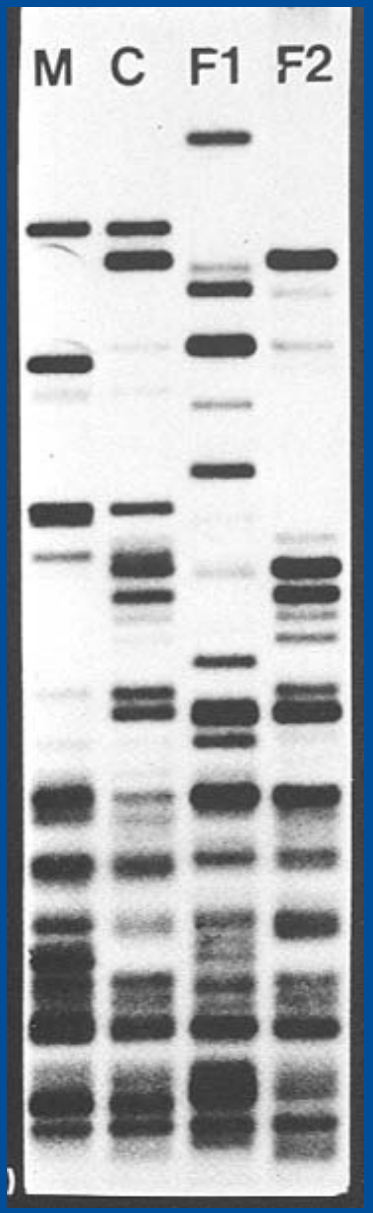
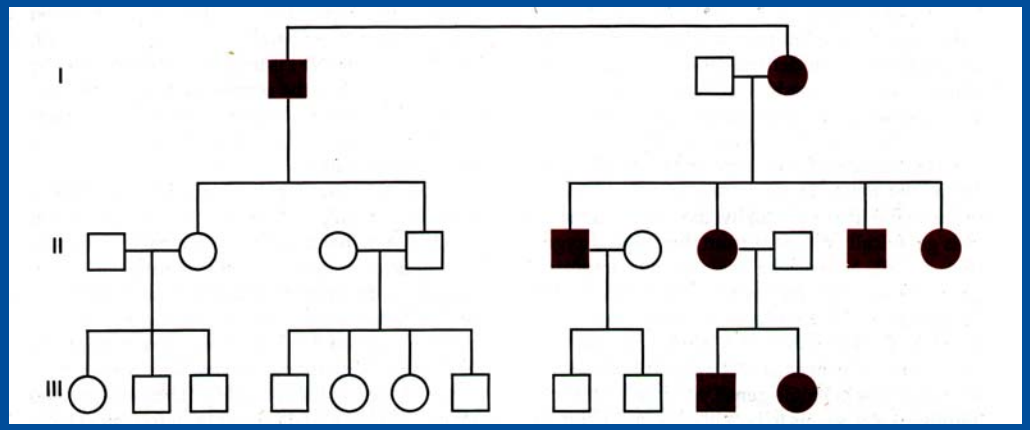
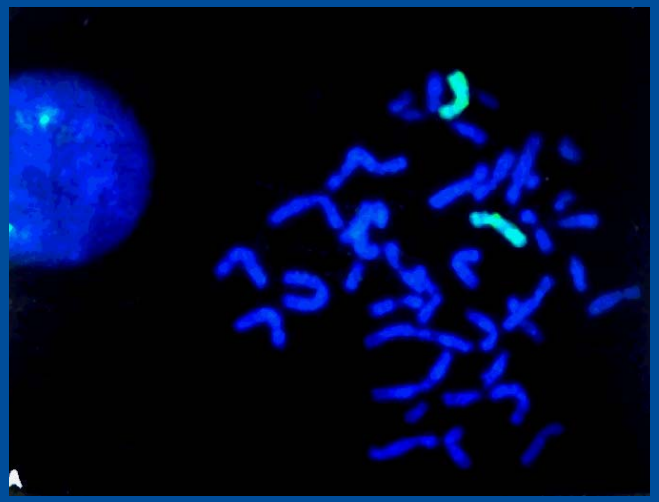
Genetic Testing: Understanding Definitions and Key Concepts

