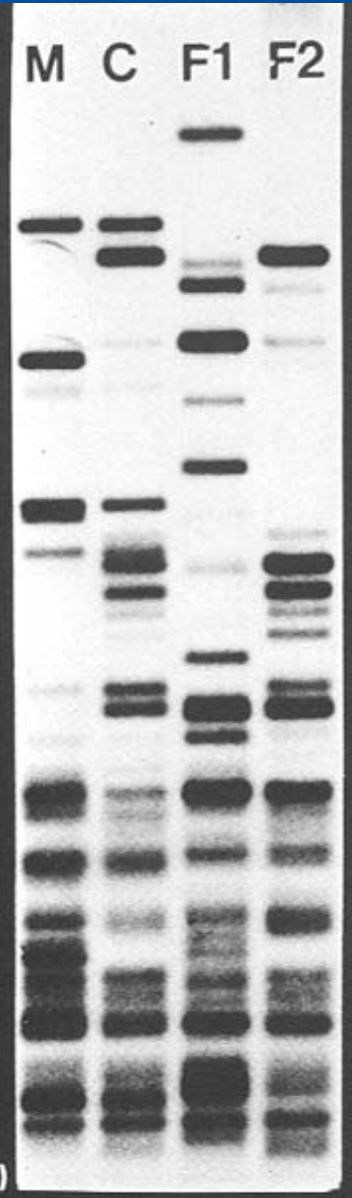


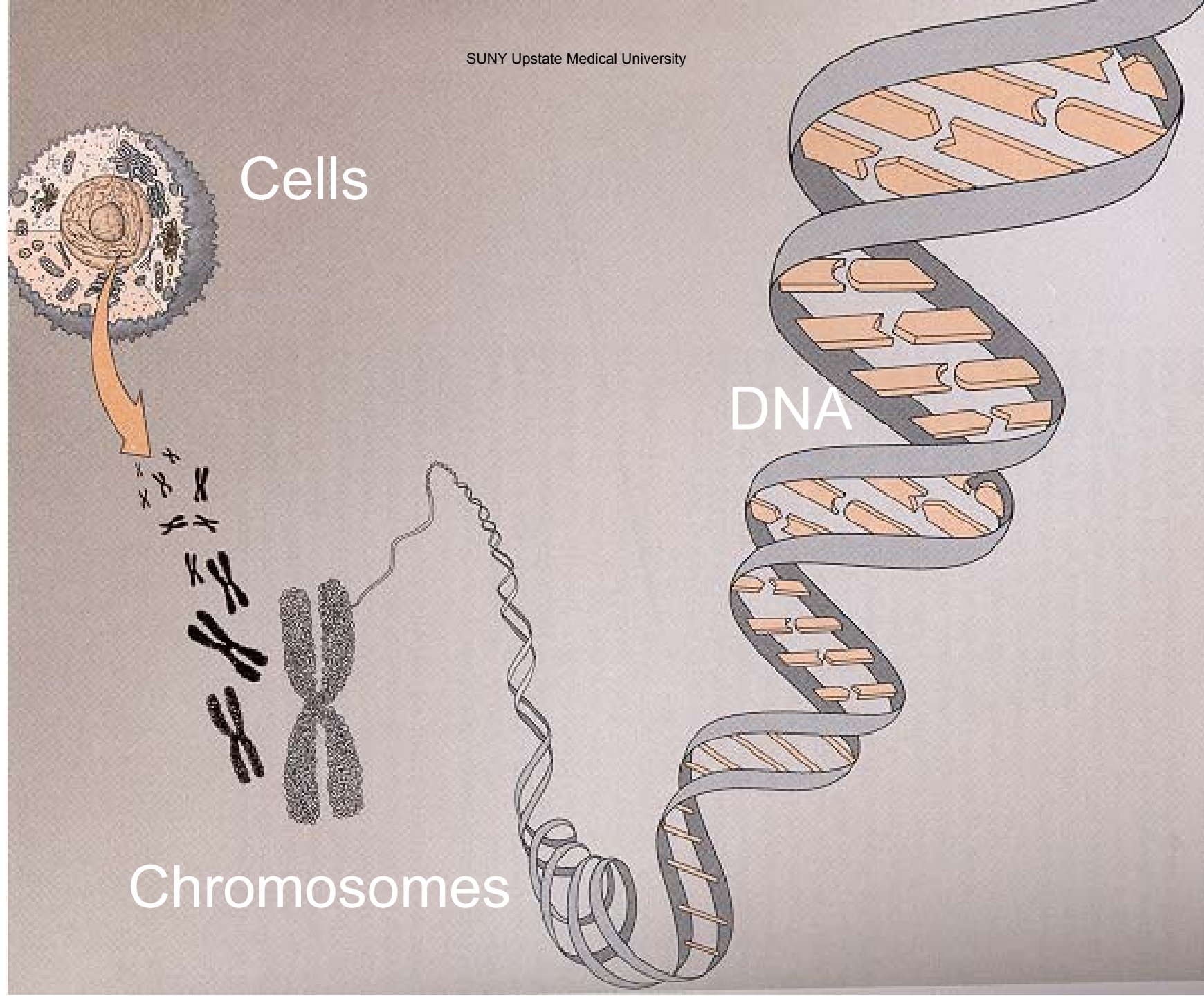


# Genetic Testing: Understanding Definitions and Key Concepts

**Constance K. Stein, PhD**

# Genetics: the study of heredity





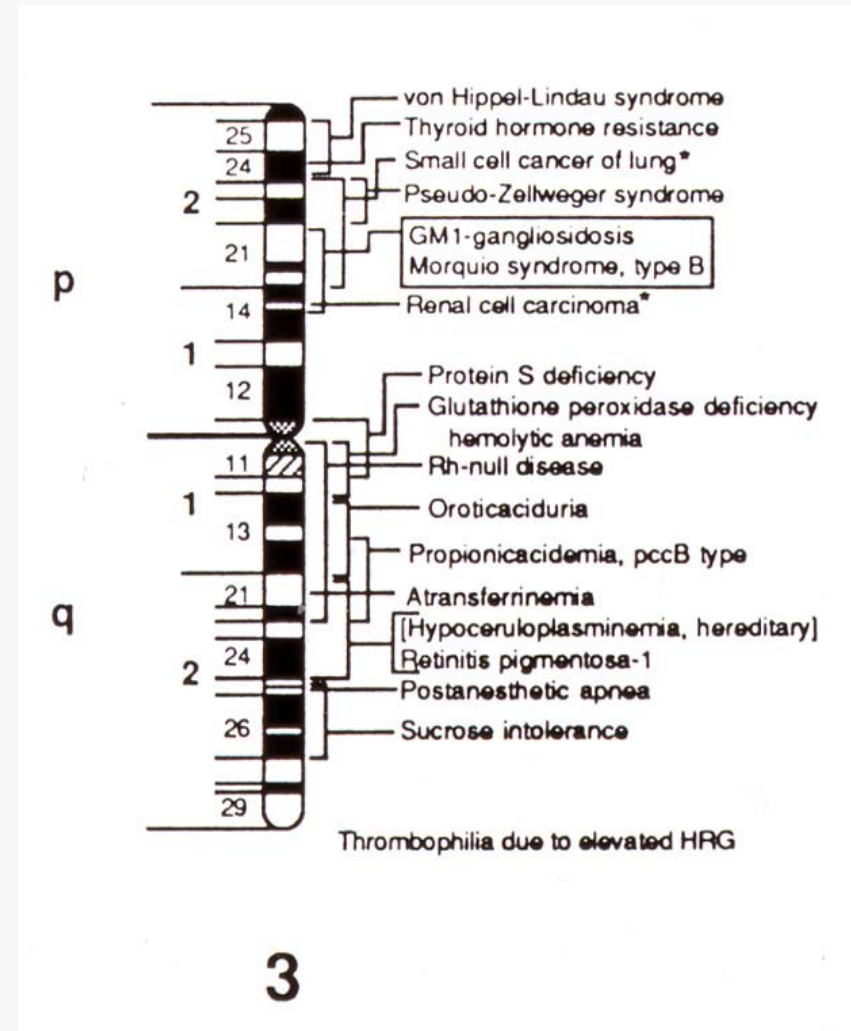
Cells

DNA

Chromosomes

**Gene:** A region of DNA which represents a functional unit of inheritance

**Chromosome:** A highly ordered structure composed of DNA and proteins which carries the genetic information

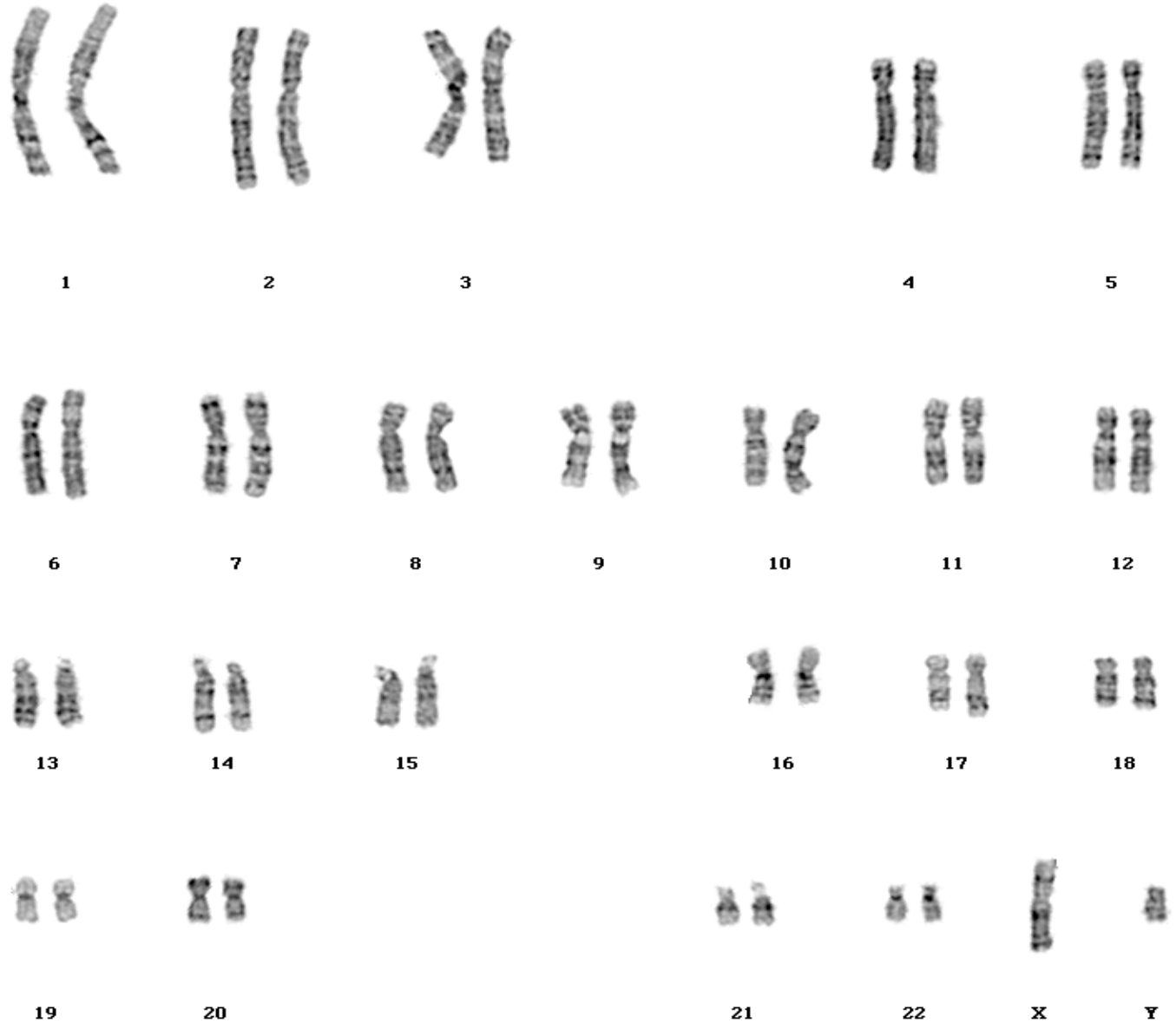


# Chromosomal Basis of Inheritance

SUNY Upstate Medical University



Metaphase



Karyotype

