GENETICS: Introductory Concept

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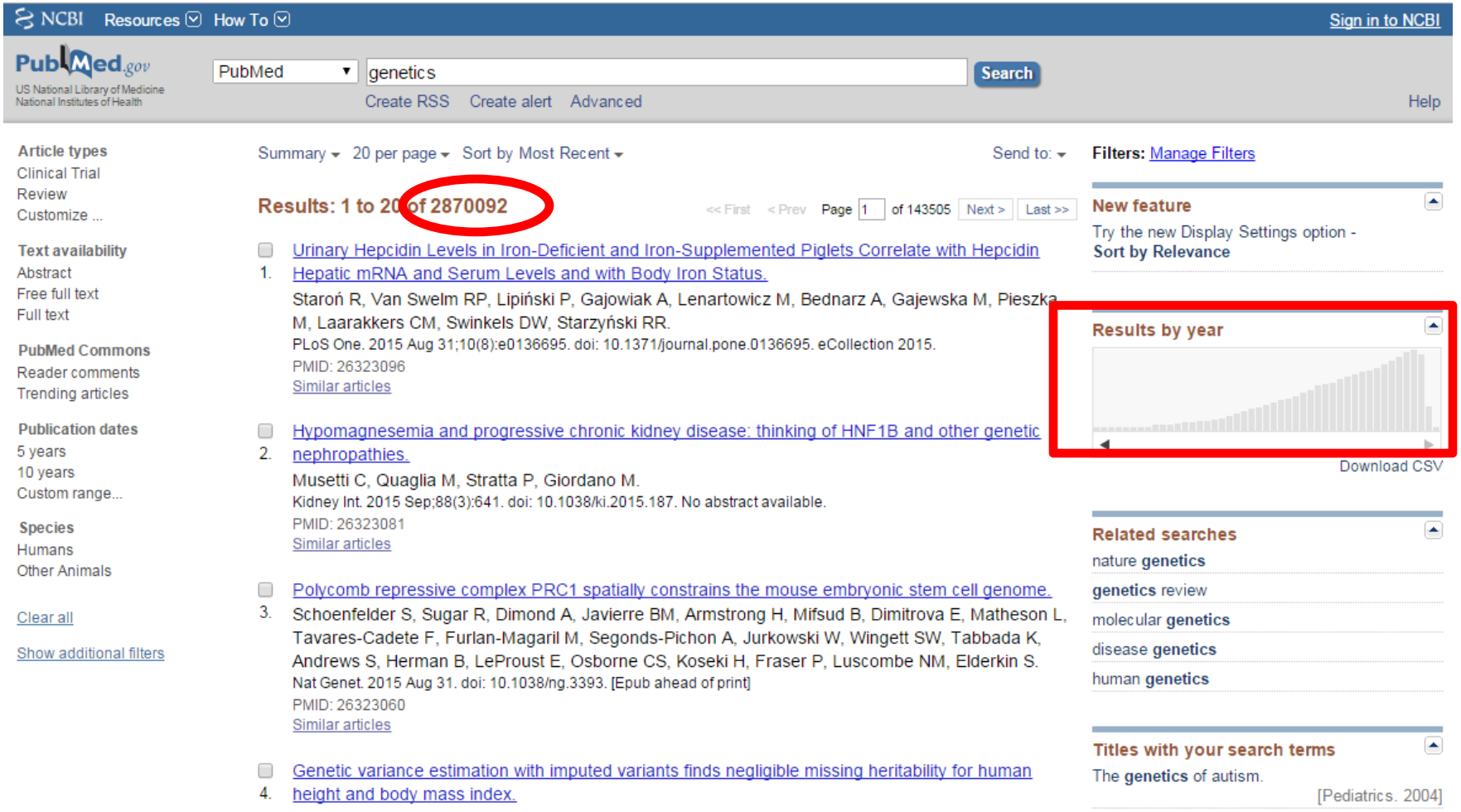
CONGRESS OF FREAKS AT RINGLING BROTHERS AND BARNUM & BAILEY COMBINED CIRCUS