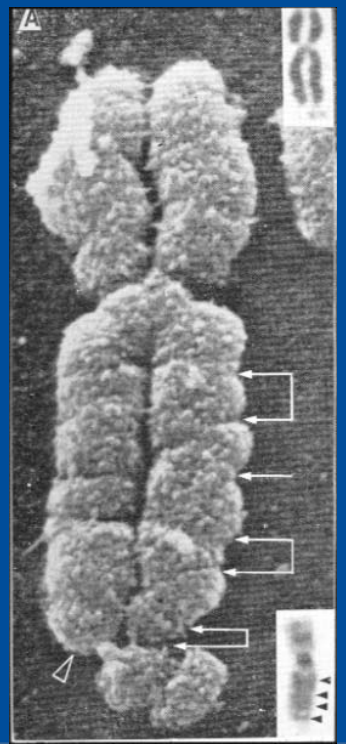
Constance K. Stein, PhD

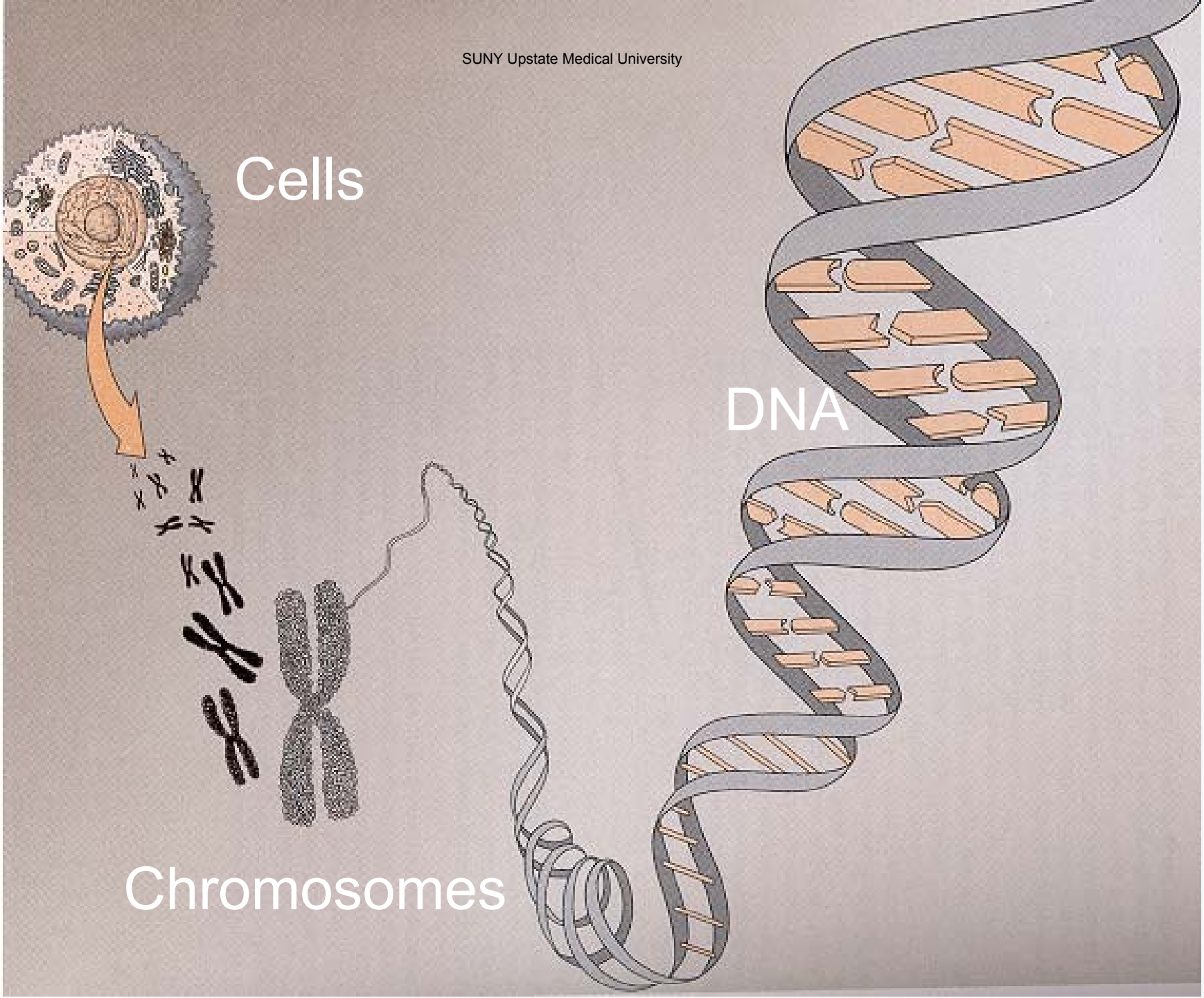
Genetics: the study of heredity





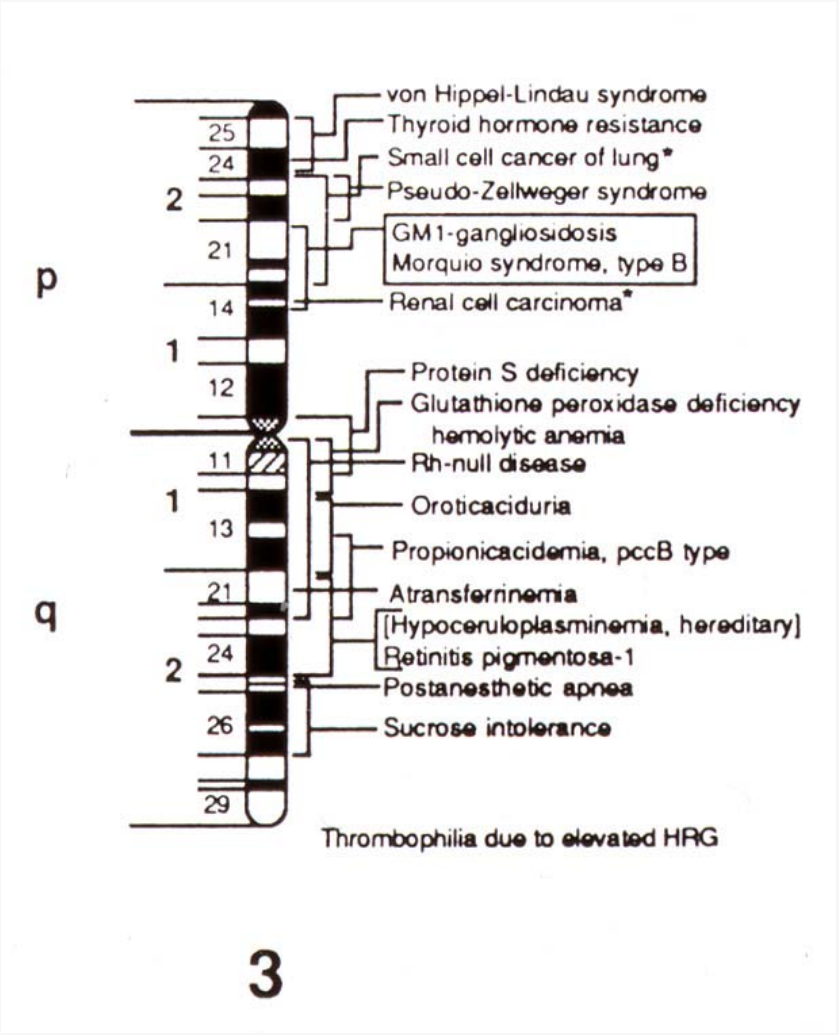





SUNY Upstate Medical University
Cells
DNA
Chromosomes

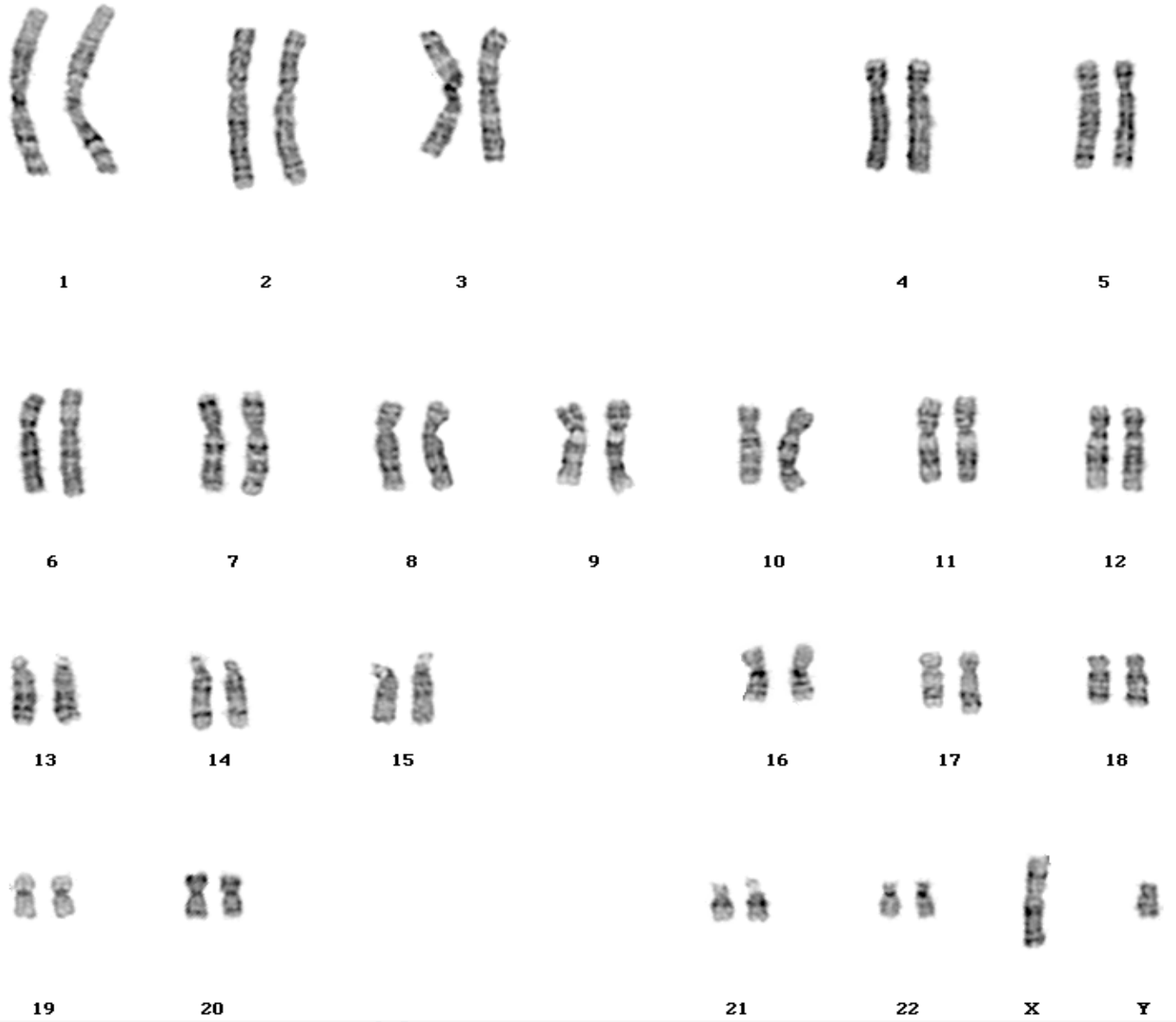
Gene: A region of DNA which represents a functional unit of inheritance

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



Chromosomal Basis of Inheritance

Metaphase



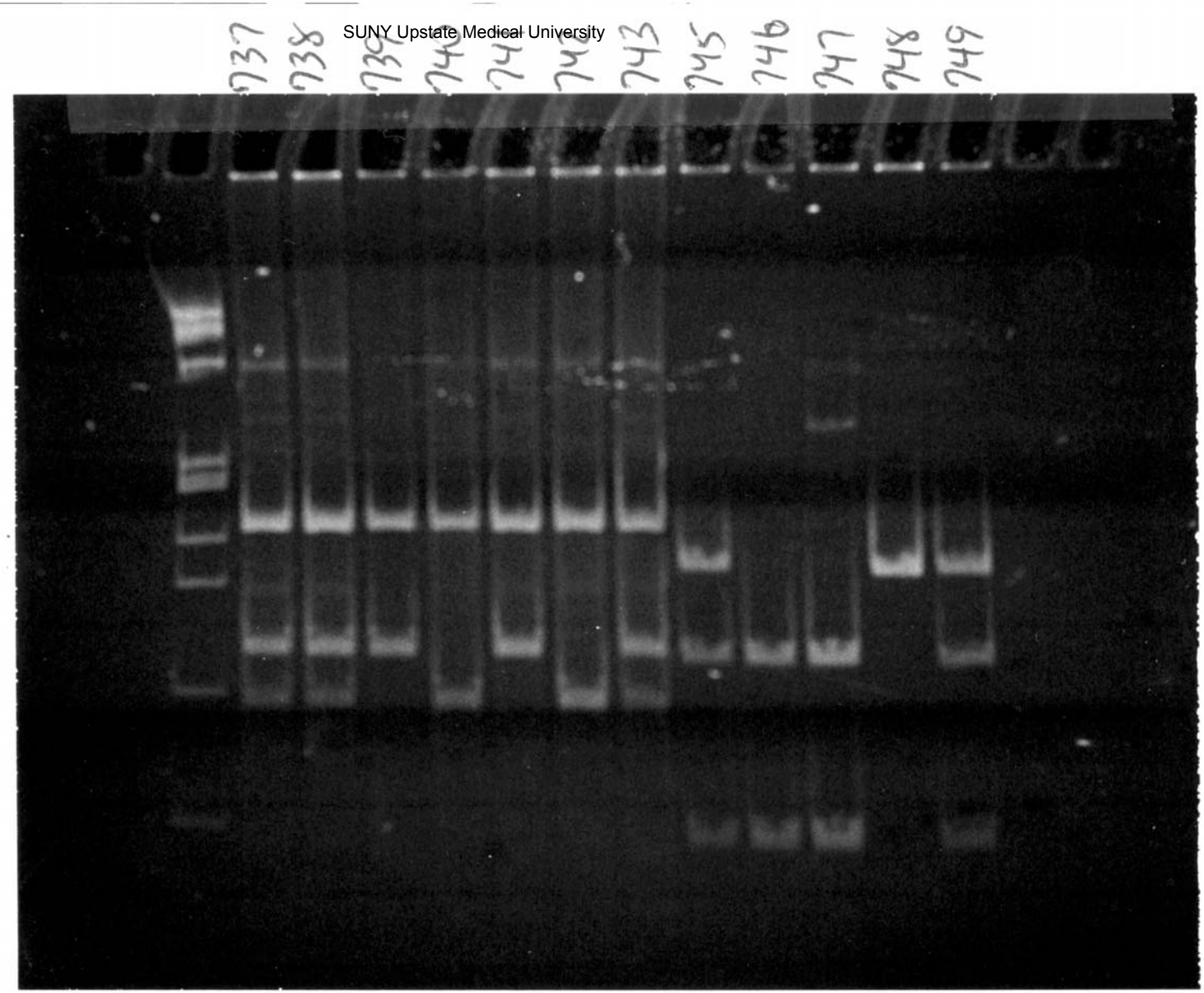
Karyotype

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

Molecular



RsaI Bcl1

Chromosomal Abnormalities

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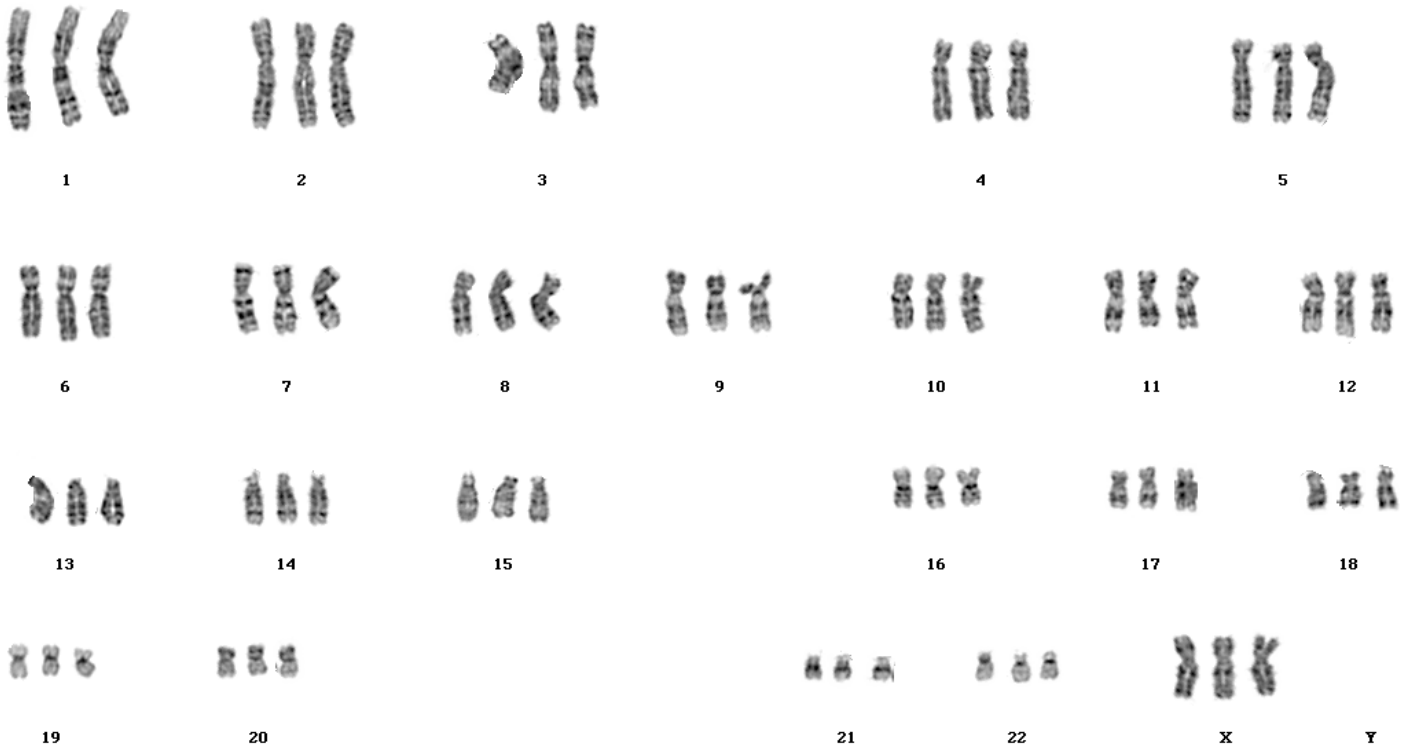
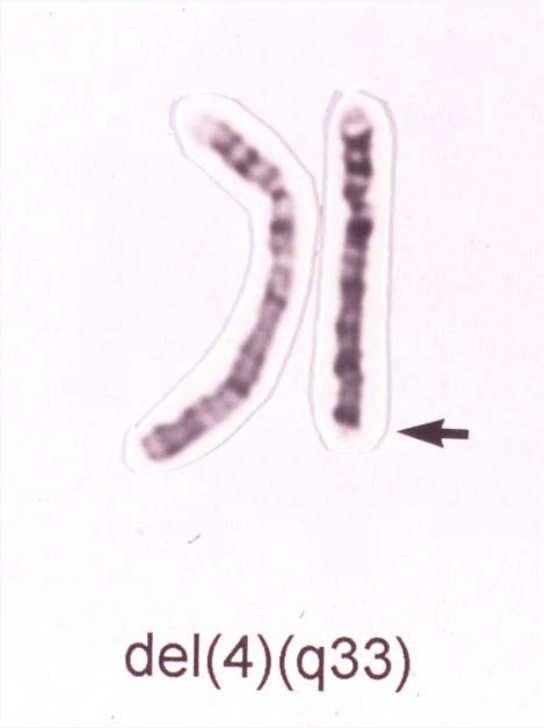