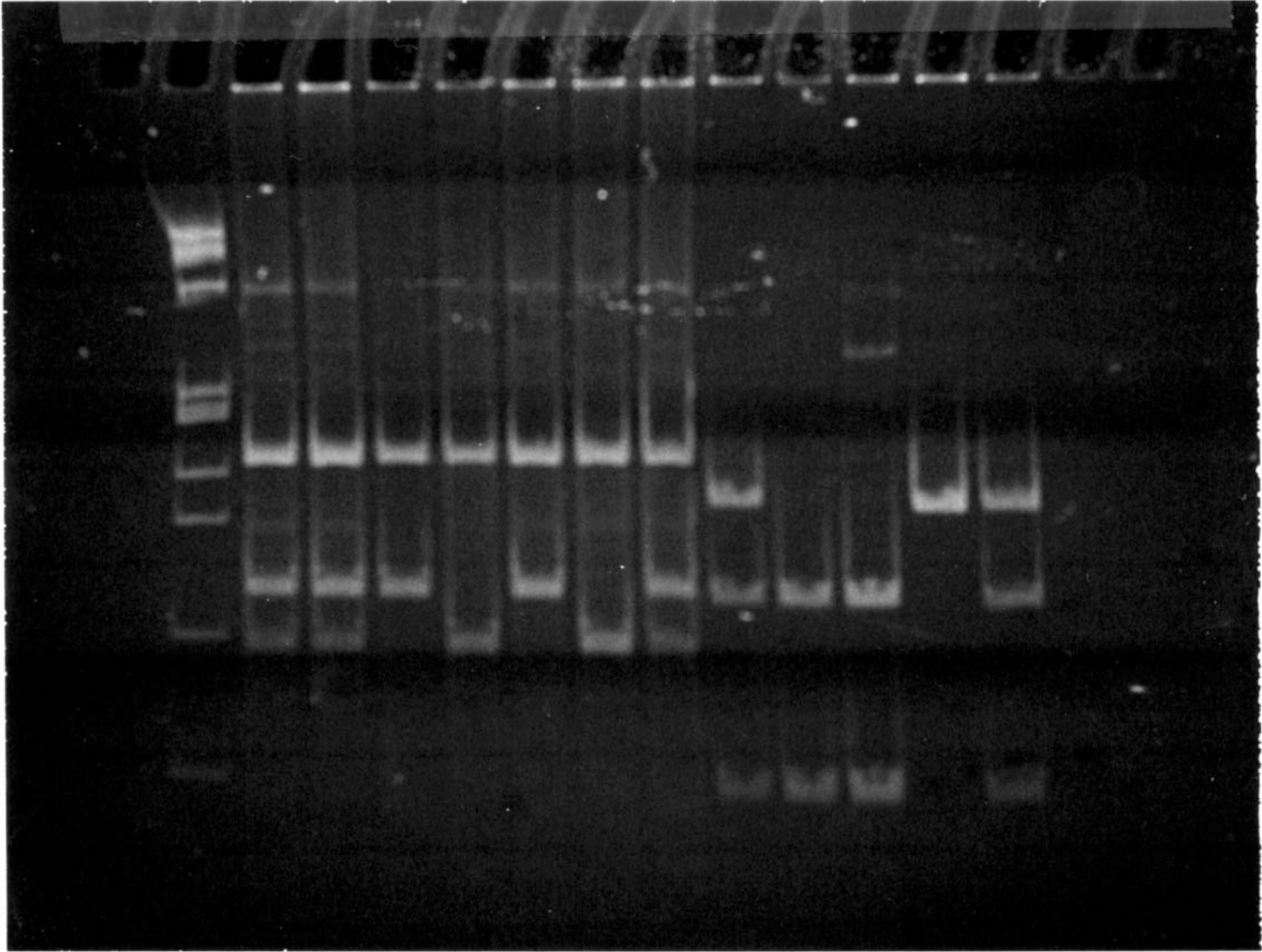


# Mutation

A permanent heritable change in the sequence of genomic DNA

- **Can be clinically significant**
- **Important mechanism of population variation**
  - ◆ **Negative – disease**
  - ◆ **Benign – blue vs. brown eyes**
  - ◆ **Positive – sickle cell trait and malaria**

737 738 739 740 741 742 743 745 746 747 748 749



*RsaI*

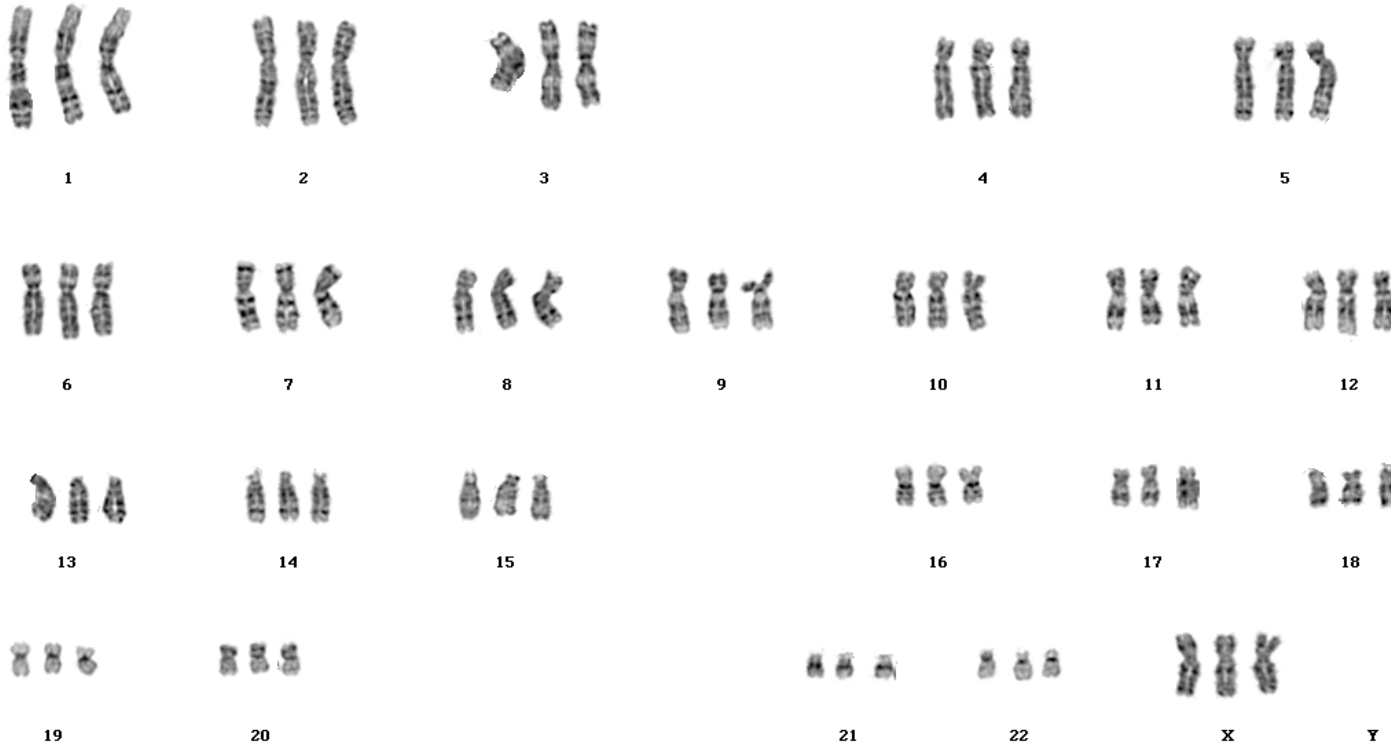
*BclI*

Molecular

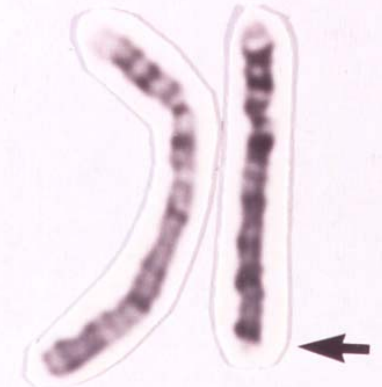


# Chromosomal Abnormalities

SUNY Upstate Medical University



## Structural



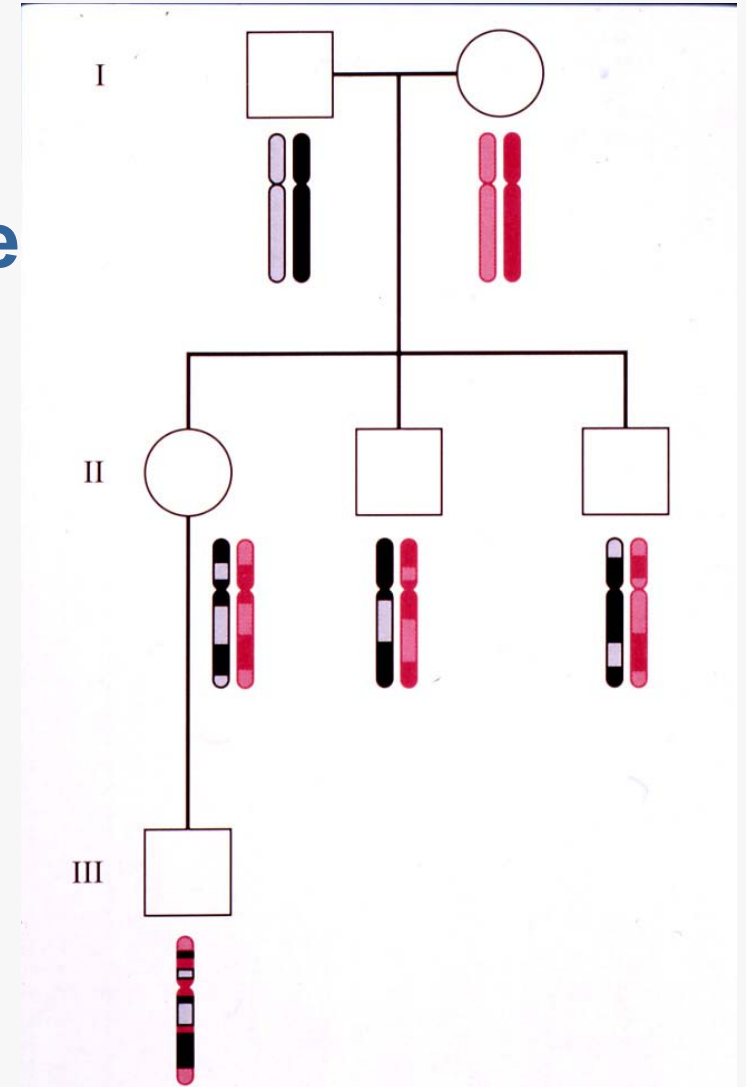
del(4)(q33)