A society is judged by how it treats its most vulnerable members…

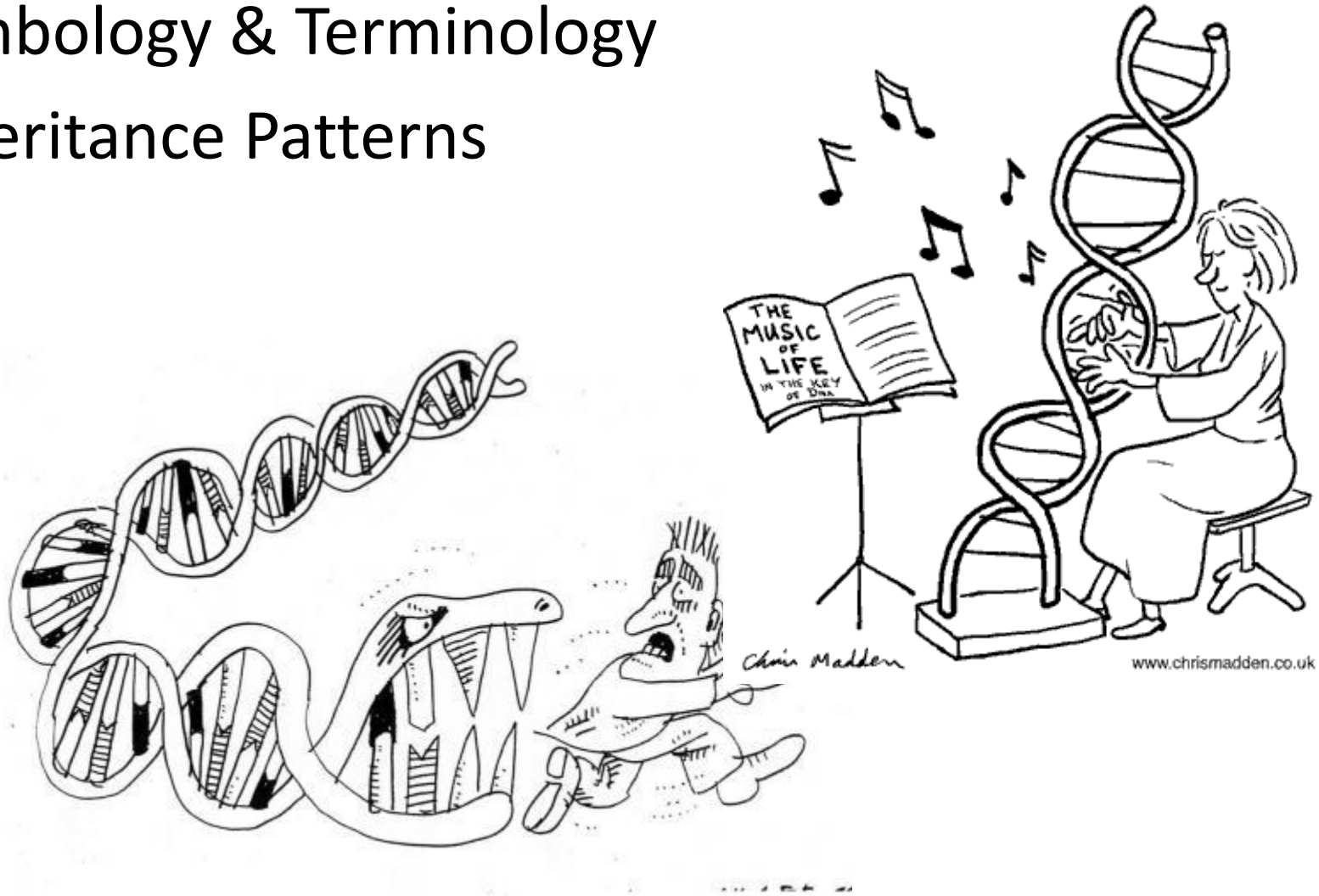
- Original author unknown;
repeated by Gandhi, Churchill, Truman, etc.