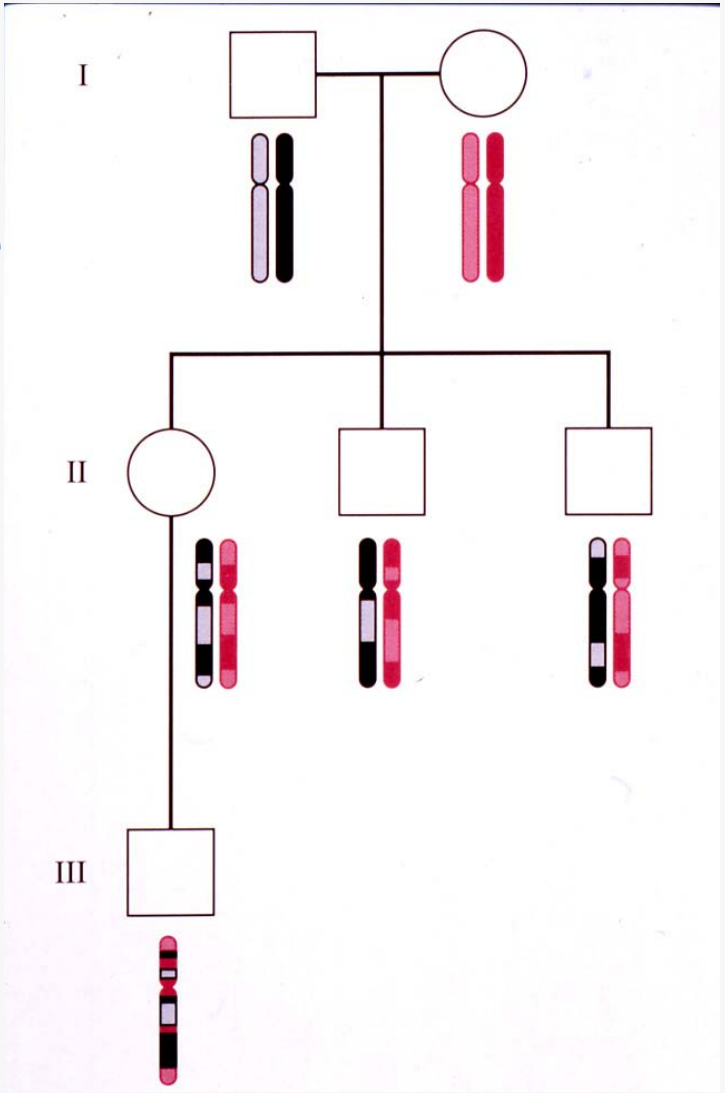
Structural

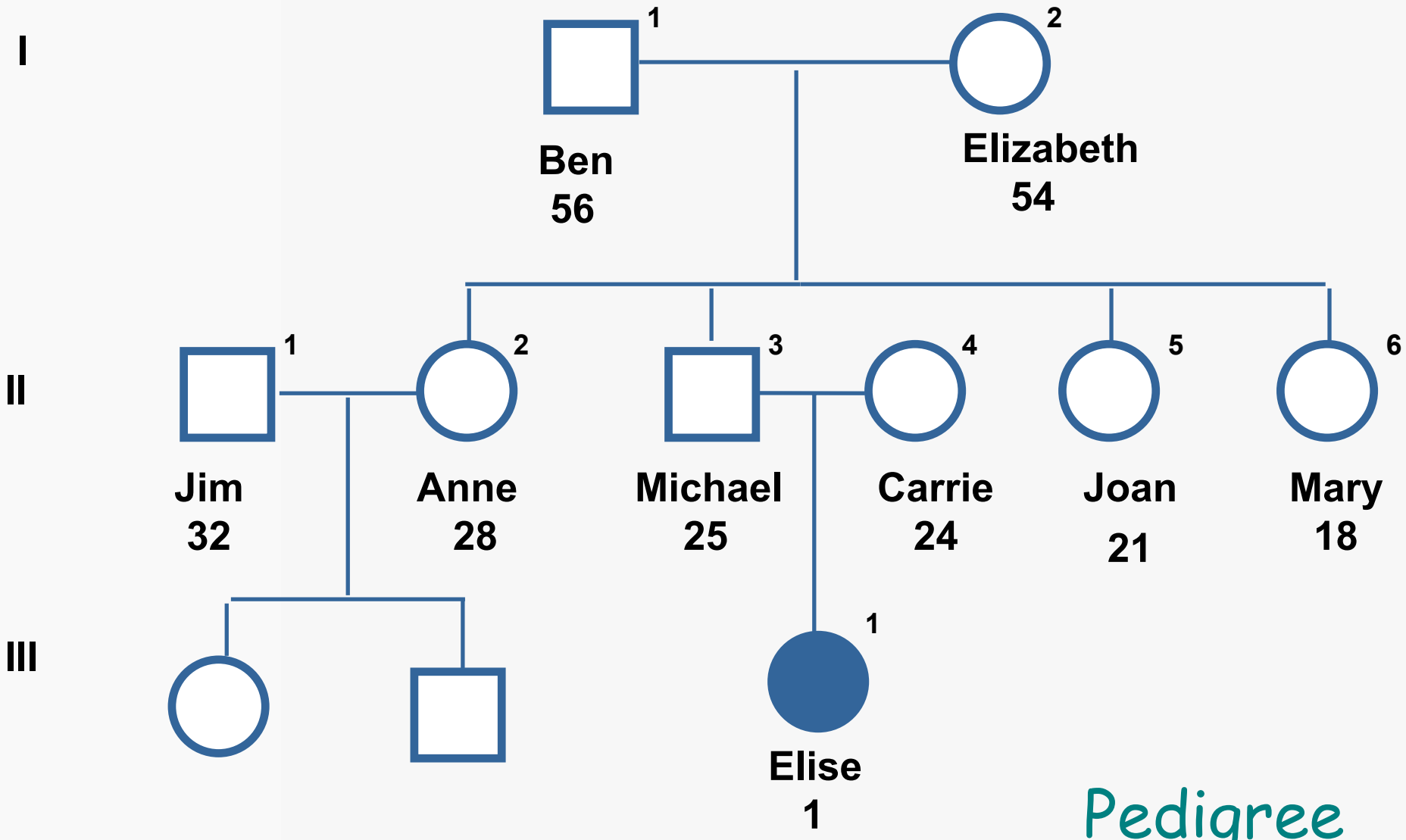


Numerical

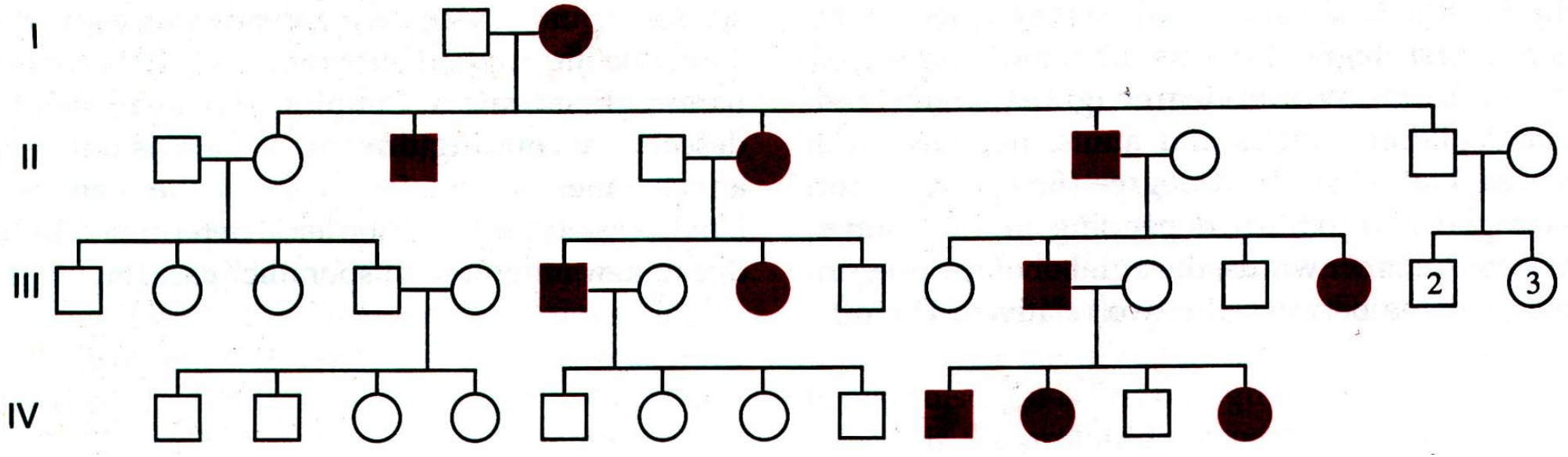
Patterns of Inheritance

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




I
II
III
1
2
Ben
56
Elizabeth
54
1
2
3
4
5
6
Jim
32
Anne
28
Michael
25
Carrie
24
Joan
21
Mary
18
1
Elise
1

Pedigree


I
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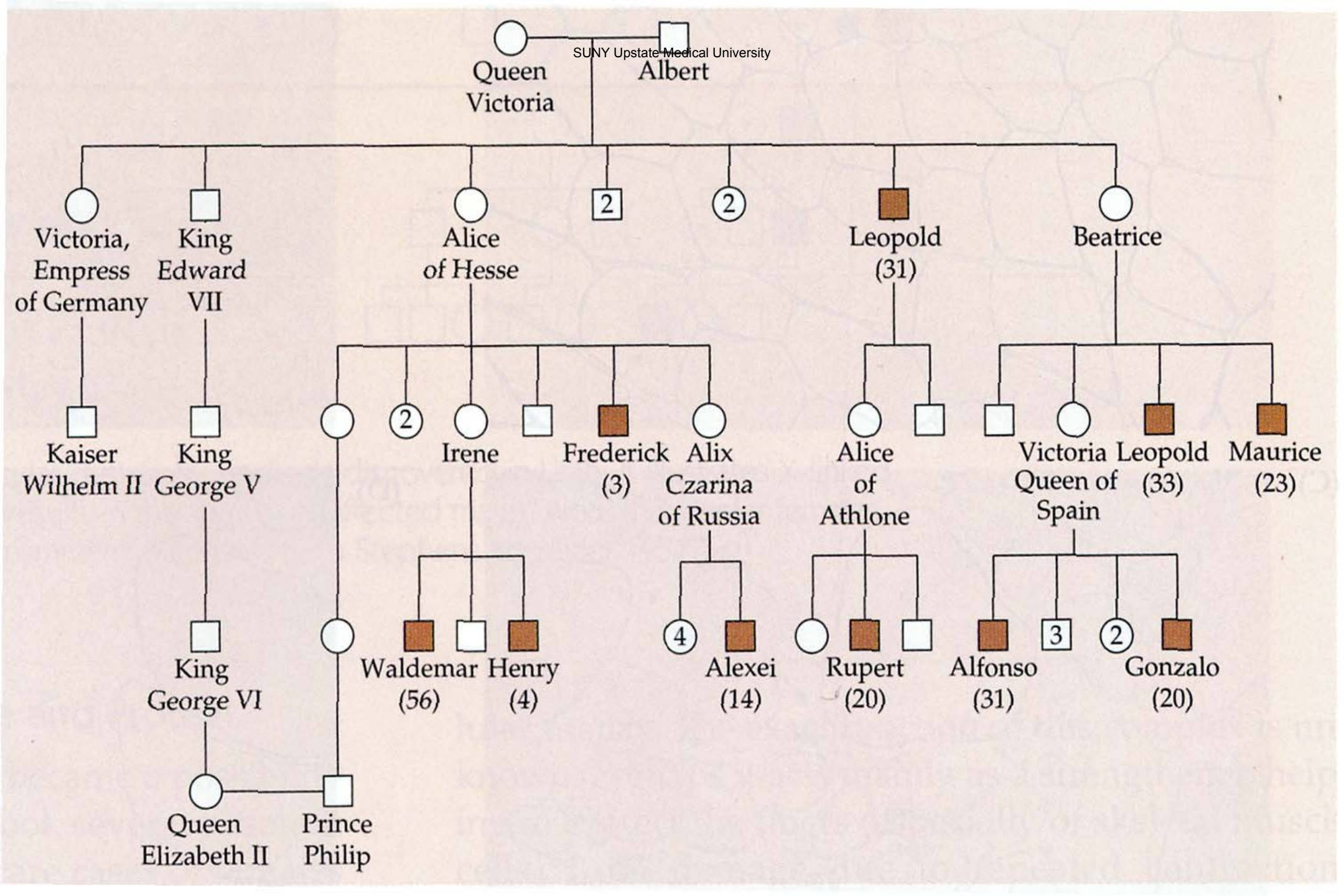
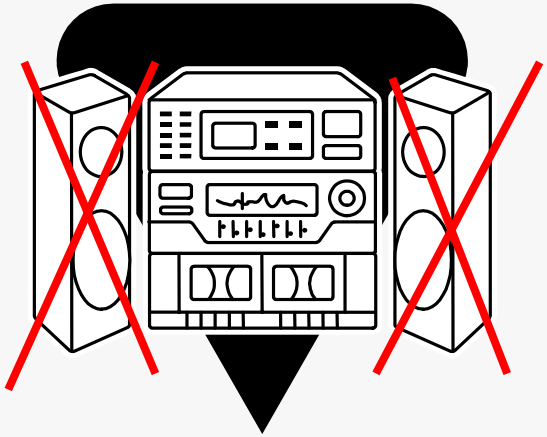
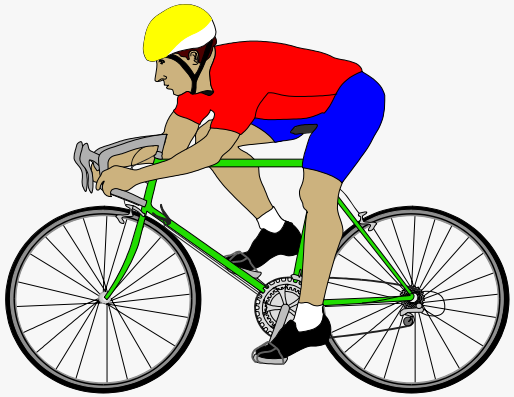