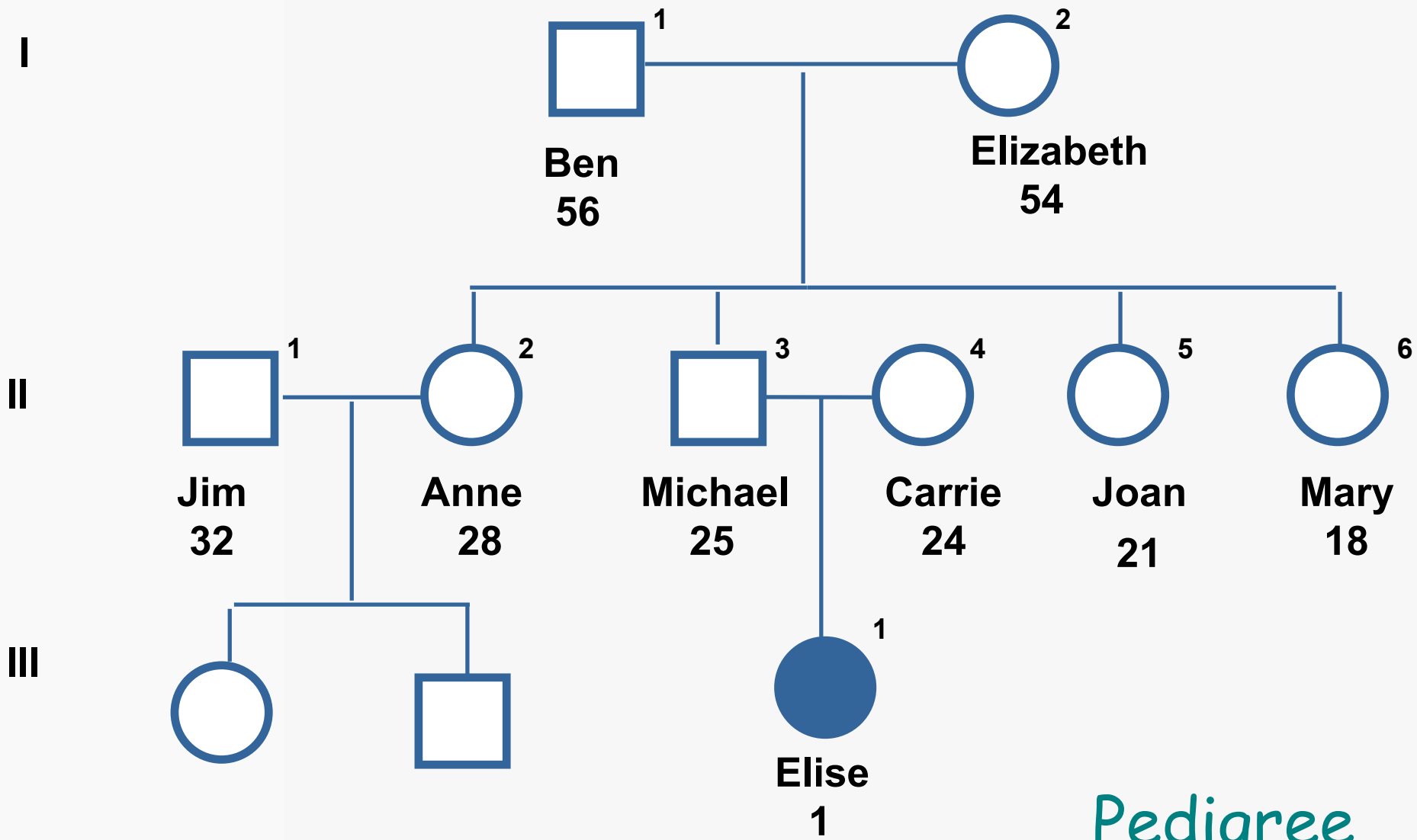
## Numerical



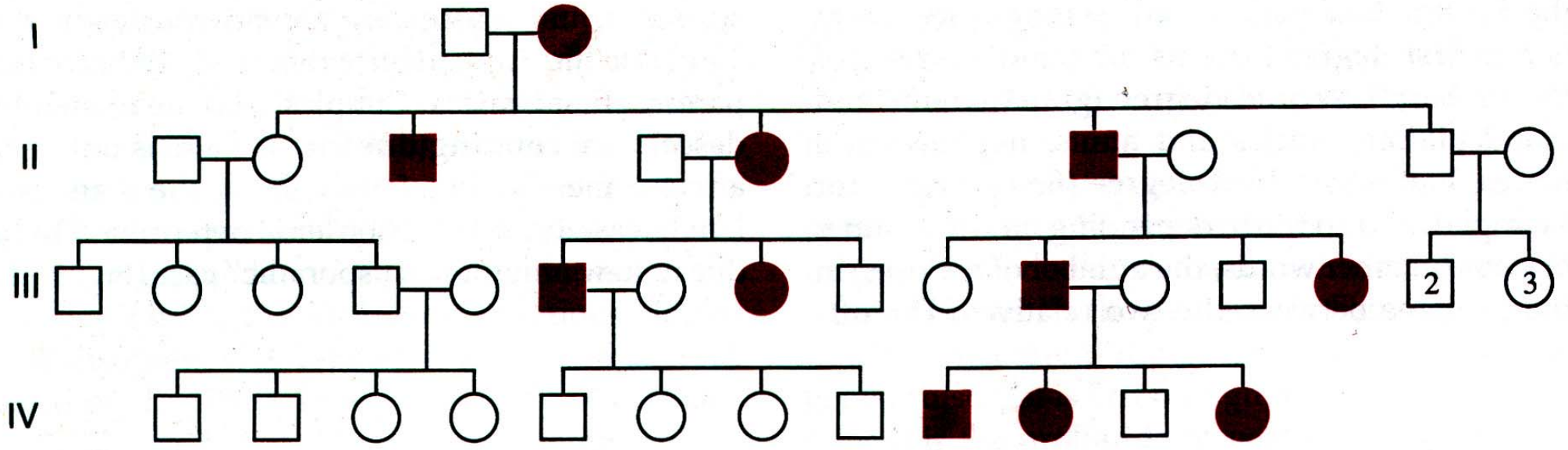
# Patterns of Inheritance

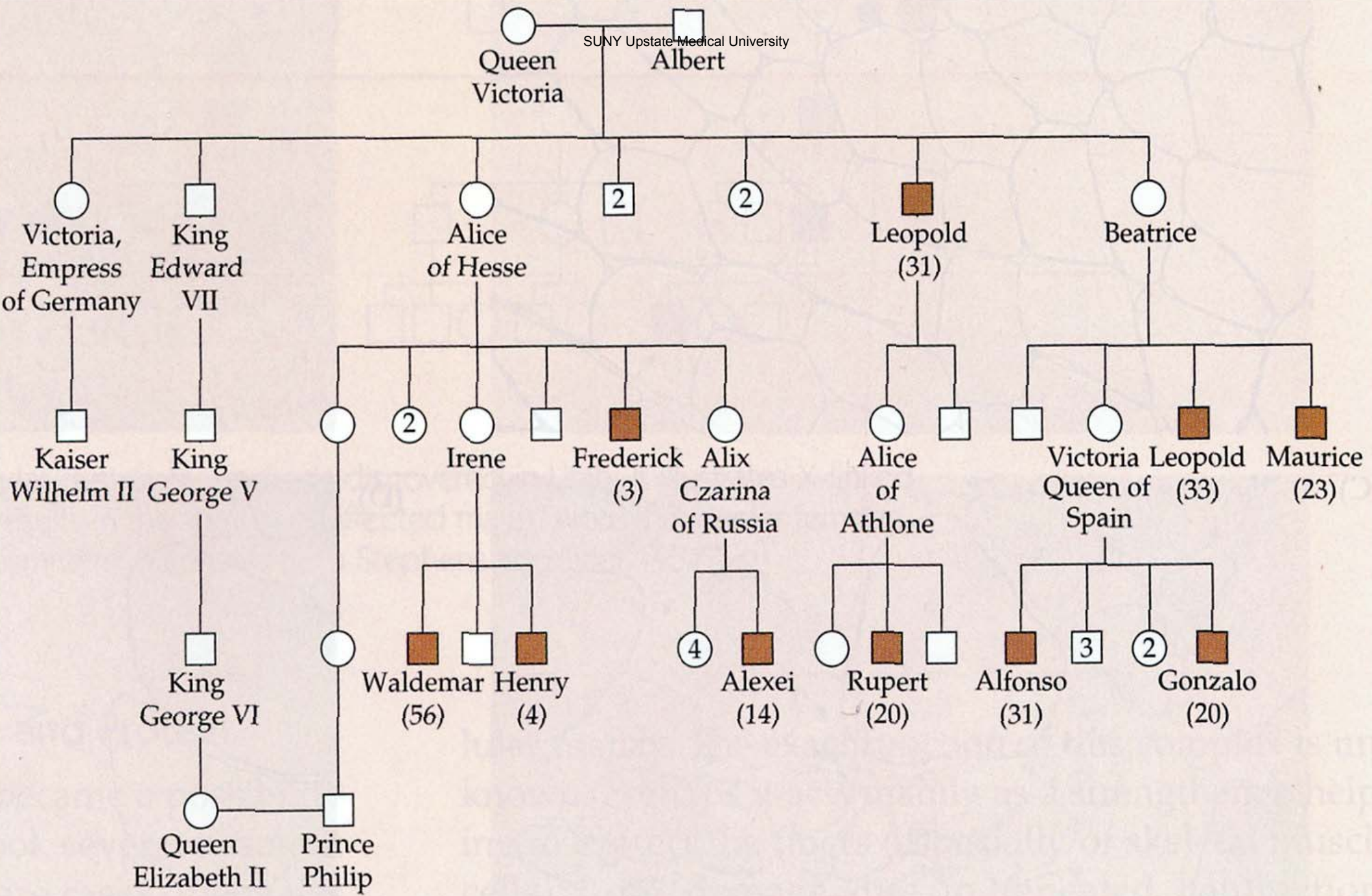
- **Dominant vs. Recessive**
- **Autosomal vs. X-linked**