September 1, 2015



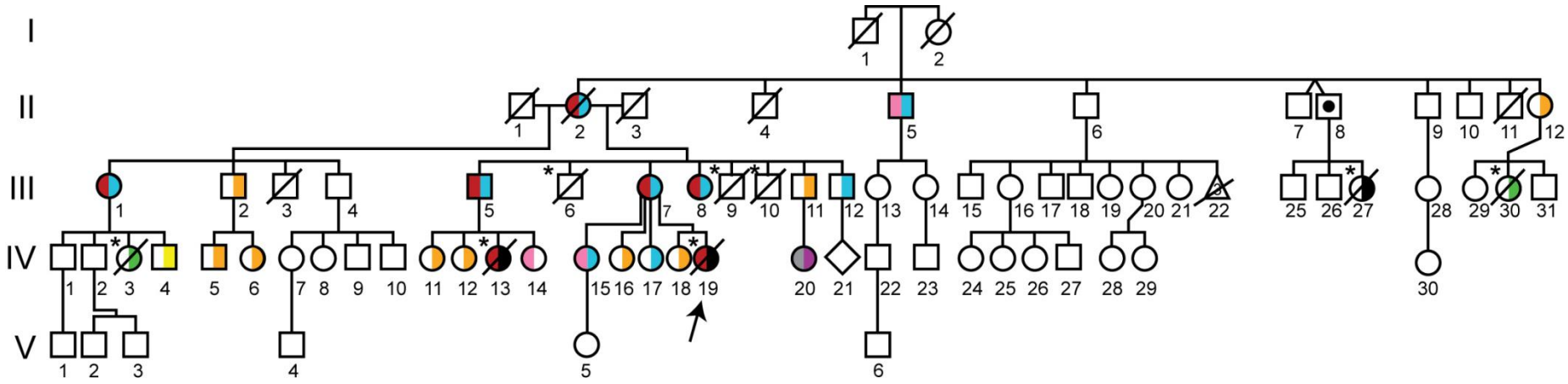
Topics/Goals

- Symbology & Terminology
- Inheritance Patterns

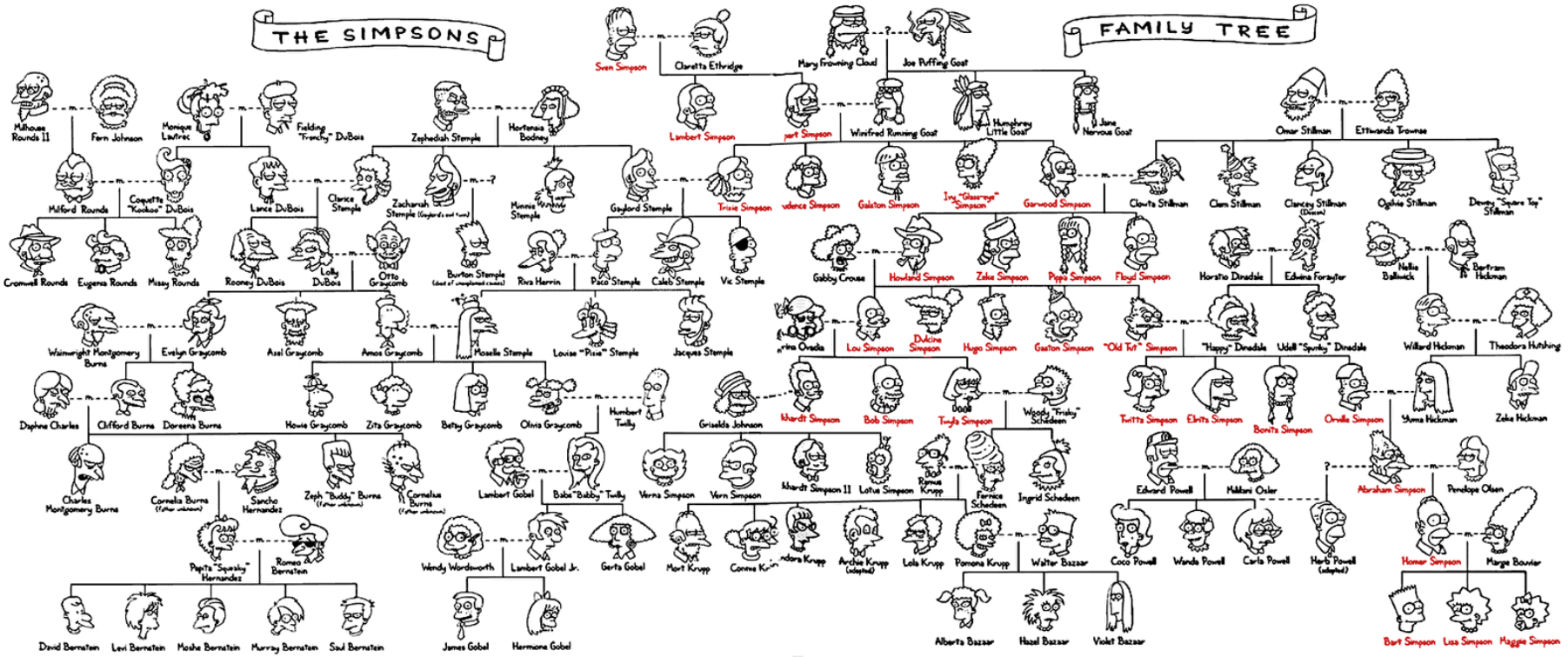


I. Symbology

Goal: Familiarity with Pedigree Symbols

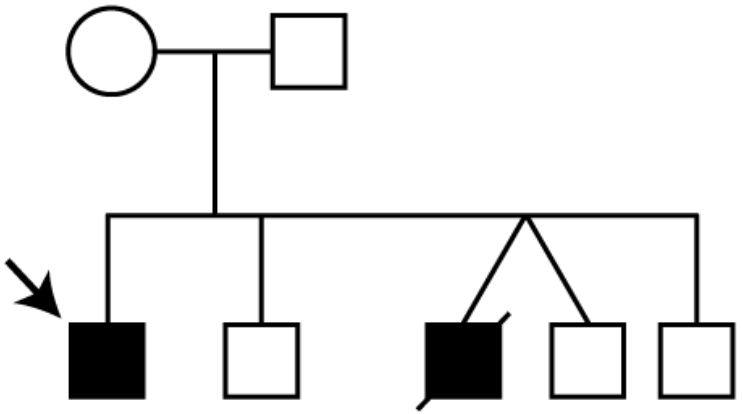


Fun With Pedigrees

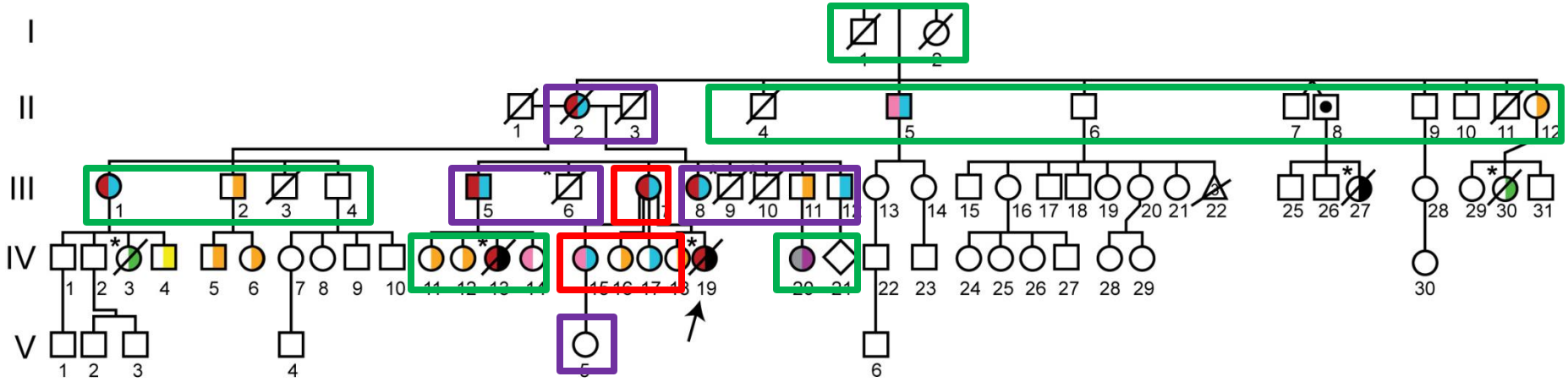


Pedigree Terminology

- **Proband/propositus/index case**
- **Consultand -** person who brings the family to medical geneticists' attention
- **Siblings/Sibs** -brothers and sisters
- **Sibship -** all siblings together
- **Kindred -** an entire family