Recessive: only expressed when 2 mutations are present



Dominant: expressed with a single mutation

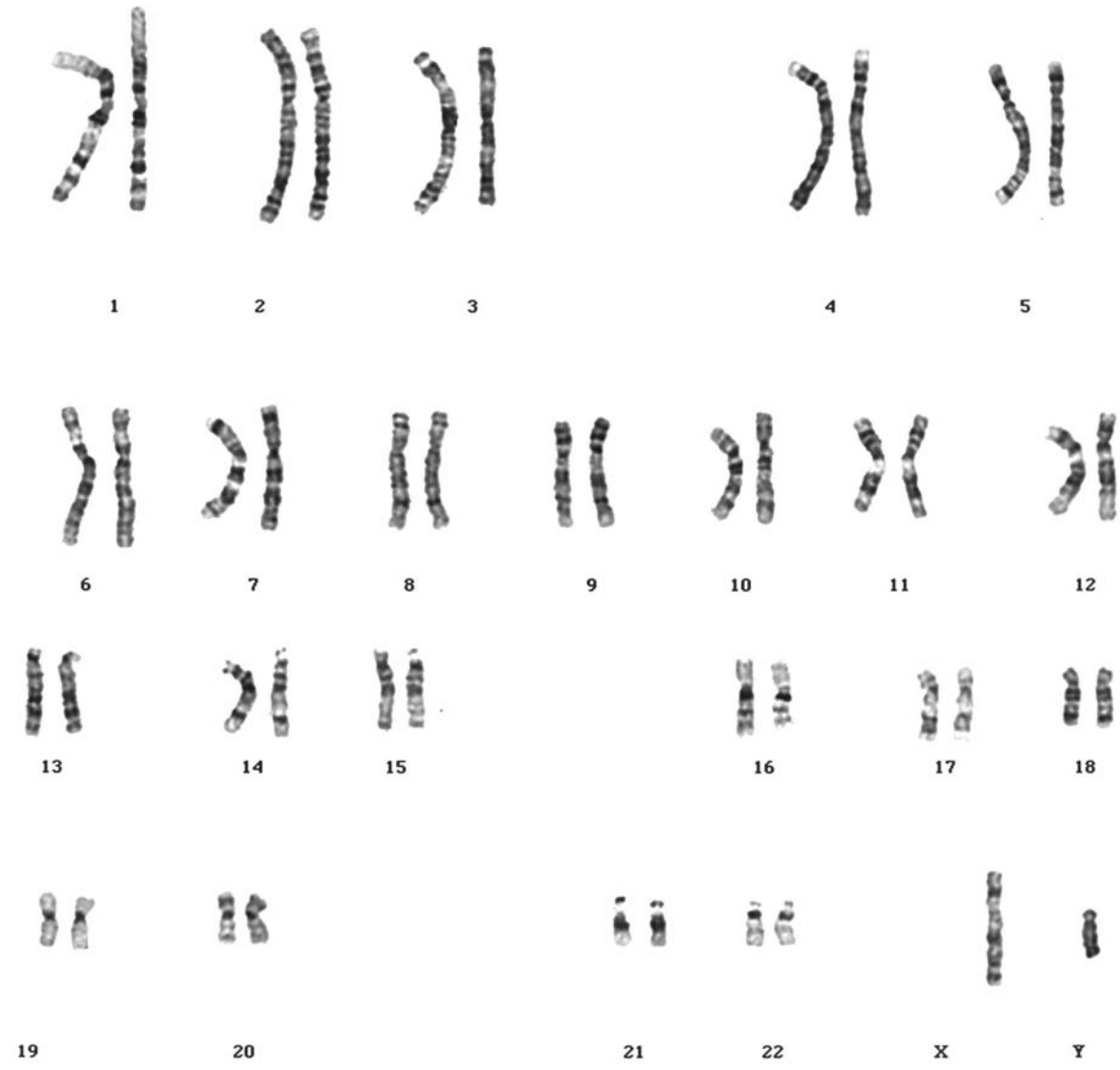


Autosomal

- Males and females equally likely to be affected

X-linked

- males more commonly affected
- no male to male transmission



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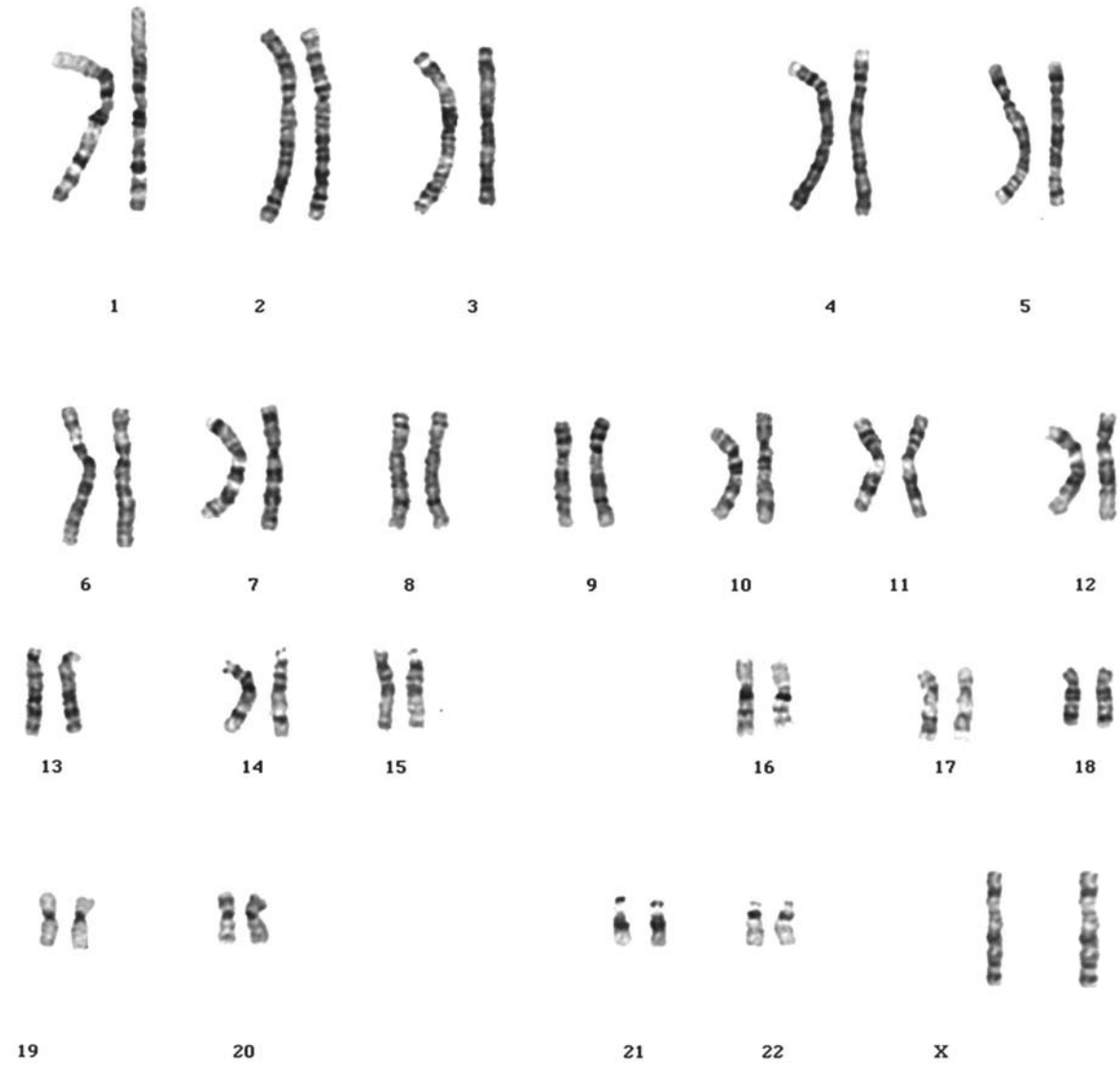
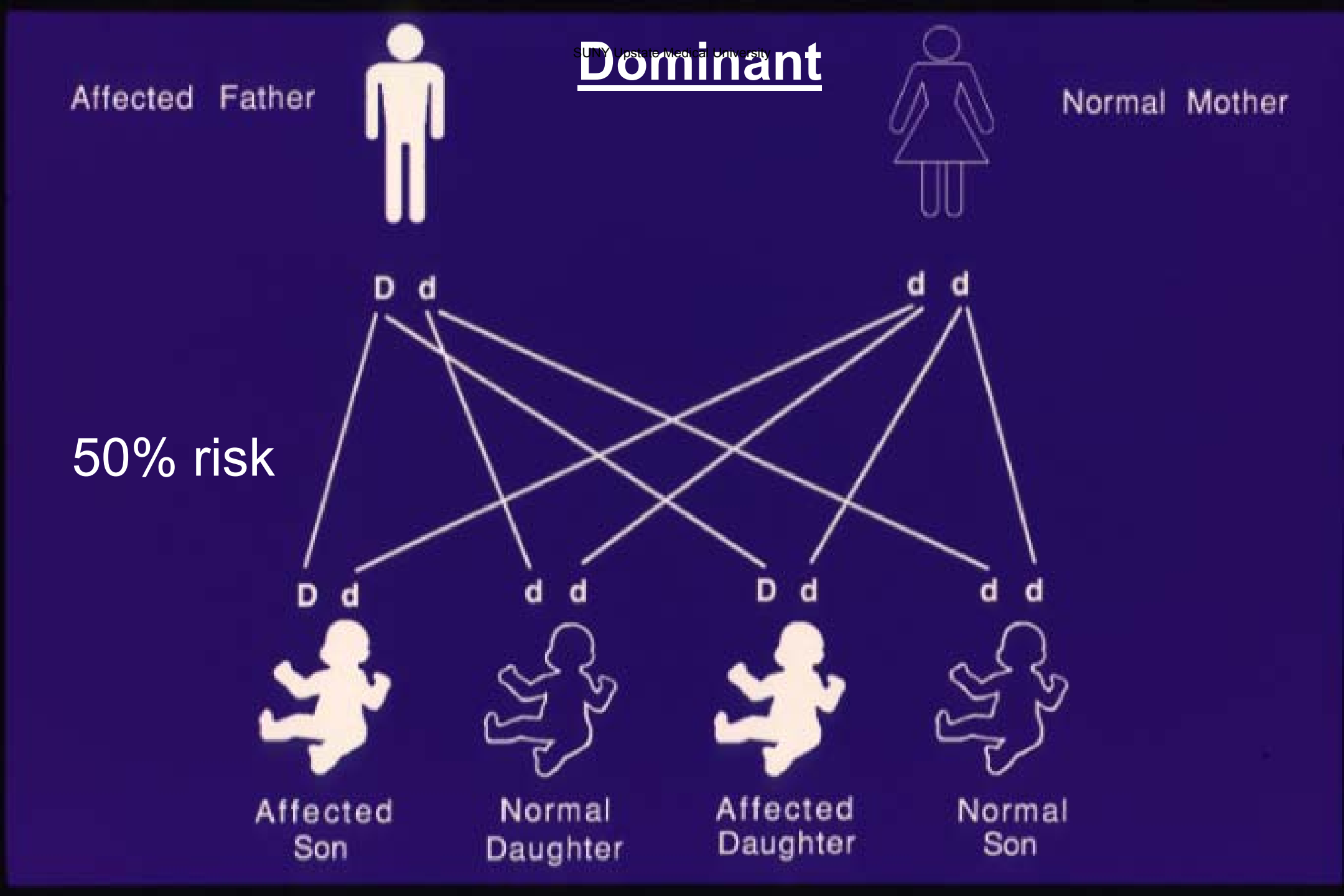
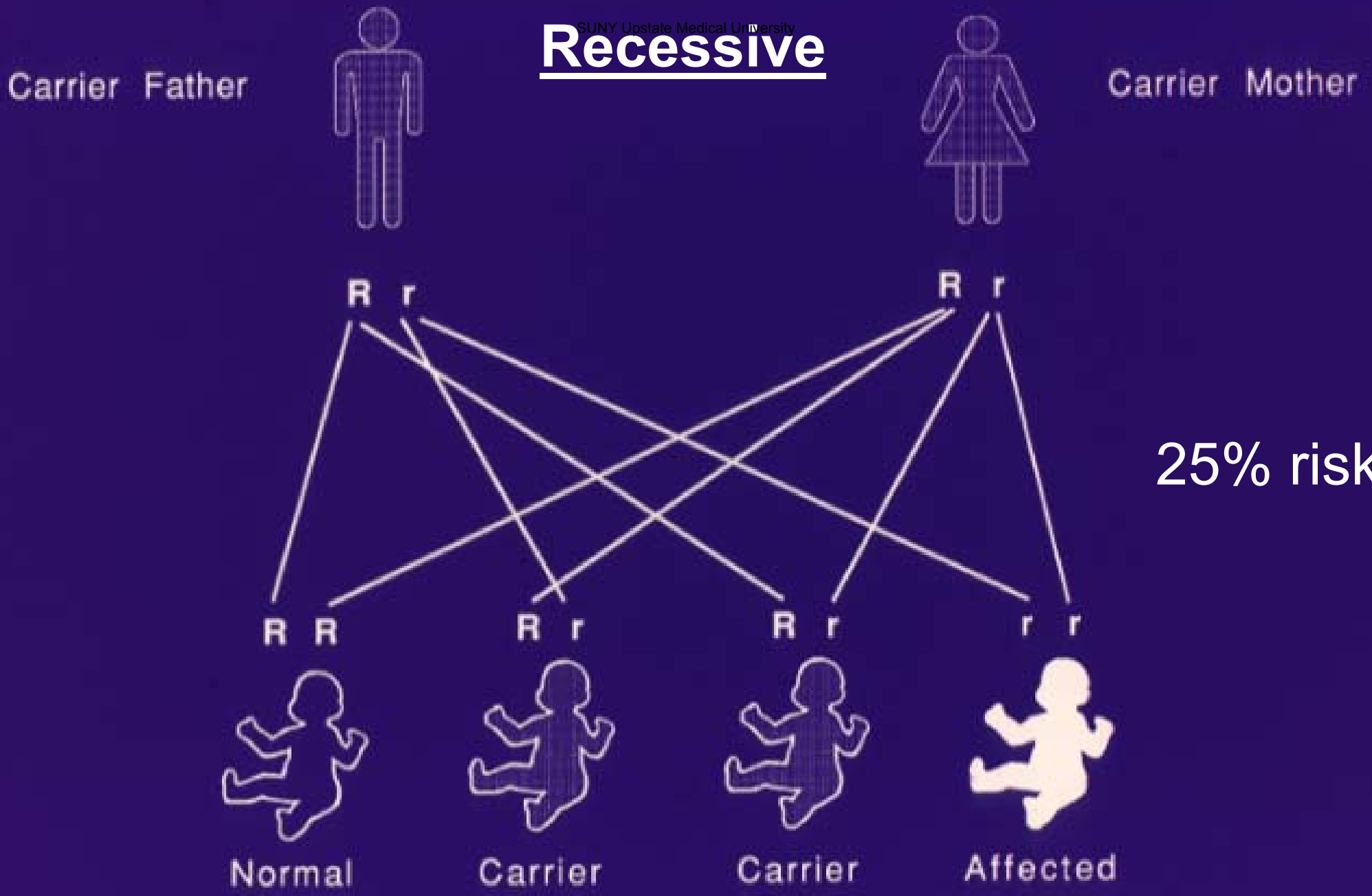