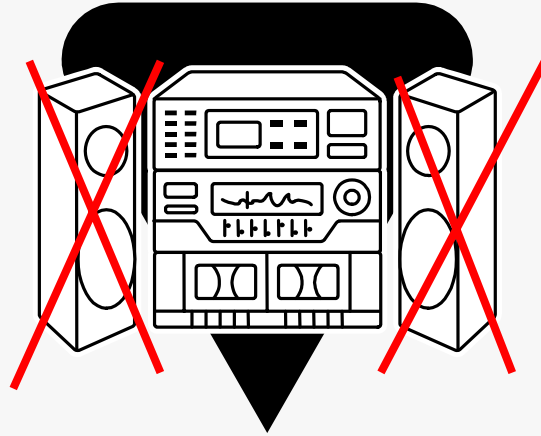


Pedigree

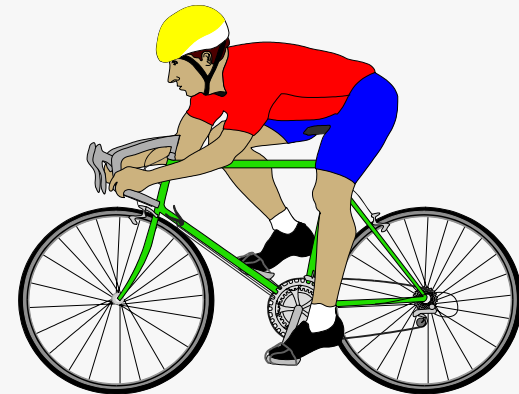




**Recessive: only expressed when 2 mutations are present**



**Dominant: expressed with a single mutation**

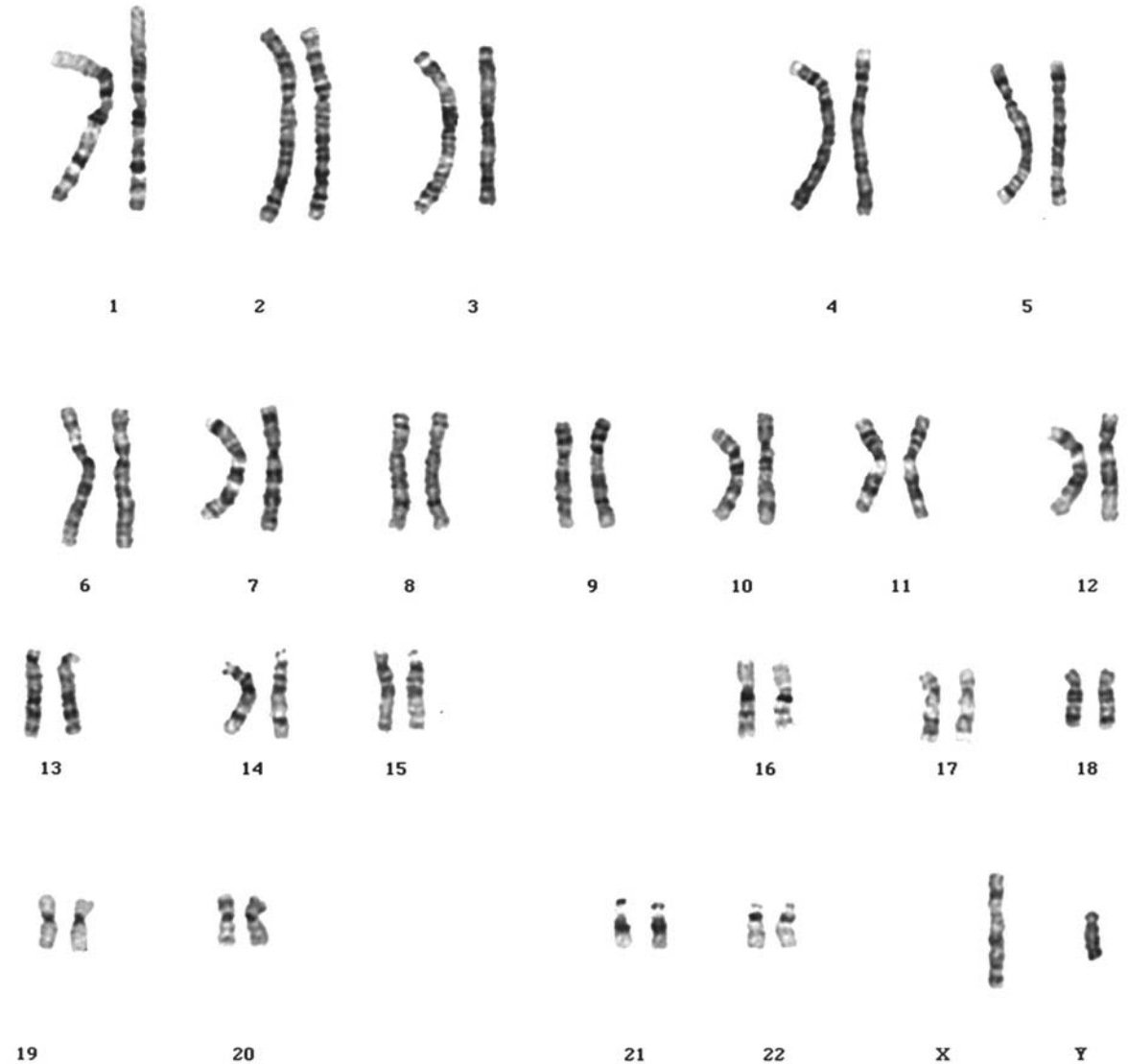


# Autosomal

- Males and females equally likely to be affected

# X-linked

- males more commonly affected
- no male to male transmission

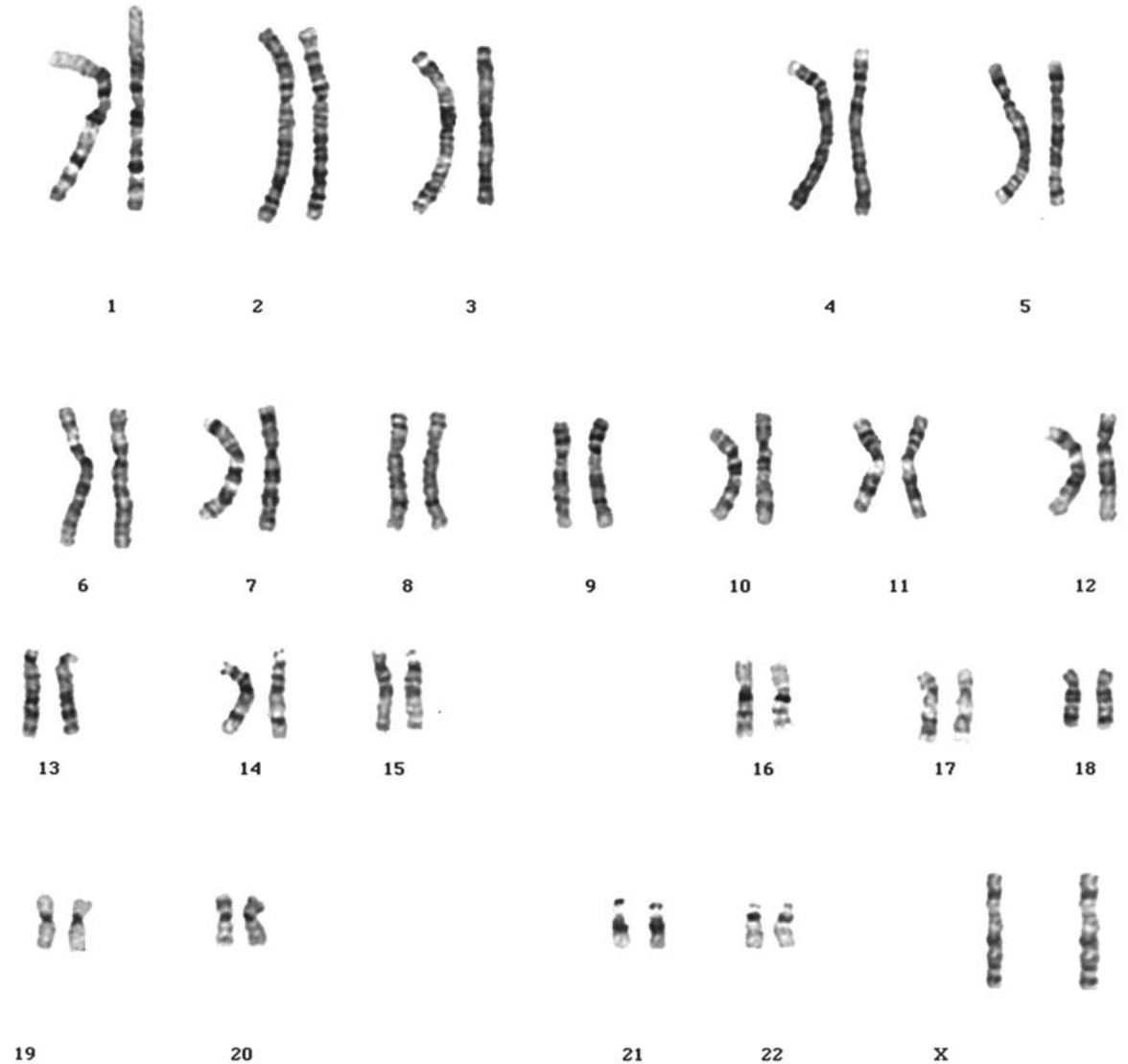


# Autosomal

- Males and females equally likely to be affected

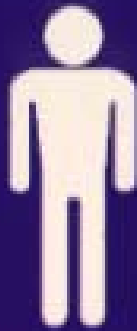
# X-linked

- males more commonly affected
- no male to male transmission



# Dominant

Affected Father



Normal Mother



D d

d d

50% risk

D d

d d

D d

d d



Affected Son

Normal Daughter

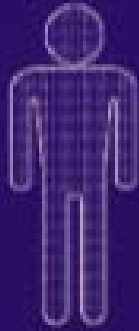
Affected Daughter

Normal Son