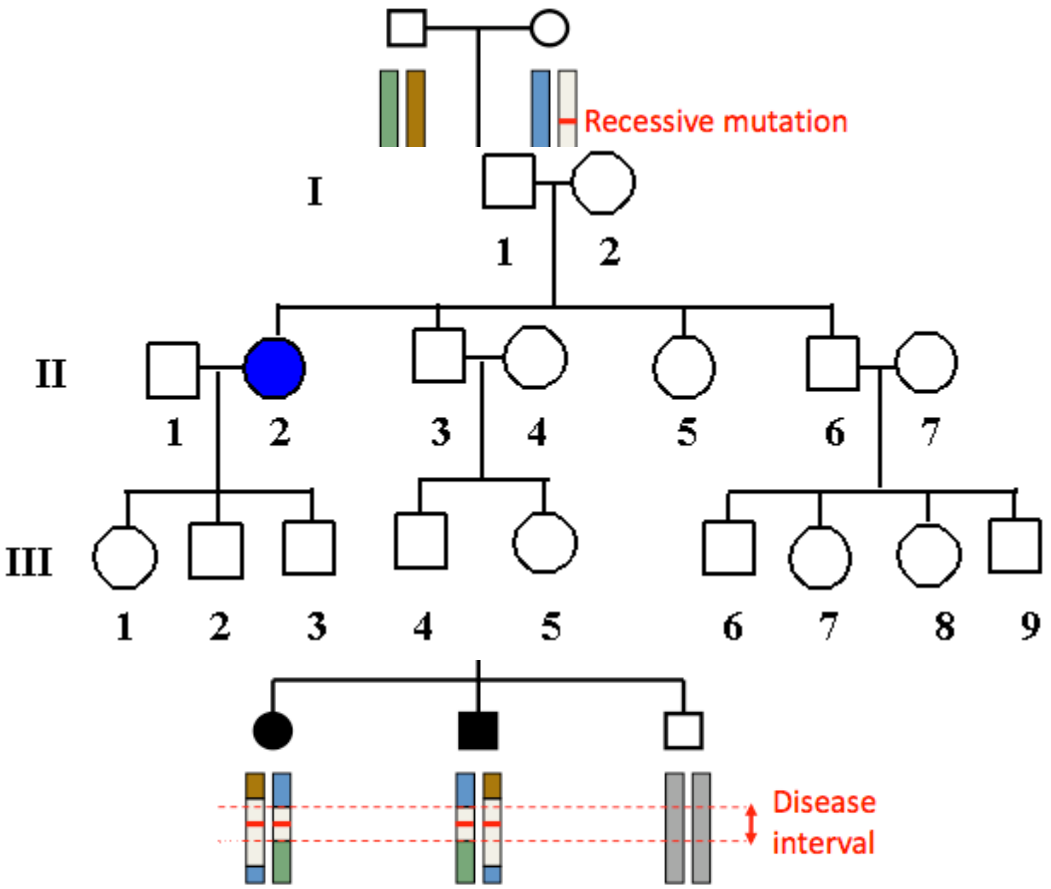


Pedigree Terminology: Degrees of Relationship



Pedigree Terminology

- **Consanguineous -** related by descent from a common ancestor
- **Isolated case -** one affected family member
- **Sporadic -** new mutation in the proband