Dominant



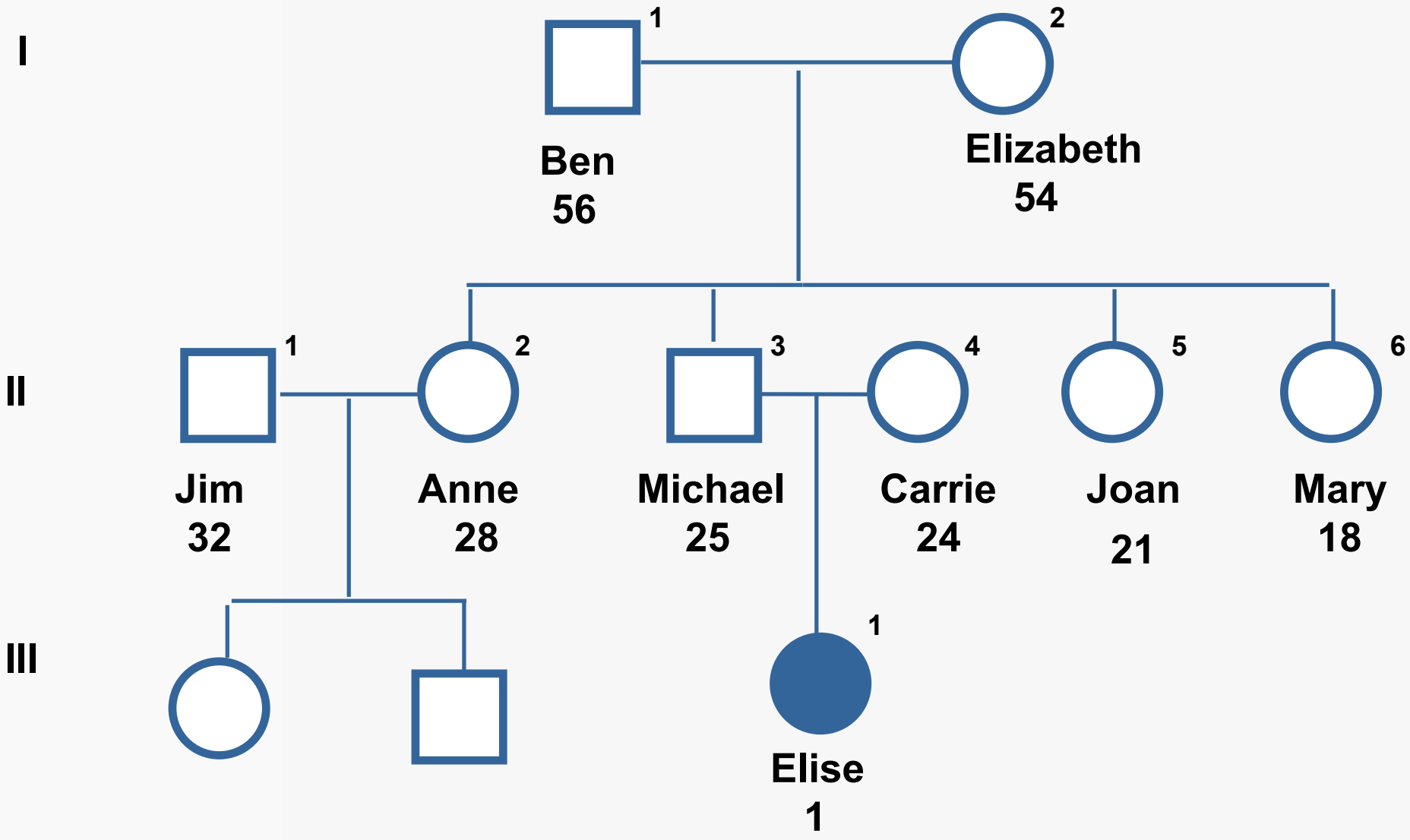
50% risk

Recessive

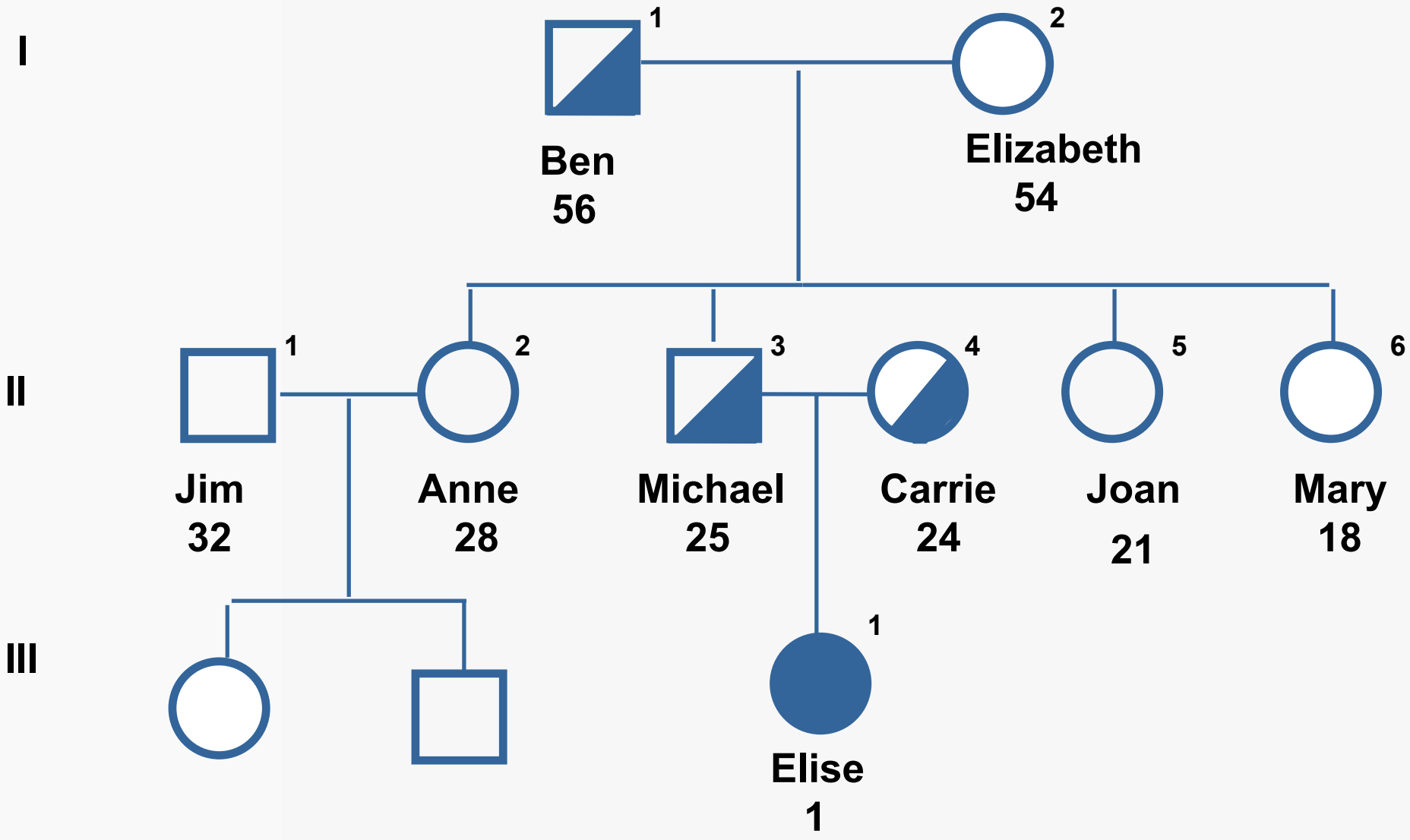


25% risk

Autosomal Recessive



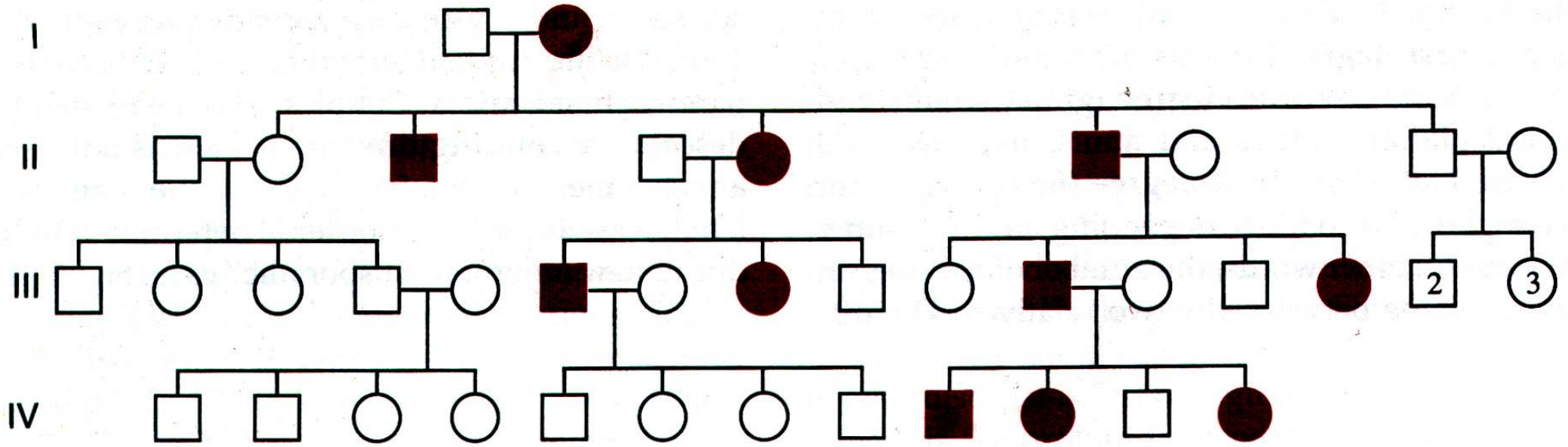
Autosomal Recessive



Autosomal Recessive

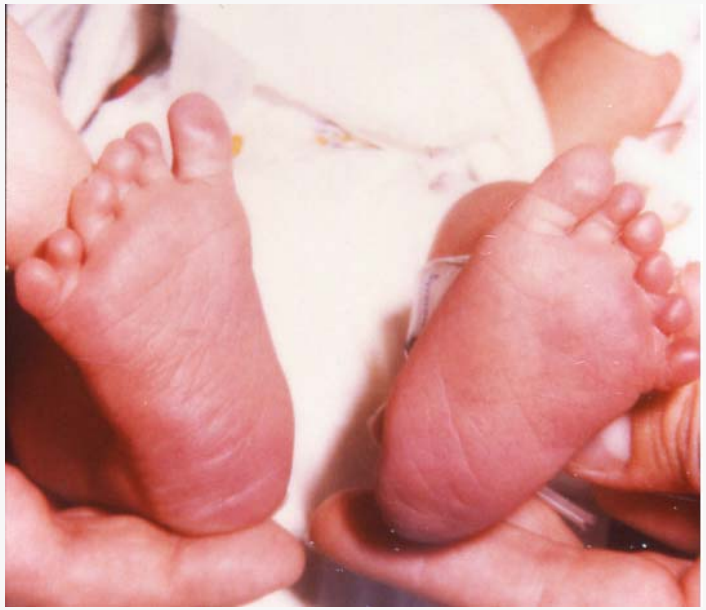
- Blue eyes
- Sickle Cell Anemia
- Cystic fibrosis
- Tay Sachs disease

Autosomal Dominant

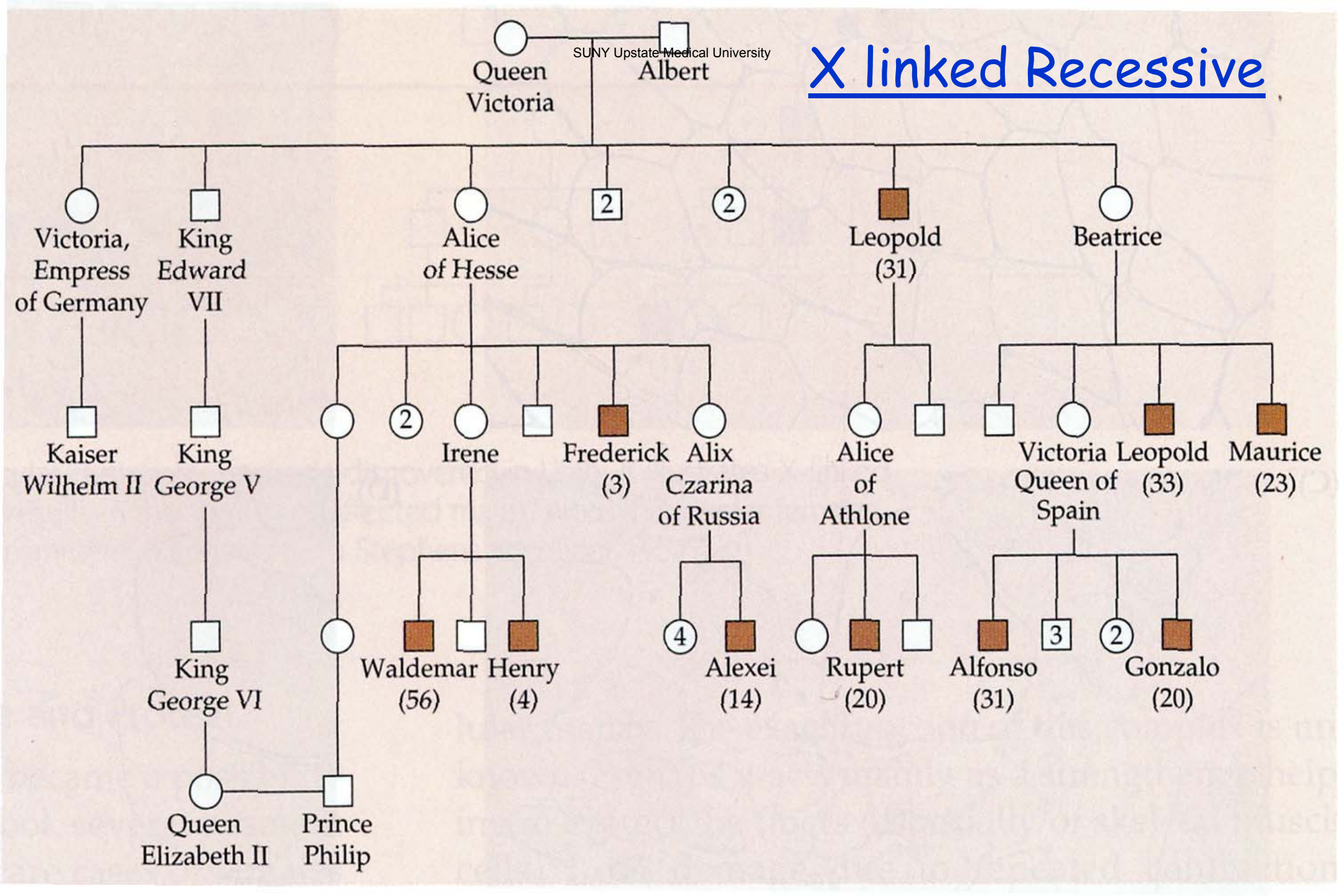


Autosomal Dominant

- Huntington disease
- Achondroplasia
- Neurofibromatosis
- Polydactyly