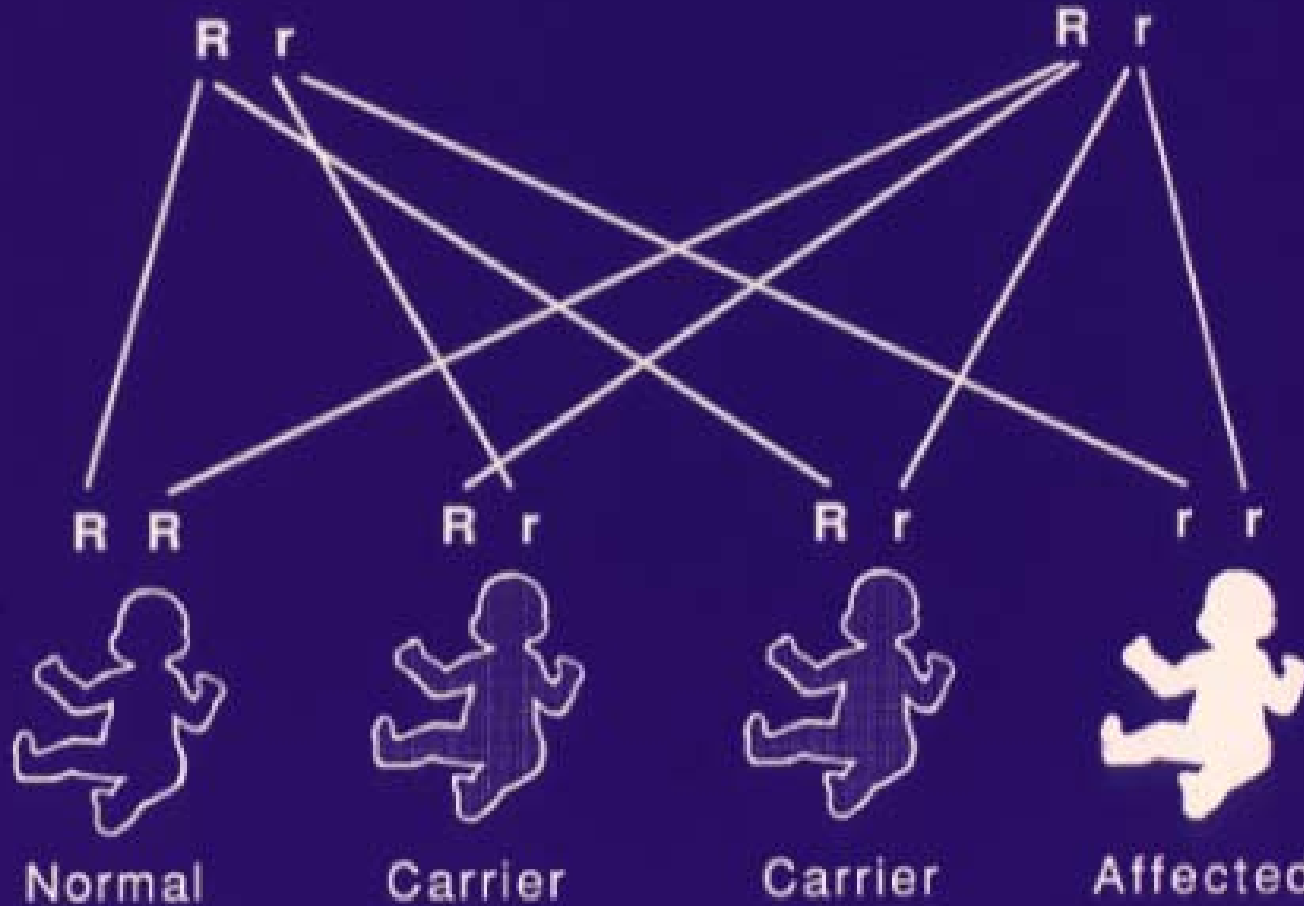


# Recessive

Carrier Father



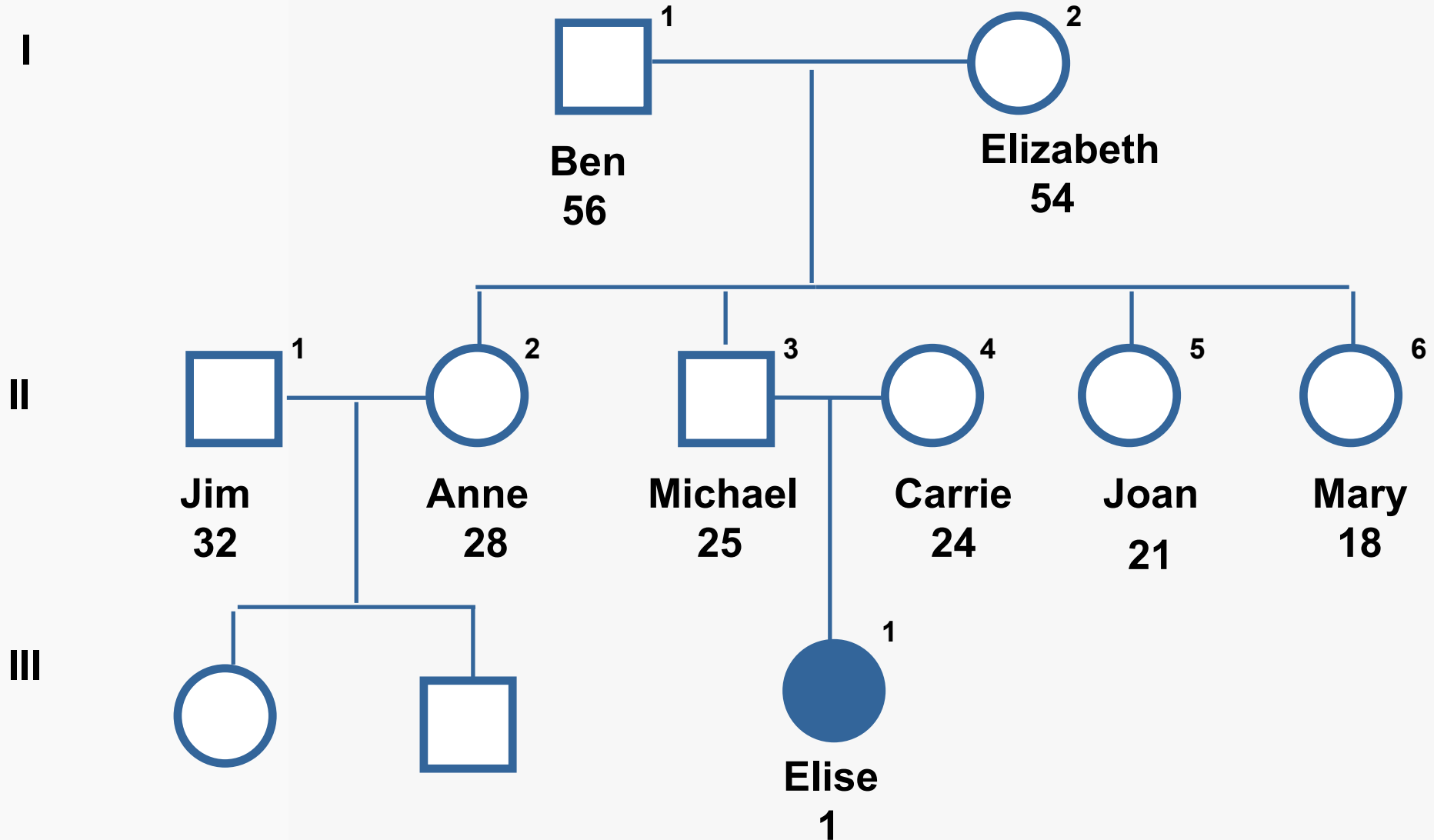
Carrier Mother



25% risk

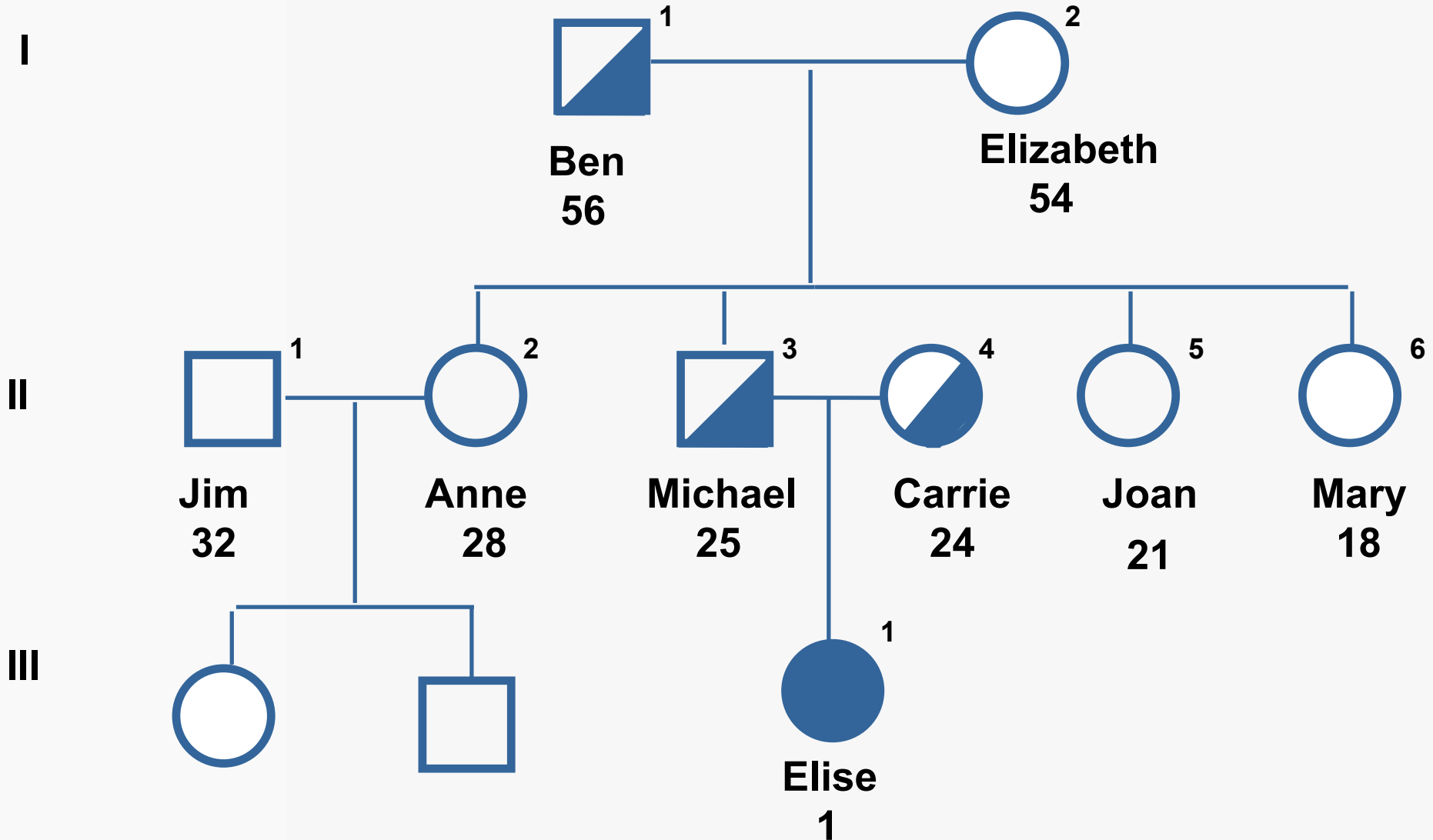
# Autosomal Recessive

SUNY Upstate Medical University



# Autosomal Recessive

SUNY Upstate Medical University

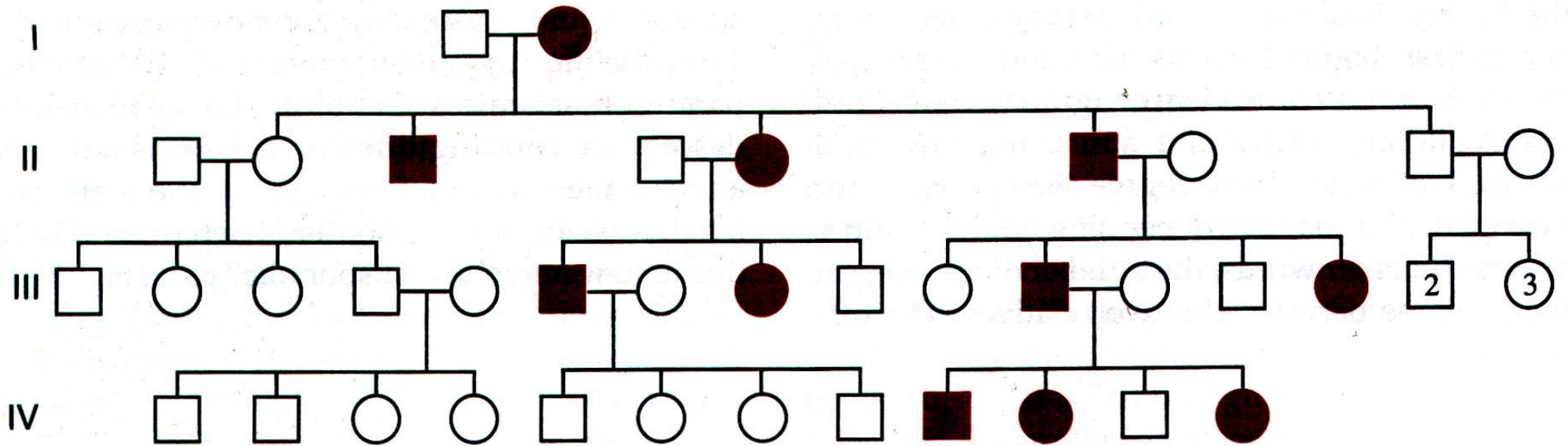




# Autosomal Recessive

- ❖ **Blue eyes**
- ❖ **Sickle Cell Anemia**
- ❖ **Cystic fibrosis**
- ❖ **Tay Sachs disease**

# Autosomal Dominant

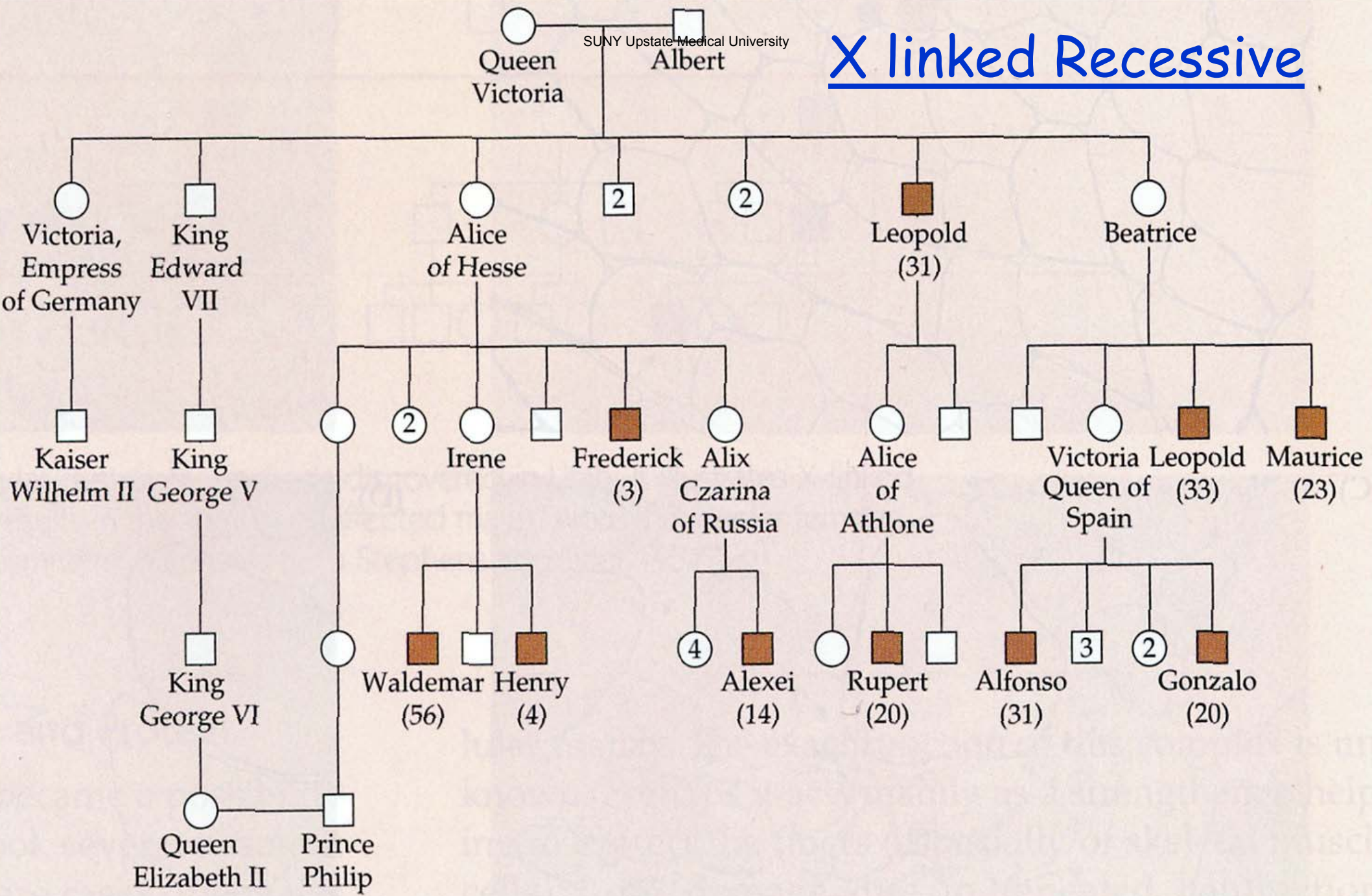


# Autosomal Dominant

- ❖ **Huntington disease**
- ❖ **Achondroplasia**
- ❖ **Neurofibromatosis**
- ❖ **Polydactyly**



# X linked Recessive





# X-linked Recessive

- ❖ **Hemophilia A/B**
- ❖ **Duchenne/Becker muscular dystrophies**
- ❖ **Colorblindness**
- ❖ **Hunter syndrome**