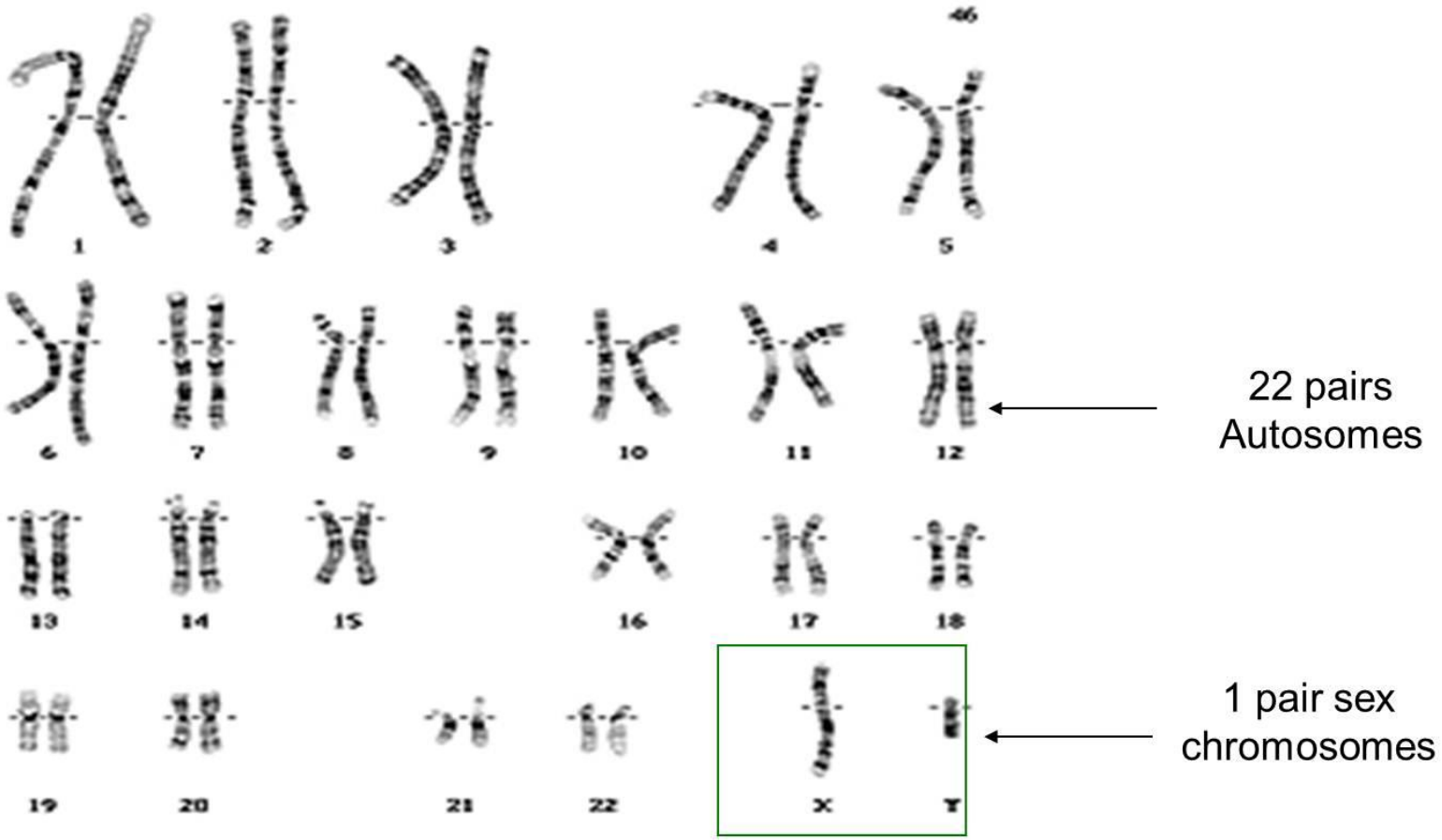


II. Terminology

Goal:

Familiarity with basic terminology in **clinical** and **research** genetics

Basic Tests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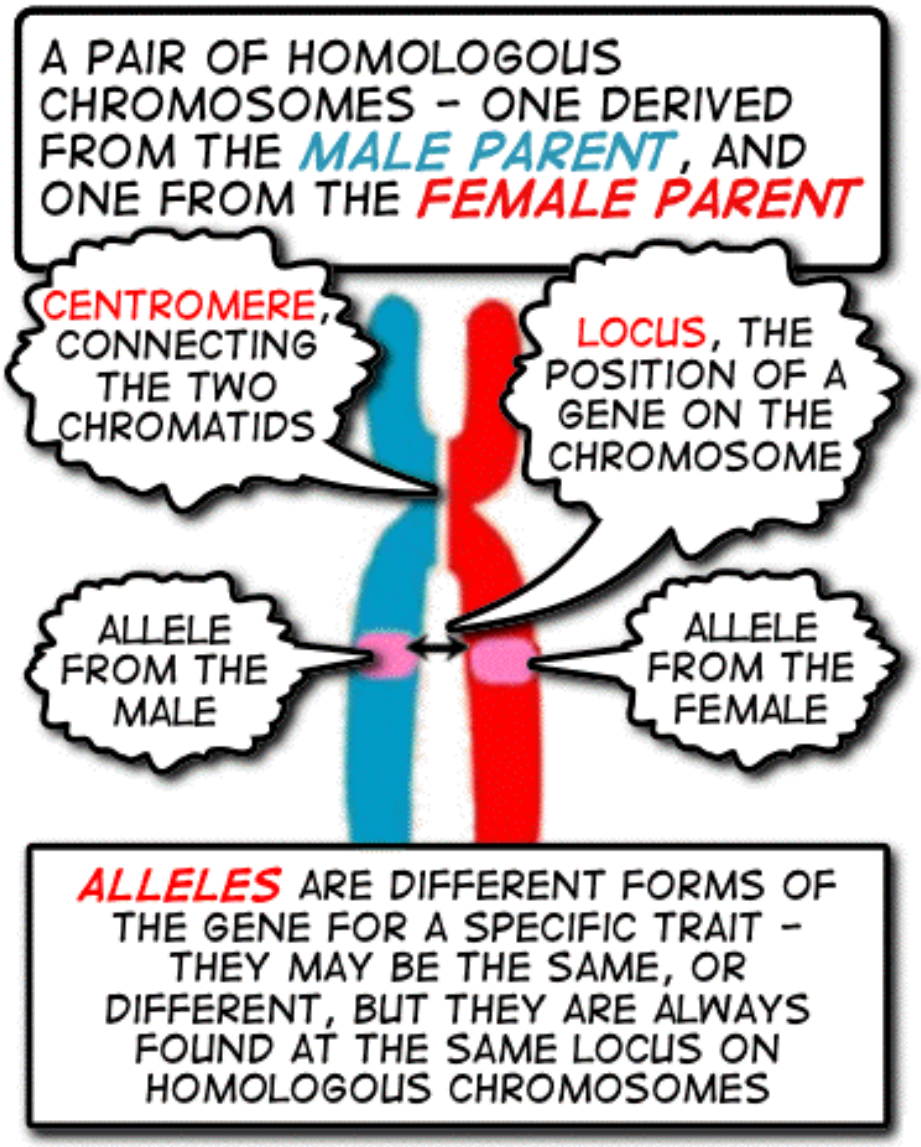
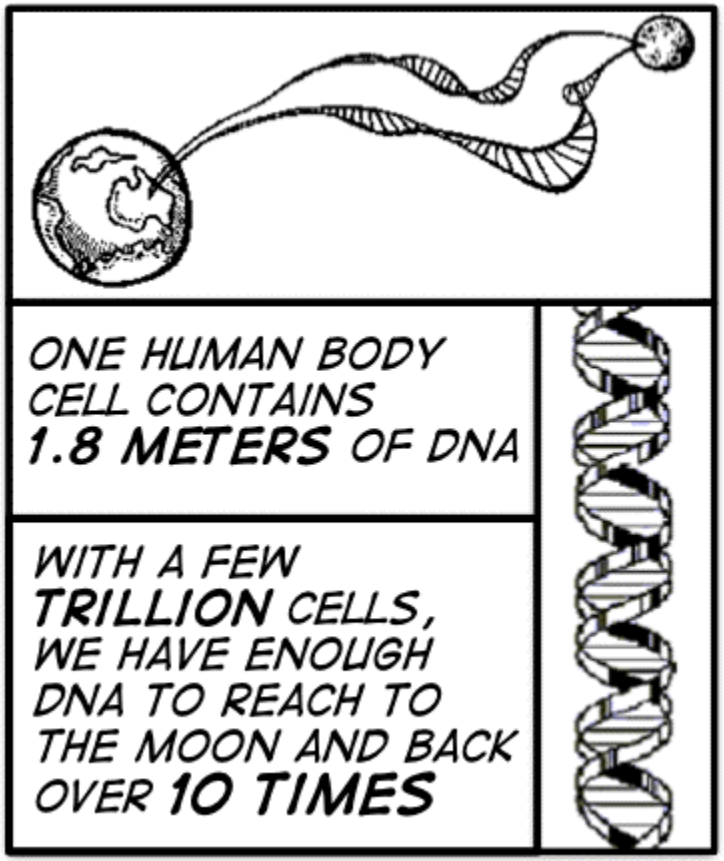
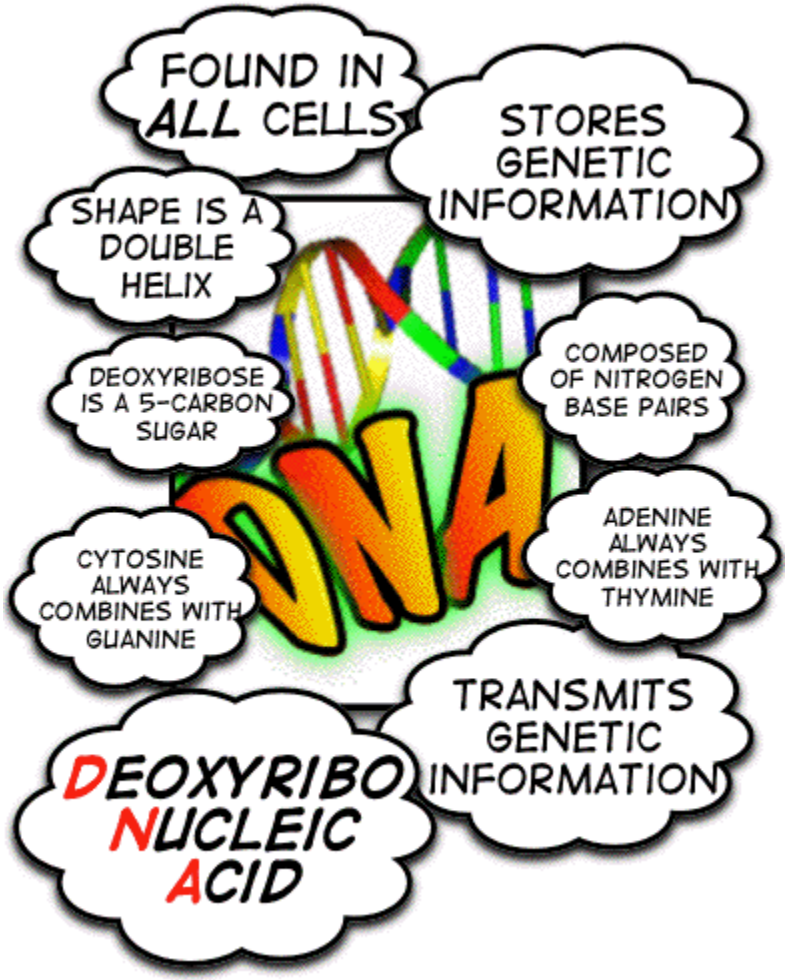
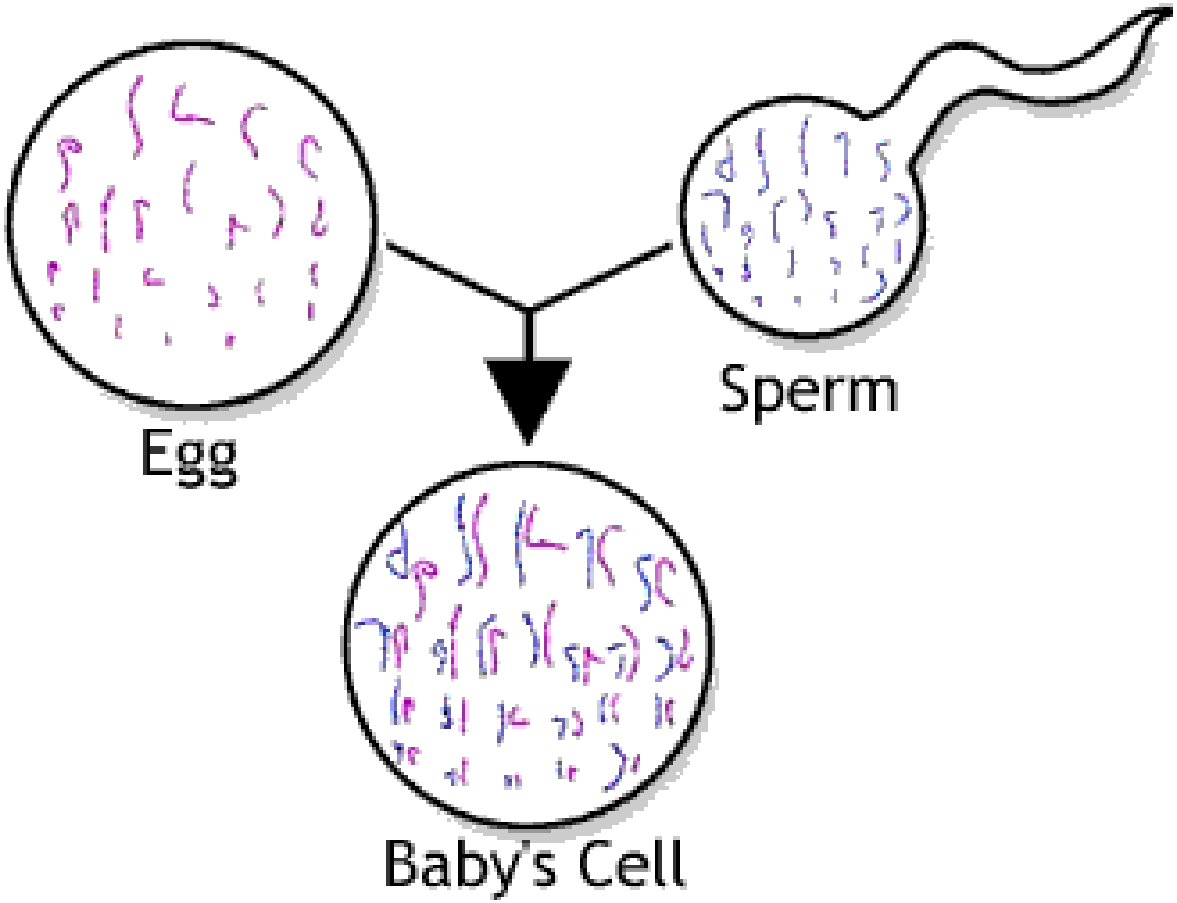
19
20
21
22
X
Y
22 pairs
Autosomes
1 pair sex
chromosomes