X linked Recessive



X-linked Recessive

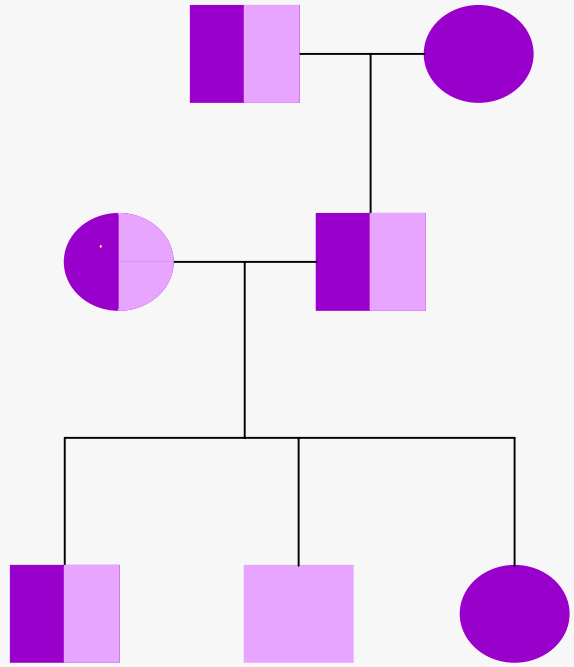
- Hemophilia A/B
- Duchenne/Becker muscular dystrophies
- Colorblindness
- Hunter syndrome

Inherited vs. Acquired Disease

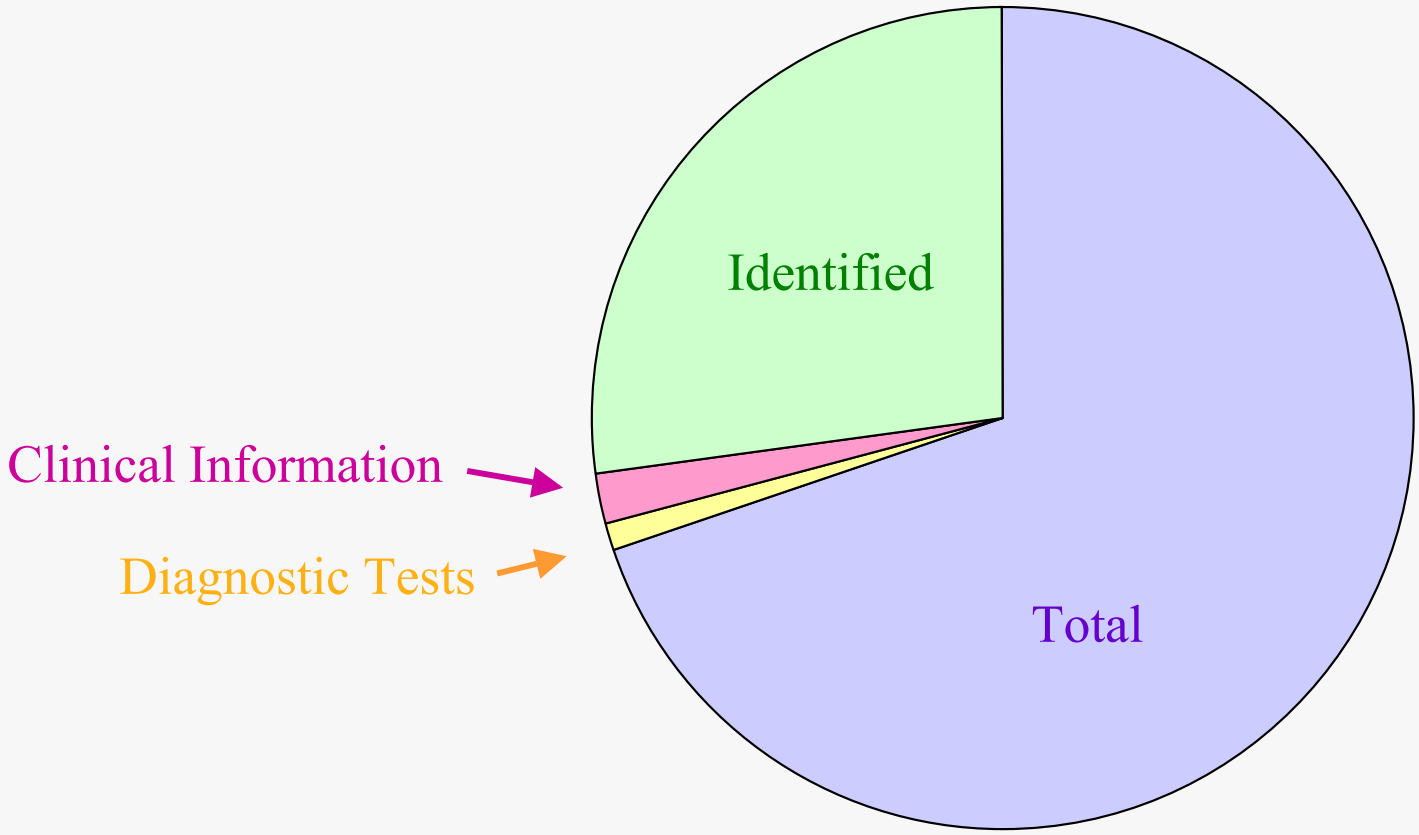
- **Inherited gene complement – genes transmitted from one or both parents**
  - **Typically called the constitutional genome**
- **Acquired gene complement – a subset of cells in an individual that arose by clonal propagation from a single mutation in one cell**