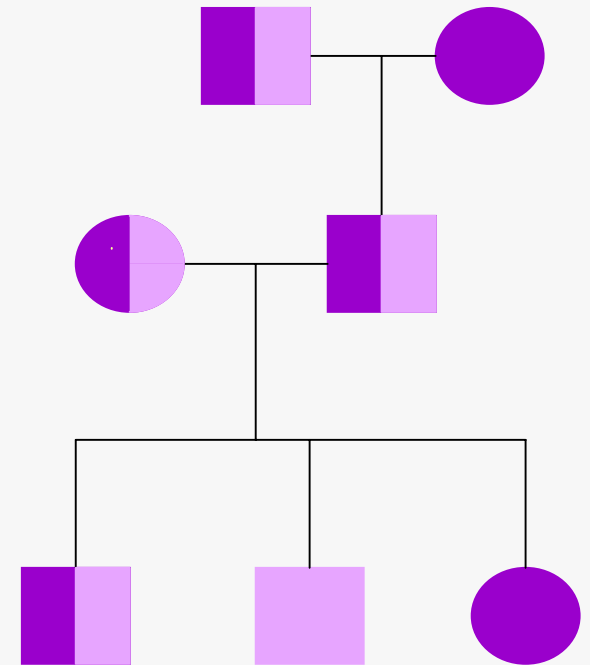


# Inherited vs. Acquired Disease

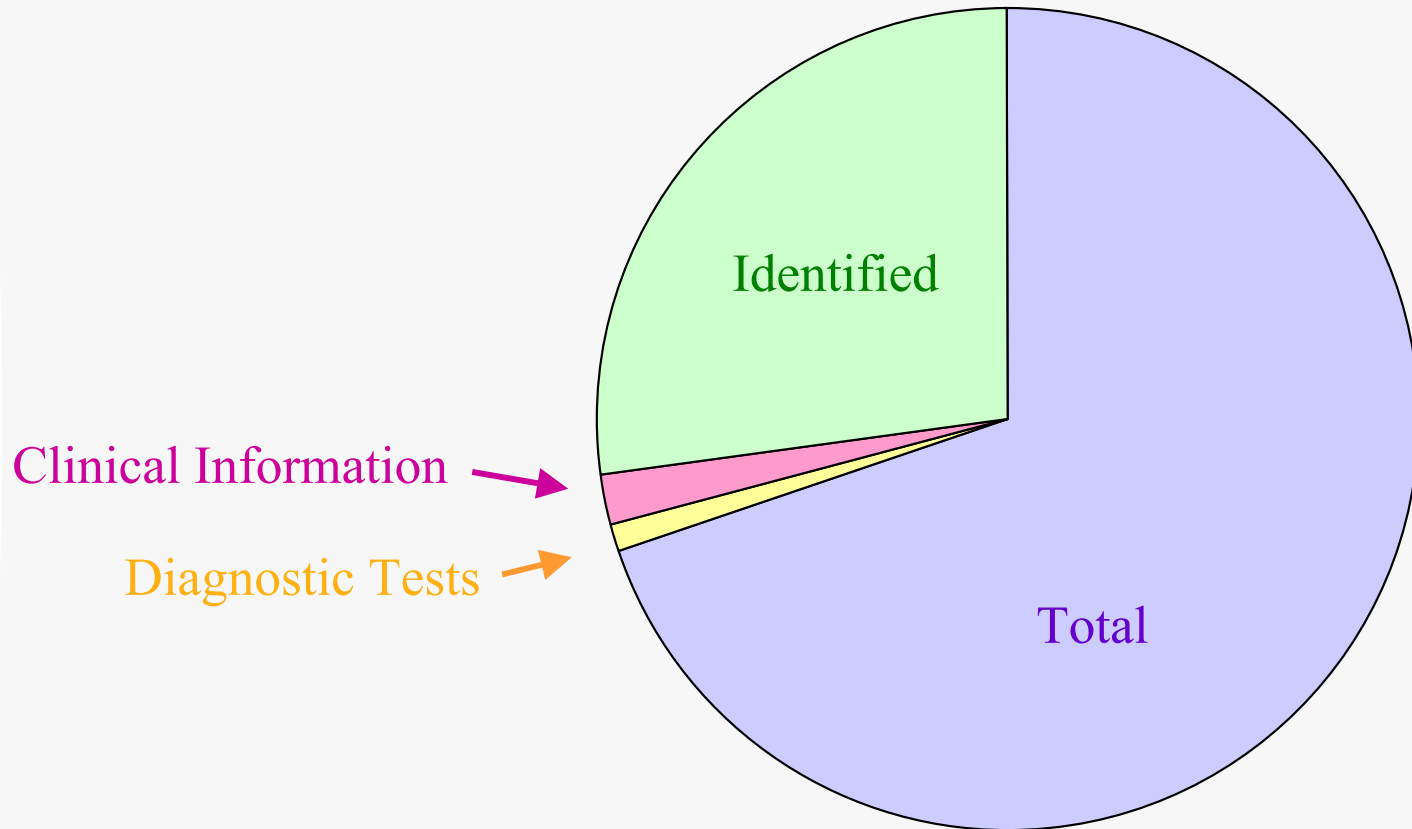
- ❖ Inherited gene complement – genes transmitted from one or both parents
  - ◆ Typically called the constitutional genome
- ❖ Acquired gene complement – a subset of cells in an individual that arose by clonal propagation from a single mutation in one cell

# Goals of Medical Genetics

- ◆ Understand the inheritance of genes and disease
- ◆ Investigate genes associated with disease
- ◆ Identify disease causing mutations
- ◆ Apply knowledge to treat disease

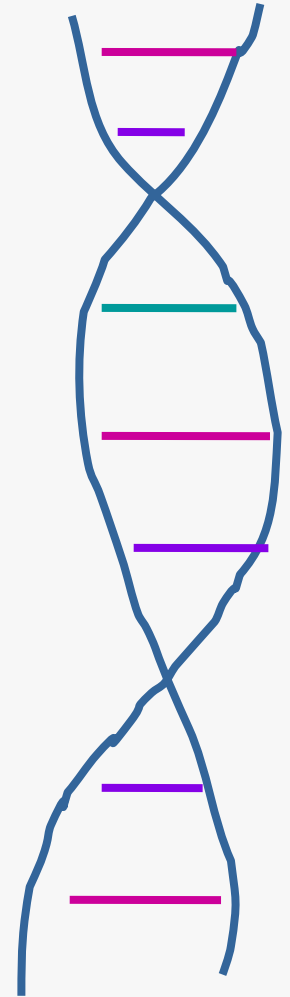


# Human Genes



# Human Genome Project

- ❖ **Goal: Sequencing of entire human genome**
- ❖ **Draft copy now done**
- ❖ **List of bases but little functional data**
- ❖ **Next step – figure out what it means!**



1 CTCGTGCCGCTTCGCACAGCCCGGAGACCGGTTCGGTGTGGAGTTTGTAGTGGCAGACCCTGTGCTC  
 67 GTTCCCGAGCGACGGAGGGTGGACTCGGCCAGAGGTGGGCTCGAGCCCCGCACCTCCTGCGCCGCC  
 133 ACCCCATGCTCCCTGACCGGGTGCAGAGCTGGACCTGGCCGAAGGTGGGCCGGGGTTGAAAGAAGCGGC  
 199 CTGCATGACCCCGGGGACCCACCGCATCGCCTGGAAGAGCCCACTCTCCCTGGAAGGAAGACCA  
 265 TCCCTGAAGAGGATGACTGAGACGTTATGGGCCACGCACTGTGTGTCTGCTCCCGGGGAAGTGTCA

M G H A L C V C S R G T V 13

331 TCATTGACAATAAGCGTTACCTCTTCGTCCAGAAATGGGGGAAGGTGGATTTCAGCTATGTGGACC  
 I I D N K R Y L F V Q K L G E G G F S Y V D 35

397 TAGTGGAGGGCTTGCATGATGGACACTTCTACGCCCTGAAGCGGATCCTGTGCCATGAGCAGCAAG  
 L V E G L H D G H F Y A L K R I L C H E Q Q 57

463 ACCAGGAAGAAGCCCAACGAGAGGCAGAGATGCATCGCCTCTTCCAGCATCCCAACATCCTTCGCC  
 D Q E E A Q R E A E M H R L F Q H P N I L R 79

529 TCATGGCTTACTCTCTGAAAGAACGAGGTGCTAAGCATGAAGCCTGGCTGCTGCTGCCCTTCTTCA  
 L M A Y S L K E R G A K H E A W L L L P F F 101

595 AGAAAGGTACTGTGGAATGAGATAGAAAGGCTGAAGGACCAAGGCAGCTTCTGACTGAAGACC  
 K K G T L W N E I E R L K D Q G S F L T E D 123

661 AGATCCTGCCGCTTGTGCTGGGTATCAGCAGAGGCCCTTGAGGCTATTCATGCCAAAGGTTATGCAC  
 Q I L P L L L G I S R G L E A I H A K G Y A 145

727 ACAGGGACTGAAAGCCCAACCAATATTTTGTGTTGGTATGAGGGGAGCCAGTTTAAATGGACTTGG  
 H R D L K P T N I L L G D E G Q P V L M D L 167

793 GTTCTATGAATCAAGCATGCATTCAGTGGAGGGCTCTCGCCAGGCACTAGCTCTTCAGGACTGGG  
 G S M N Q A C I Q V E G S R Q A L A L Q D W 189

859 CAGCTCAGCGGTGCACCATCTCCTACCGGCACCTGAACTTTTTCGTGCAAAGCCACTGTGTCA  
 A A Q R C T I S Y R A P E L F S V Q S H C V 211

925 TCGATGAGCGGACTGATGTCTGGTCCCTAGGCTGTGTCTTATGCCATGATGTTTGGGGGAAGGCC  
 I D E R T D V W S L G C V L Y A M M F G E G 233

991 CTTACGATATGGTGTTCAGAAGGGTGACAGTGTGGCCCTTGCTGTGAGAATGAACTCAGCATCC  
 P Y D M V F Q K G D S V A L A V Q N E L S I 255

1057 CACAAAGCCCCAGGCATCTTTCAGCATTGCGACAGCTATTGTCTTCTATGATGACTGTGGACCCCC  
 P Q S P R H S S A L R Q L L S S M M T V D P 277

1123 AGCAGAGGCTCACATCCCTGCTCCTCAGTCACTGGAGGCATTGCAGCCACCAGCTCCTGGCC  
 Q Q R P H I P V L L S Q L E A L Q P P A P G 299

1189 AGCACACCACCAATCTGATCAAATCAGTGGACATATTGGGAAGATGACCTTGAAGTGGCTTTCA  
 Q H T T Q I \* 305

1255 TCCCTCATTGGAACCTCTCCATTCTCCAGGATGGCTCTCACAGCTAGTGGCAAGGATAGTGGGT  
 1321 CCTGTATATTCTGCCCTTCTACCCCAATACCTGGGCAAGGAACCTAGGGTGTAGTTGGGGGAAAAAT  
 1387 GAAACAGAAAAATATGGCTCAAAGCTAGGCTGCTGGGTGCACATCTCATTTCTGTCTCCAGATCTGGG  
 1453 AGCAGGAGAAATACATAAAAAGGAGATAAAGTAAAAACAGACAAAAAATAAAAAAAAAAAAAA

# Cloned Genes

Cystic fibrosis

Phenylketonuria

Duchenne/Becker dystrophy

Prader-Willi syndrome

Fragile X syndrome

Hemophilia A,B

Marfan syndrome

DiGeorge syndrome

Familial hypercholesterolemia

Retinoblastoma

Medullary thyroid cancer

Williams syndrome

Tay Sachs disease

Myotonic dystrophy

Angelman syndrome

Huntington disease

Sickle cell anemia

Osteogenesis  
imperfecta

Hunter syndrome

Familia polyposis coli

Neurofibromatosis

Breast and ovarian  
cancer



# Genetic Testing

- Prenatal diagnosis
- Newborn screening
- Cytogenetics
- Cancer diagnosis
- Blood tests (ABO, Rh, histocompatibility)
- DNA fingerprinting



# Clinical Laboratory Testing

- **Cytogenetics**
  - \* Karyotype analysis
  - \* FISH





# Clinical Laboratory Testing

- **Molecular - mutation analysis**

Fragile X syndrome

Huntington disease

Duchenne muscular dystrophy

Cystic fibrosis

Sickle cell anemia

Breast cancer



# Clinical Laboratory Testing

## Biochemical - Enzymes and proteins

Tay Sachs

PKU (phenylketonuria)