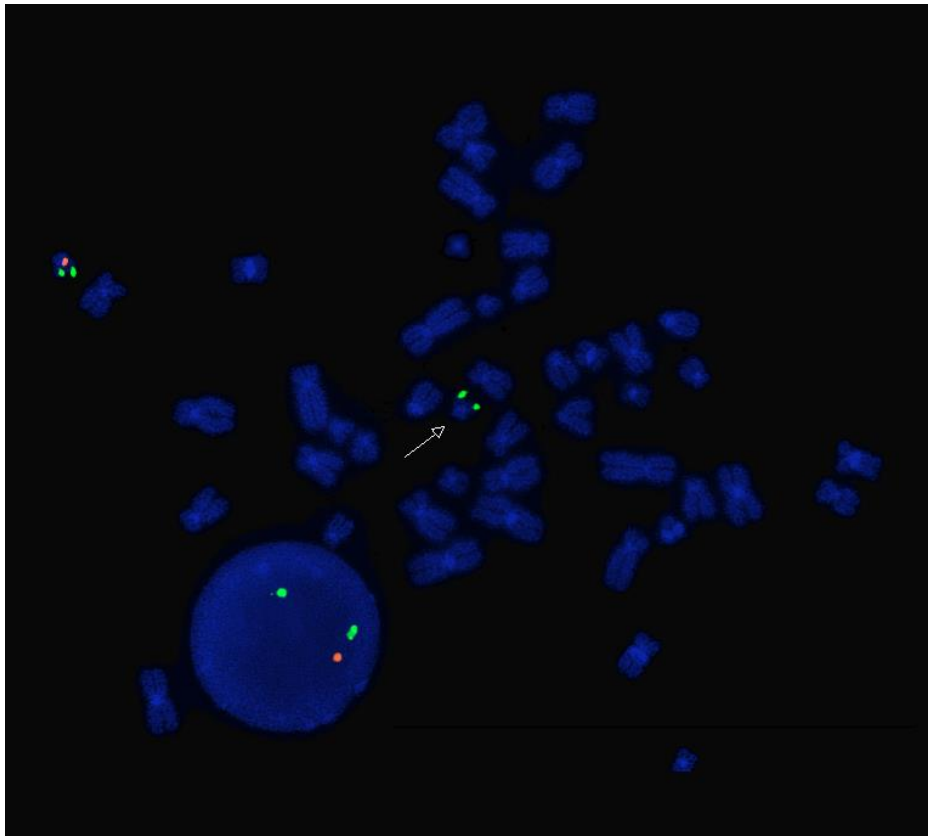

A PAIR OF HOMOLOGOUS CHROMOSOMES - ONE DERIVED FROM THE MALE PARENT, AND ONE FROM THE FEMALE PARENT
CENTROMERE, CONNECTING THE TWO CHROMATIDS
LOCUS, THE POSITION OF A GENE ON THE CHROMOSOME
ALLELE FROM THE MALE
ALLELE FROM THE FEMALE
ALLELES ARE DIFFERENT FORMS OF THE GENE FOR A SPECIFIC TRAIT - THEY MAY BE THE SAME, OR DIFFERENT, BUT THEY ARE ALWAYS FOUND AT THE SAME LOCUS ON HOMOLOGOUS CHROMOSOMES