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

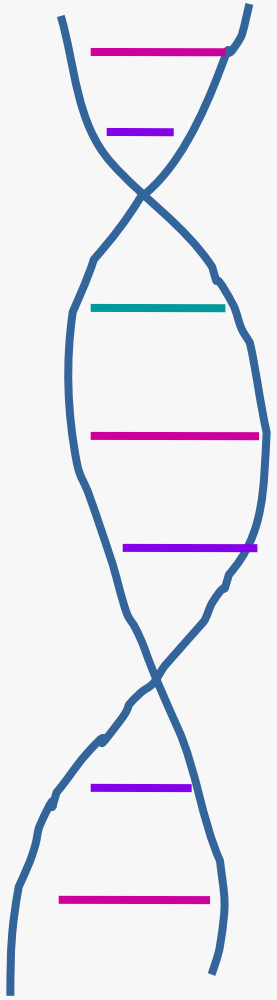


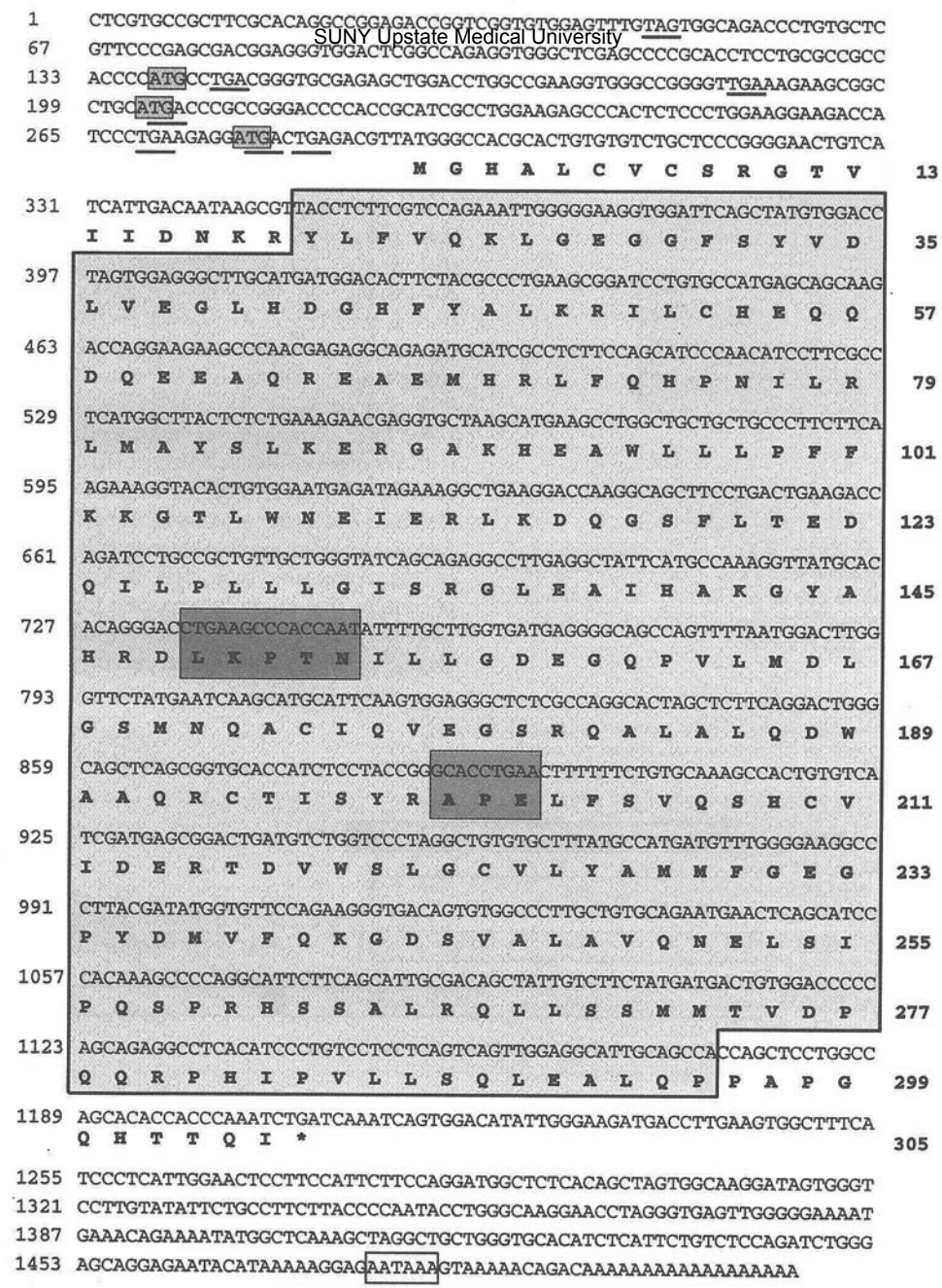
Human Genes



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!





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

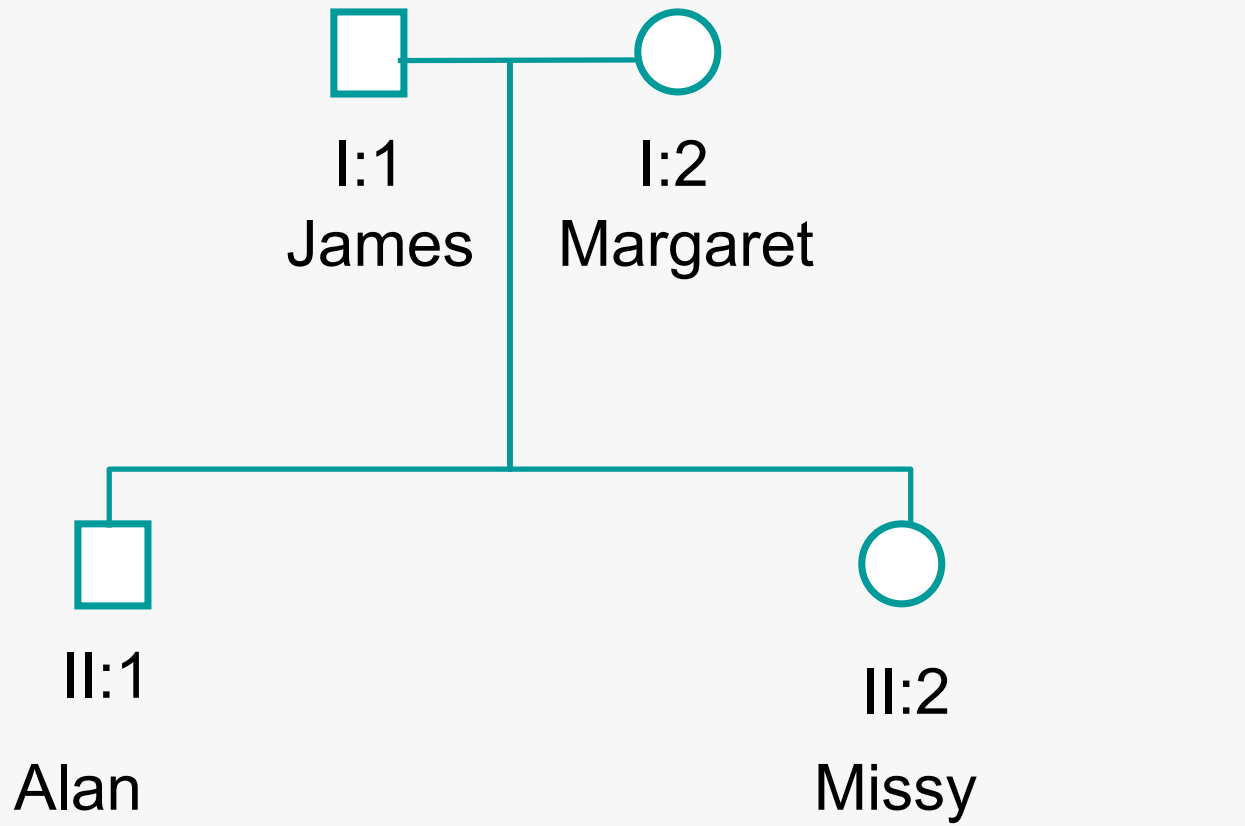
Hereditary Hemochromatosis

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

Limitations of Genetic Tests

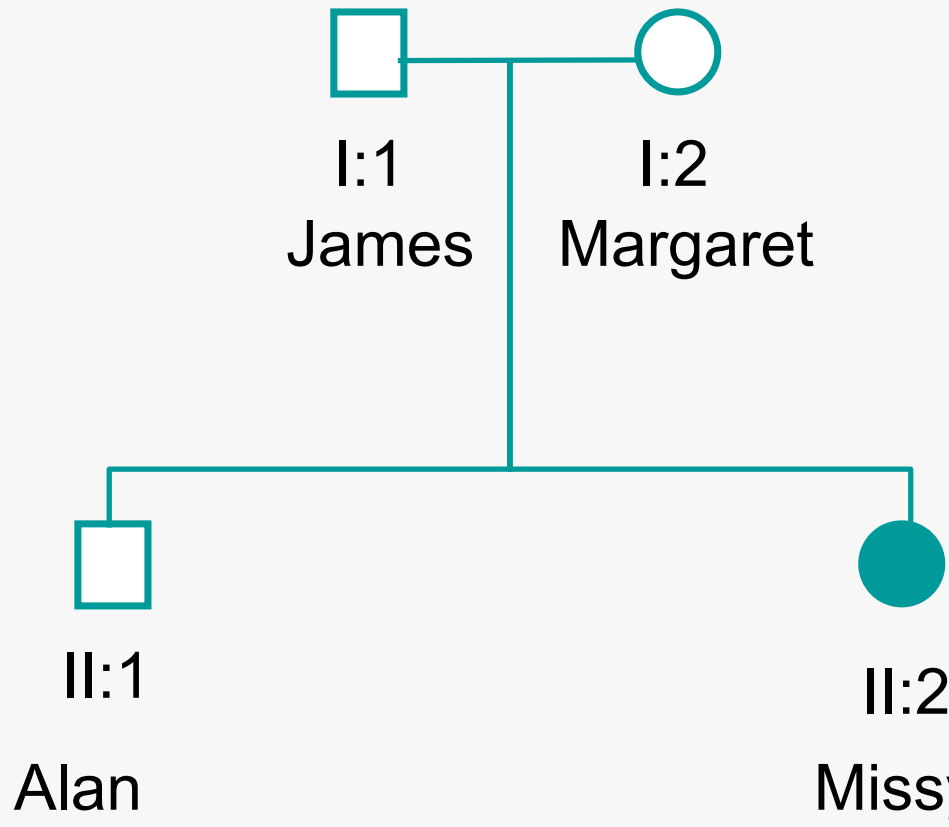
- Requires knowledge of disease specific mutations
- May not be possible to identify all mutations
- Unable to tell age of onset for late onset diseases