Galactosemia



# Benefits of Genetic Diagnosis

- ★ **Confirm a diagnosis**
- ★ **Identify proper treatment**
- ★ **Provide a basis for risk assessment**
- ★ **May eliminate the need for other, more invasive testing**

# Hereditary Hemochromatosis

- ◆ Iron storage disorder
- ◆ Incidence: 1 in 400
- ◆ Carrier frequency: 1 in 10
- ◆ Can lead to severe liver damage and death
- ◆ Other complications include diabetes, dark pigmentation of the skin, heart failure
- ◆ Difficult to diagnosis

# Hereditary Hemochromatosis

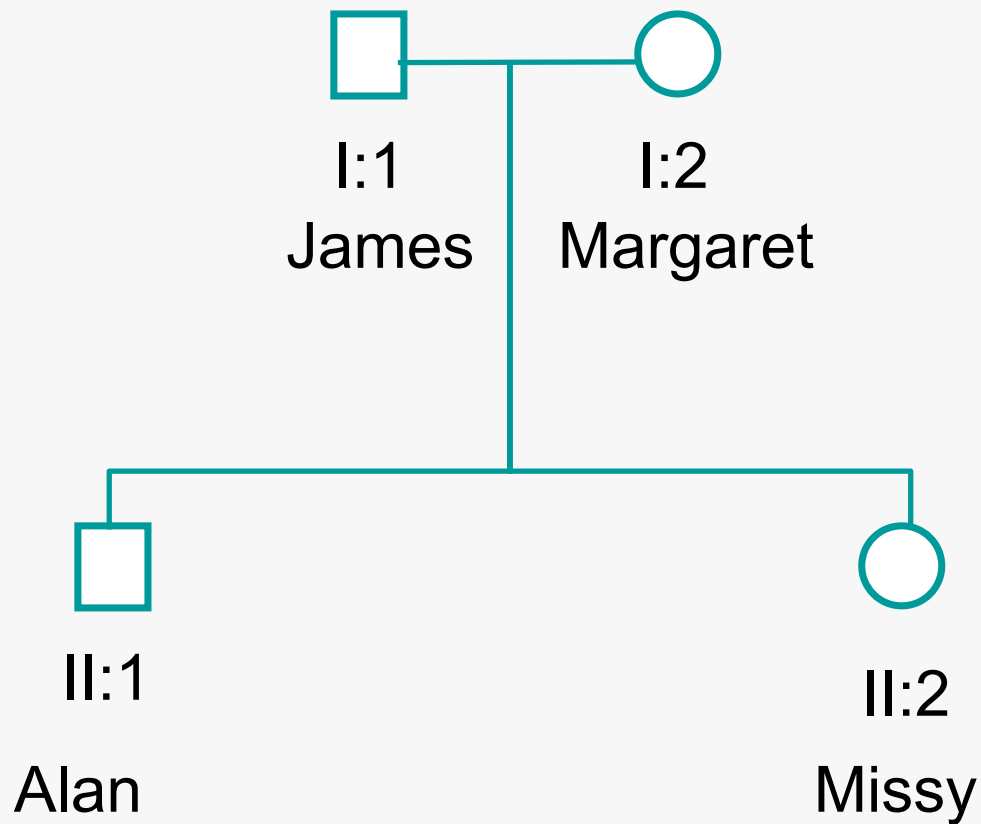
- ◆ *Get a direct diagnosis of disorder*
- ◆ *Reduce need for liver biopsy*
- ◆ *Identify at risk individuals earlier in life*

# Limitations of Genetic Tests

- ◆ Requires knowledge of disease specific mutations
- ◆ May not be possible to identify all mutations
- ◆ Unable to tell age of onset for late onset diseases