Example : Cystic Fibrosis



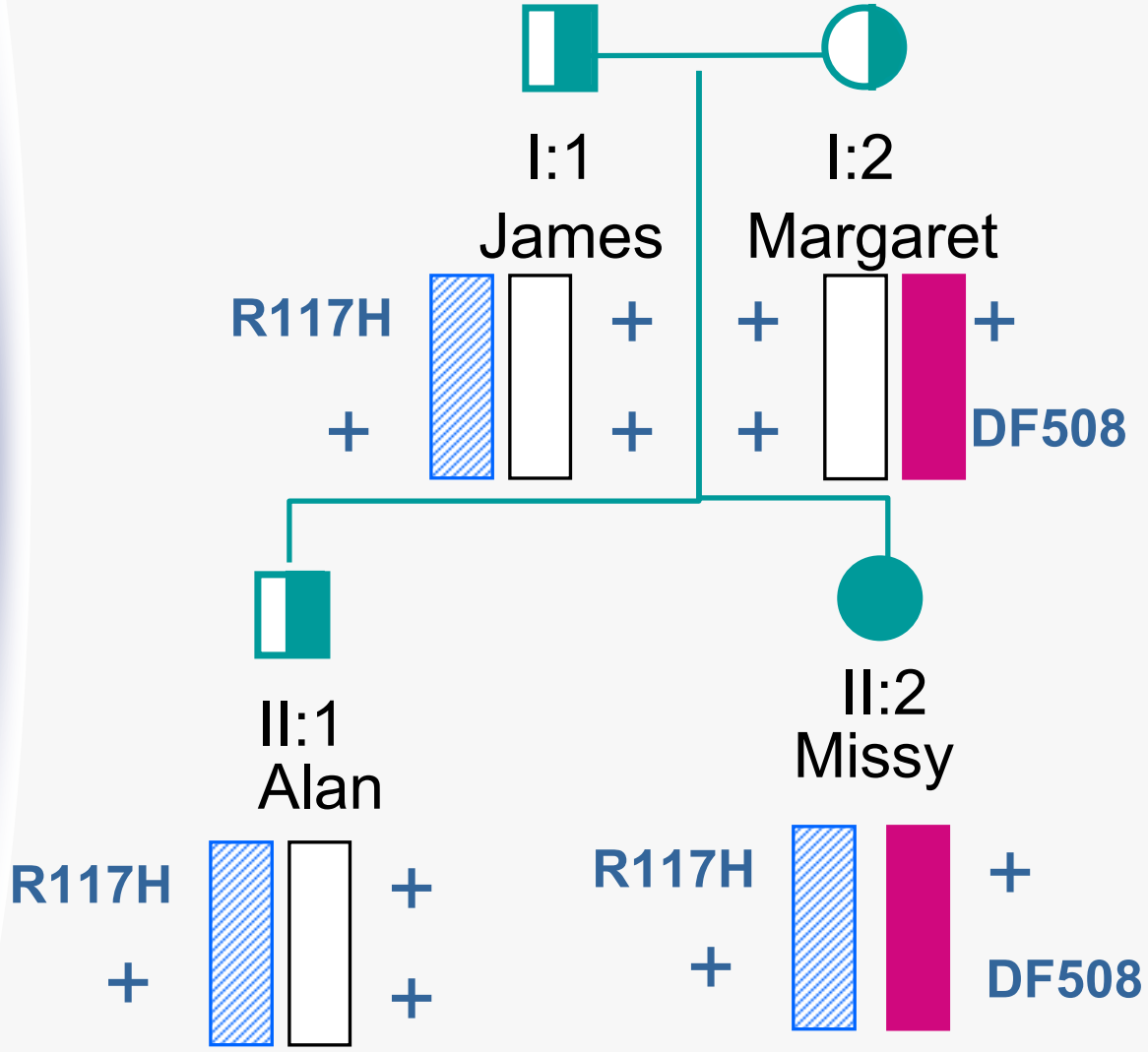
Born with
multiple abnormalities

Cystic Fibrosis



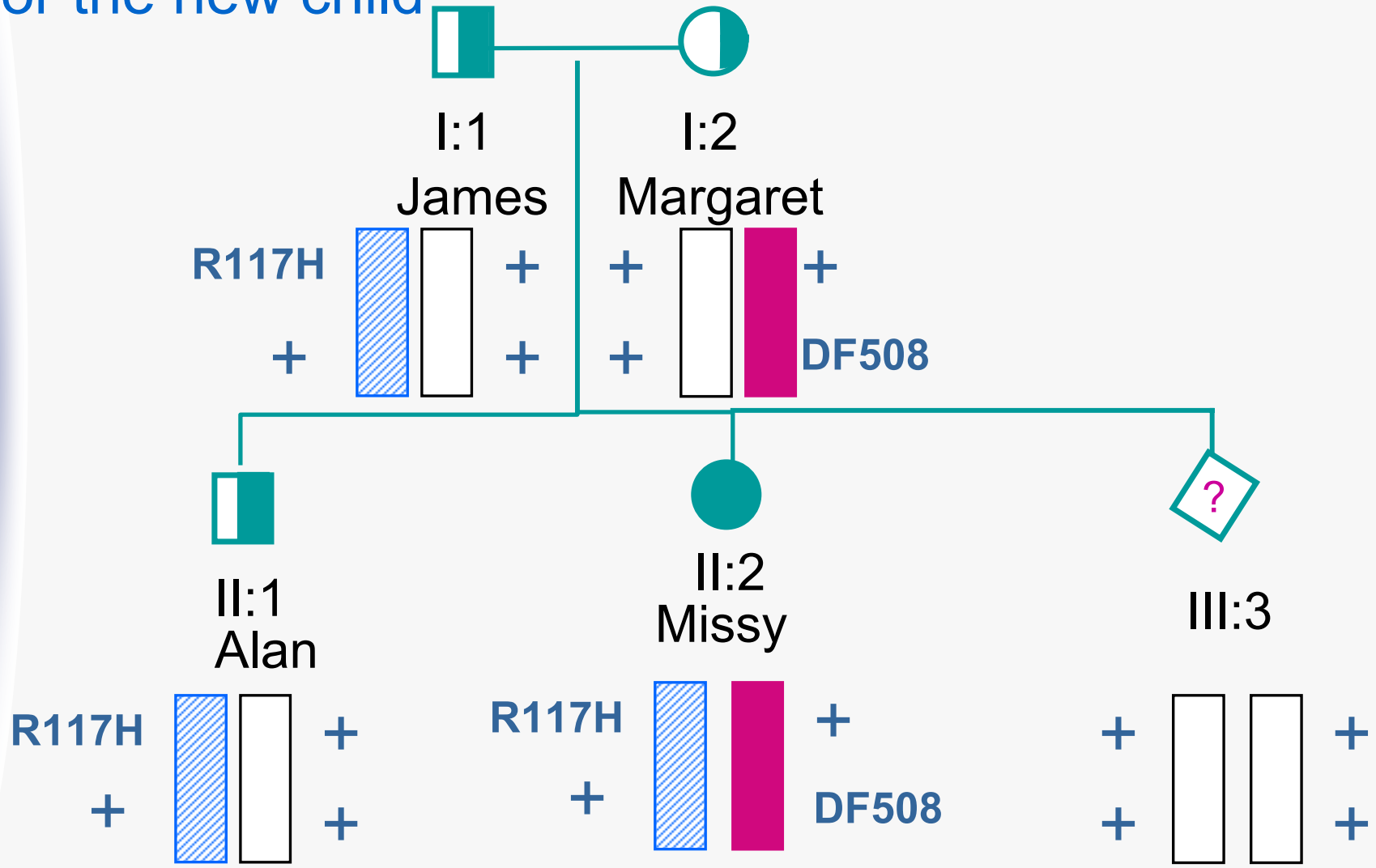
Clinical diagnosis reveals: CF

Molecular testing: Cystic Fibrosis

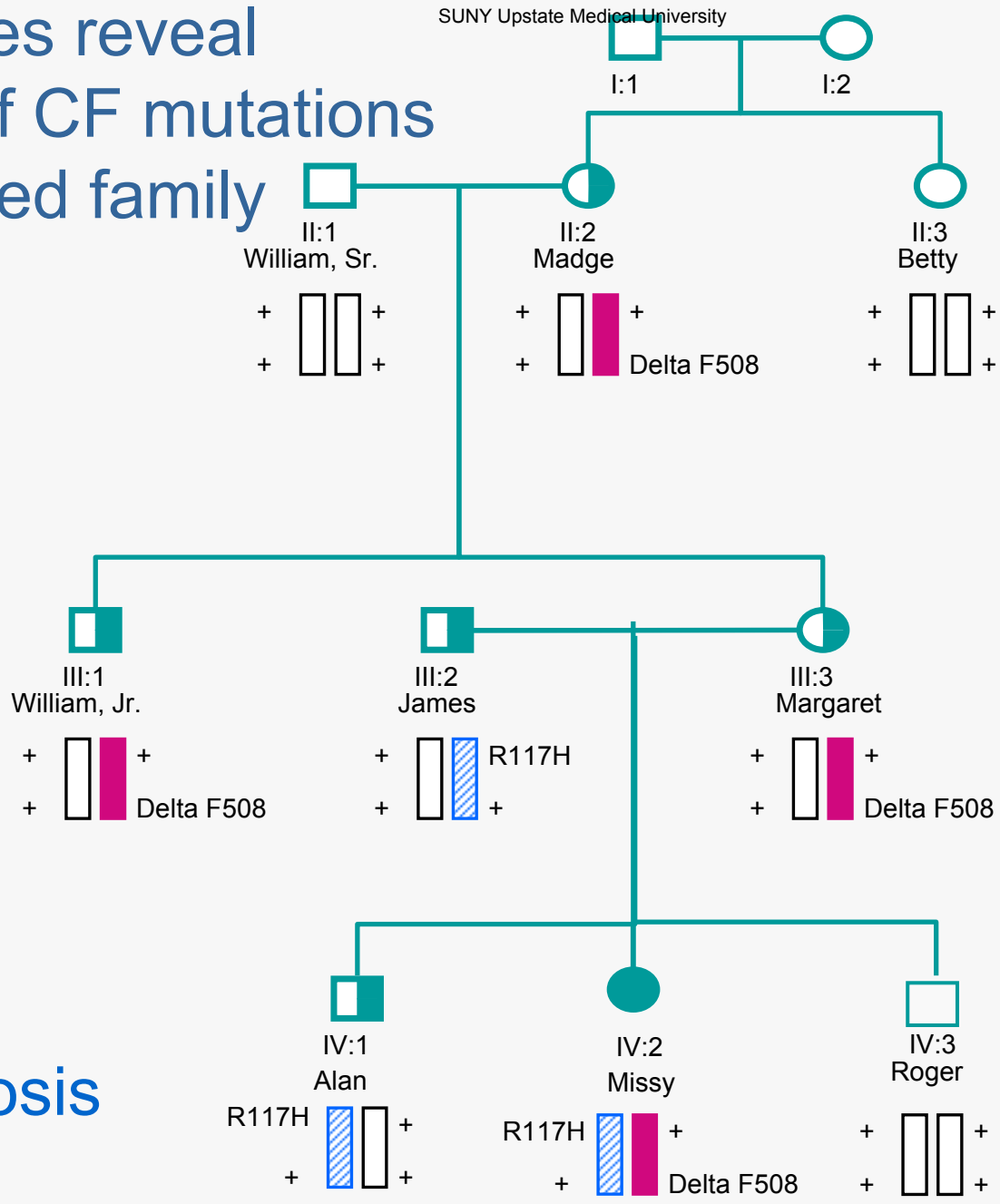


Cystic Fibrosis

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.)

IRB: Research subjects participating in an IRB approved research study involvoing 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?

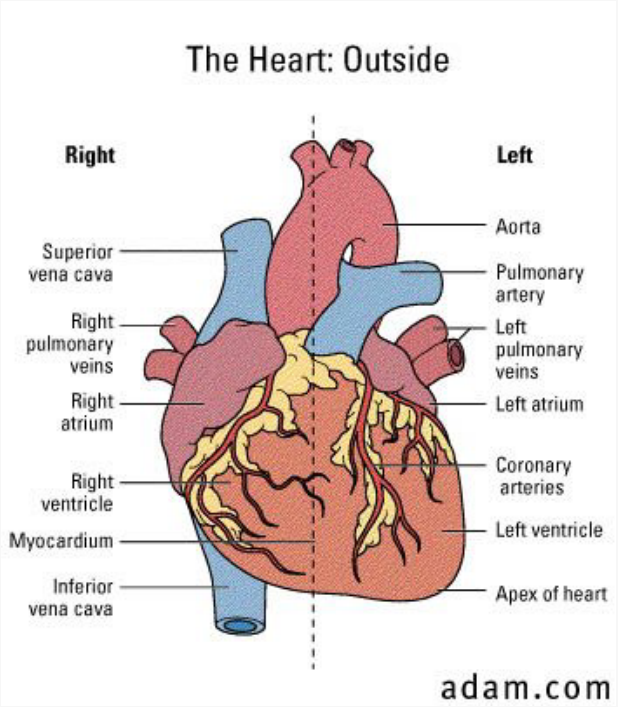
Only those disorders arising solely from a somatic mutation or mutations are exempt from current regulation.

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