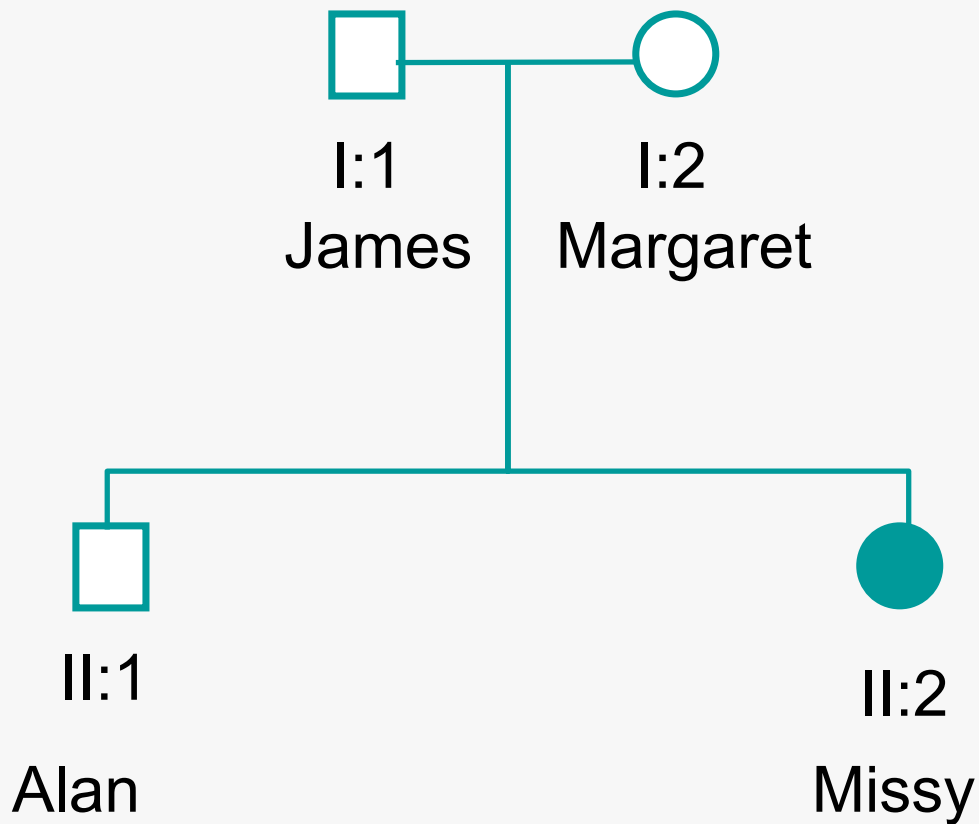


# Example : Cystic Fibrosis



Born with  
multiple abnormalities

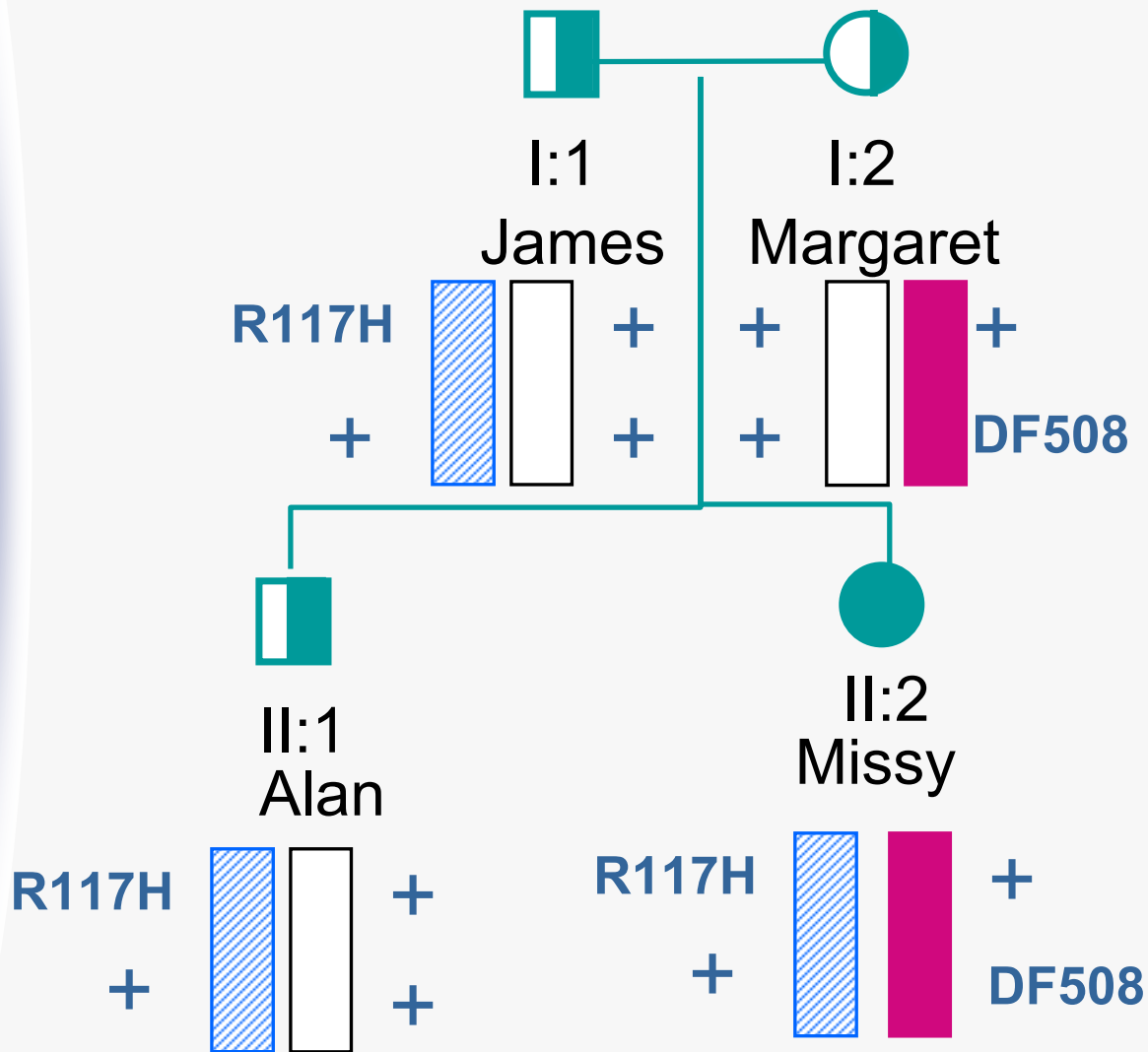
# Cystic Fibrosis



Clinical diagnosis  
reveals: CF

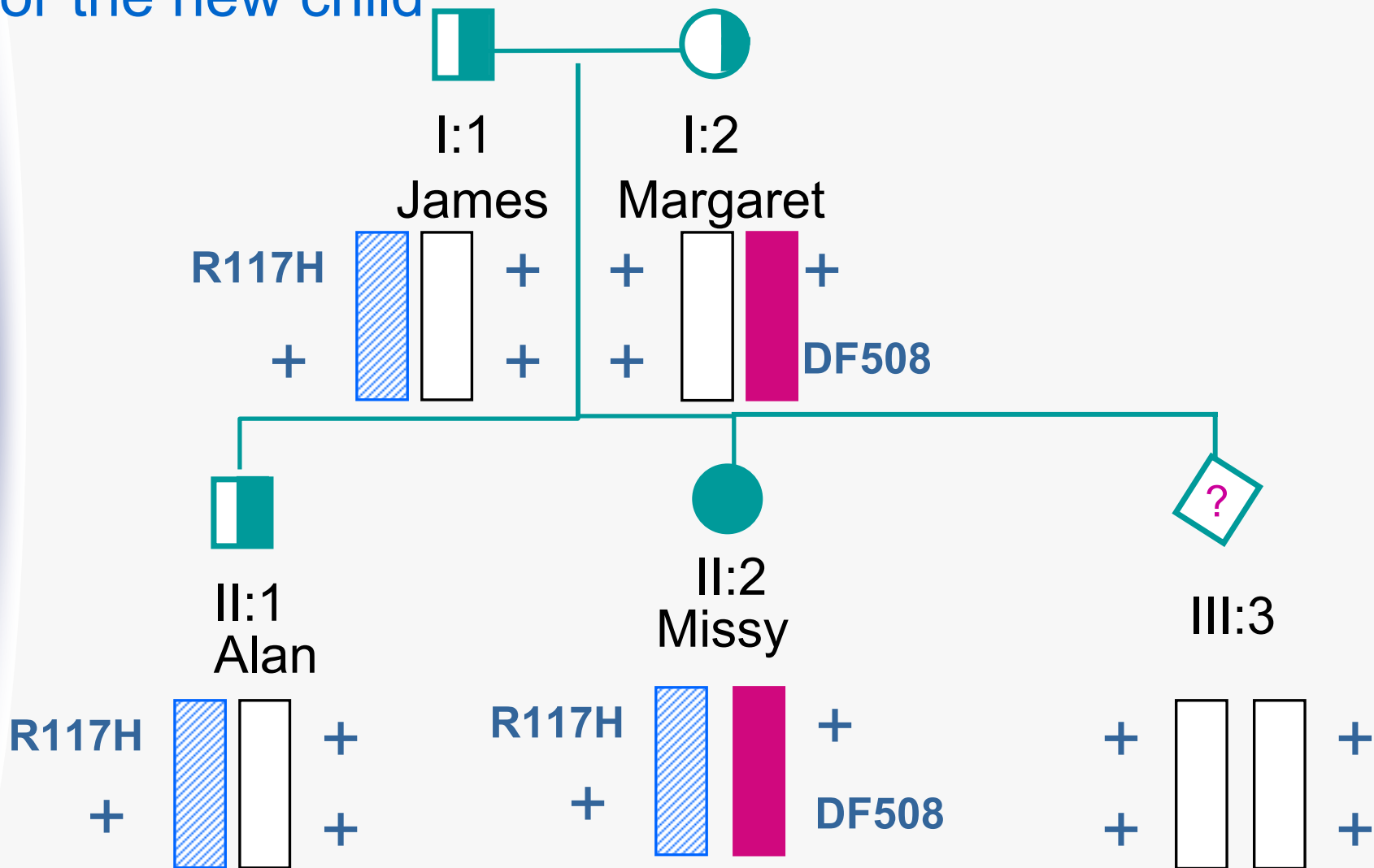


# Molecular testing: Cystic Fibrosis

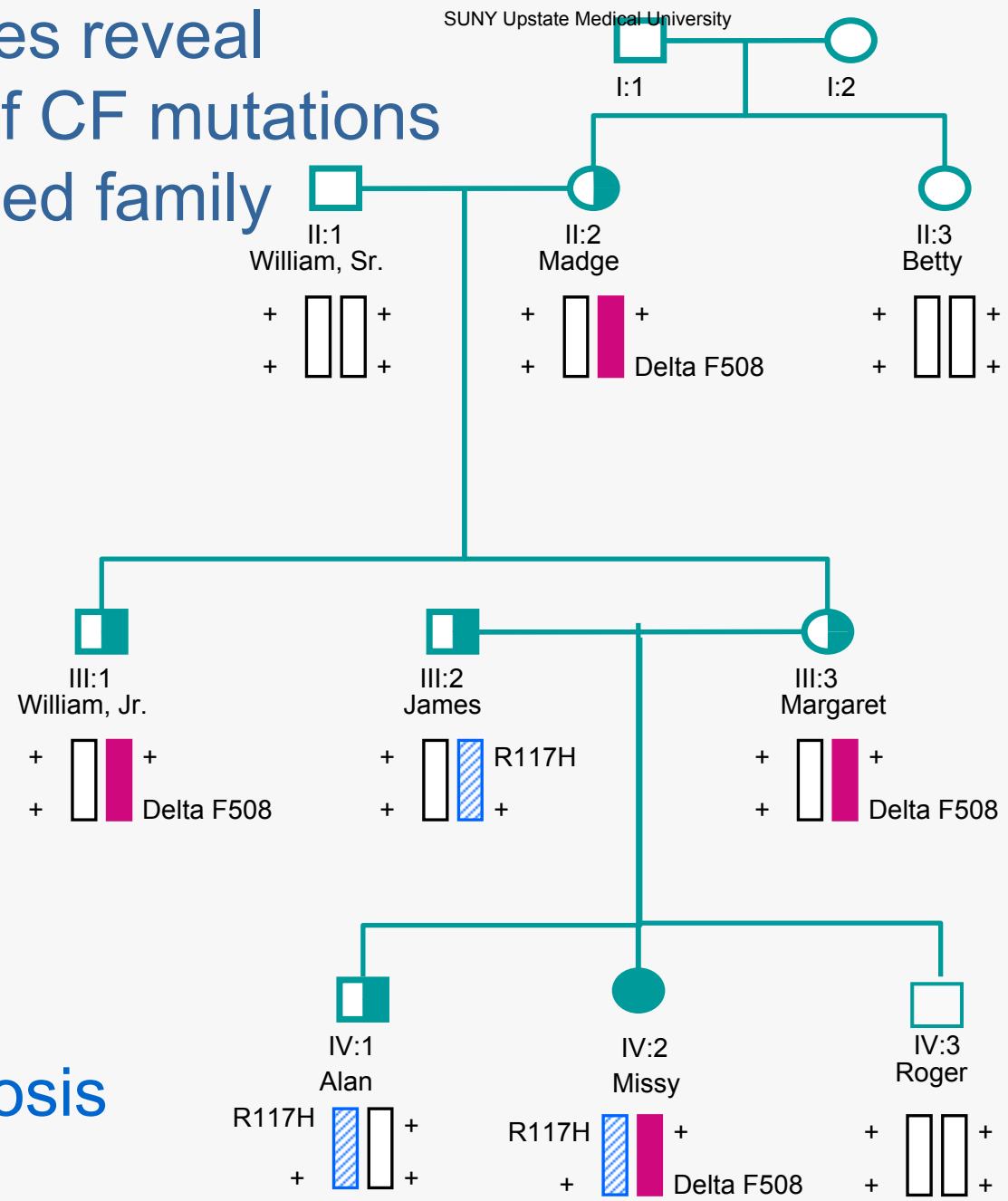


# Cystic Fibrosis

Further information can now be obtained for the new child



# Further studies reveal Inheritance of CF mutations In the extended family



Cystic Fibrosis



# New York State Regulations

- ◆ **Patients must be informed of**
  - ★ the type of test being done
  - ★ the limitations of the test
  - ★ what benefit the results will have for them
  - ★ What ramifications there may be with respect to insurance coverage, etc.
- ◆ **Patients must sign an informed consent**
- ◆ **If no consent is obtained, no testing can be done**



# New York State Regulations

- ◆ All specimens from NYS residents must be processed by a laboratory that has been inspected and approved by the NYS Dept. of Health
- ◆ If genetic testing is performed by any laboratory that has not been approved, the results cannot be used for diagnosis and cannot be provided to the physician or the patient/subject, unless.....



# New York State Regulations

## “Orphan Disease Exemption”

- ◆ If testing for a genetic disorder is only done by a non-permitted laboratory, a request can be submitted to the NYS DOH to use that laboratory’s results for clinical purposes



# IRB Protocols

These must be written to meet:

- ◆ **IRB regulations**
- ◆ **NYS regulations**
- ◆ **HIPAA regulations**



# IRB Protocols

## When do you need to be concerned about genetic regulations???


15. B. Does this study involved Genetic Testing? Yes No

If yes, answer the following question:

1. Is the genetic variant inherited? Yes No

If YES (the variant IS inherited), additional consent document language is required . (See template for genetic research on the IRB web site.)



A decorative vertical bar on the left side of the slide, featuring a colorful triangle (purple, blue, green) pointing right. The bar has a blurred, multi-colored background.

## IRB: Research subjects participating in an IRB approved research study involving genetic testing must be informed about:

1. Whether or not they or their physician will be told the test results.
2. The risk to insurability (the ability to get/keep insurance)
3. Potential discovery of non-paternity (genetic tests may prove “dad” is not the biological father).
4. If genetic counseling is provided (who pays?).
5. If a portion of the sample collected will be stored for future studies.



# Research applications

What is *genetic testing*?

A study that investigates human DNA, chromosomes, genes, or gene products, including DNA profile analysis.



# Research applications

## Inherited vs. *Acquired?*

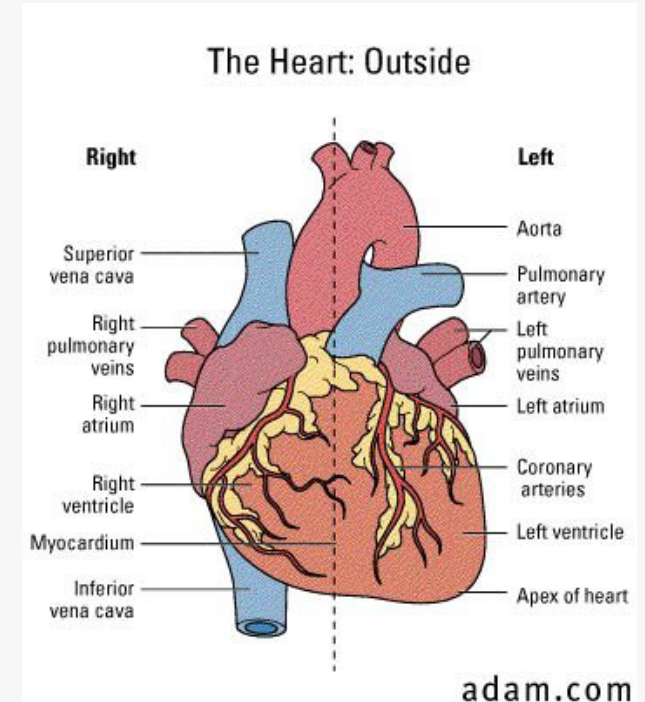
Only those disorders arising solely from a somatic mutation or mutations are exempt from current regulation.

Examples:

Leukemia, lymphoma, sporadic breast cancer, other types of sporadic solid tumors

# Examples of types of studies not included

- ◆ Techniques
- ◆ Devices
- ◆ Drug treatment protocols





# What is included

- ◆ Delineation of disease
- ◆ Population genetics and risk analysis
- ◆ Gene Therapy
- ◆ Pharmacogenetics
- ◆ Most family studies



# Research Applications - Delineation of Disease

- ◆ Multiple members of several extended families with a known genetic disorder
  - ★ Find the gene(s) responsible
- ◆ Multiple members of an extended family and/or multiple families with the same set of clinical abnormalities
  - ★ Is this a known clinical entity or can we define a new disease?
  - ★ What gene(s) is/are causing this to occur?



# Example 1 - Drug Studies

- ◆ Random patients, same disease – comparison of drug effectiveness **OK**
- ◆ Random patients with a known genetic disease (CF) – comparison of drug effectiveness **OK**
- ◆ Family members with and without a particular disease – comparison of drug effectiveness **Genetics**



## Example 2 - Drug Studies

Random patients, same disease, one drug

- ◆ Monitoring drug metabolism **OK**
- ◆ Using DNA studies to show the relationship between certain sets of genes and how the drug is metabolized.

**Requires genetic consent**



# Pharmacokinetics vs. Pharmacogenomics

- ◆ Pharmacokinetics - rate of drug metabolism
- ◆ Pharmacogenomics - the relationship of genes to drug metabolism



## Example 3 - Complex protocols

- \* Collection of blood/tissue for genetic studies is one element of protocol
- \* Different studies are being done at different sites.
- \* Local study only ascertains subjects and collects samples to be sent elsewhere.

Requires informed consent with genetics language HERE



## Example 4 - Cancer

- ◆ Leukemia/Lymphoma - acquired
  
- ◆ Solid tumors
  - ★ Treatment protocols, delineate clinical features for diagnosis, length of survival **OK**
  - ★ Inheritance of mutations, relationship of those mutations to severity of disease, relationship of those mutations to others that are related to disease **Genetics**

# Example 5 - Known Genetic Disease

- ◆ Protocol is to further delineate the disorder to better understand it clinically
- ◆ Affected individuals and their unaffected family members will be recruited
- ◆ All subjects will be given a test to confirm their clinical status

Must inform subjects of the nature of the testing

## Example 5 - Con't

- ◆ Protocol is to further delineate the disorder to better understand it clinically
  - ◆ Affected individuals and their unaffected family members will be recruited
  - ◆ All subjects will be given a test to confirm their clinical status - inform
  - ◆ The results of the testing will be provided to the subjects' family physicians
- 1) Must get genetic informed consent
  - 2) Must get "NYS DOH Orphan Disease Exemption"



# Conclusions

- ◆ **All IRB protocols must conform to IRB, NYS, and HIPAA requirements.**
- ◆ **Careful evaluation of the purpose of the study and the methods used must be done**
- ◆ **If the protocol includes genetic analysis of inherited genetic variants, subjects should be informed and appropriate language included in the IRB informed consent**