ONE HUMAN BODY CELL CONTAINS 1.8 METERS OF DNA
WITH A FEW TRILLION CELLS, WE HAVE ENOUGH DNA TO REACH TO THE MOON AND BACK OVER 10 TIMES

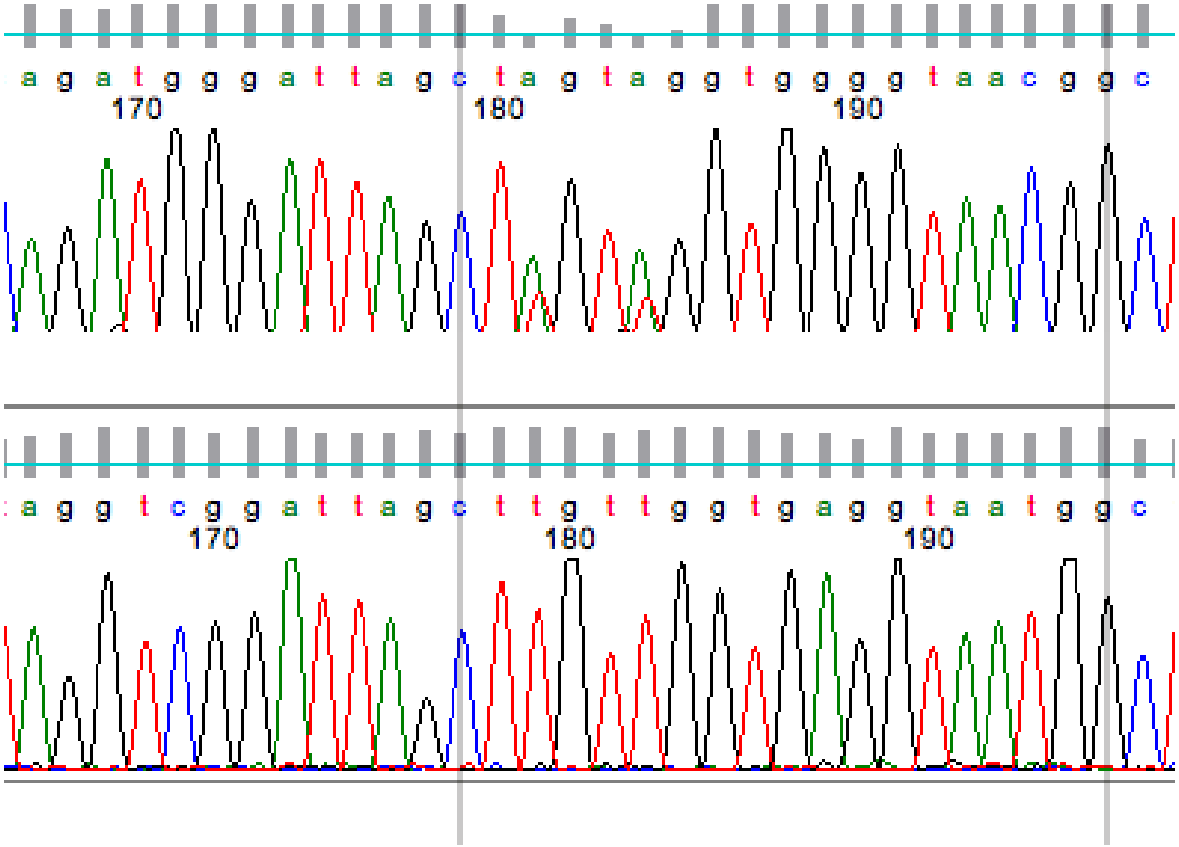

FOUND IN ALL CELLS
STORES GENETIC INFORMATION
SHAPE IS A DOUBLE HELIX
DEOXYRIBOSE IS A 5-CARBON SUGAR
COMPOSED OF NITROGEN BASE PAIRS
DNA
CYTOSINE ALWAYS COMBINES WITH GUANINE
ADENINE ALWAYS COMBINES WITH THYMINE
TRANSMITS GENETIC INFORMATION
DEOXYRIBO NUCLEIC ACID


Egg
Sperm
Baby's Cell

Basic Tests



Basic Tests


a g a t g g g a t t a g c t a g t a g g t g g g g t a a c g g c
170
180
190
a g g t c g g a t t a g c t t g t t g g t g a g g t a a t g g c
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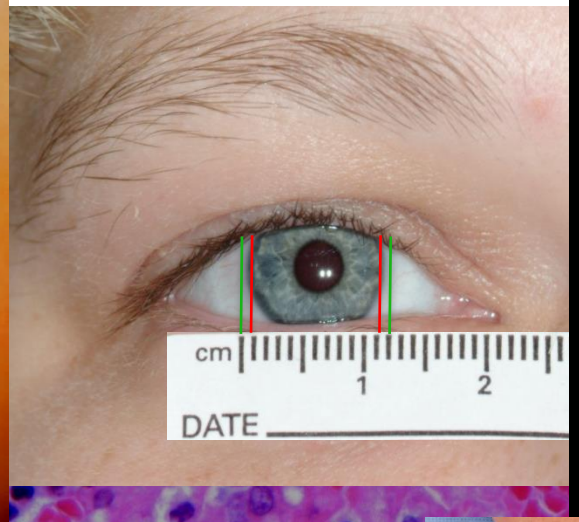
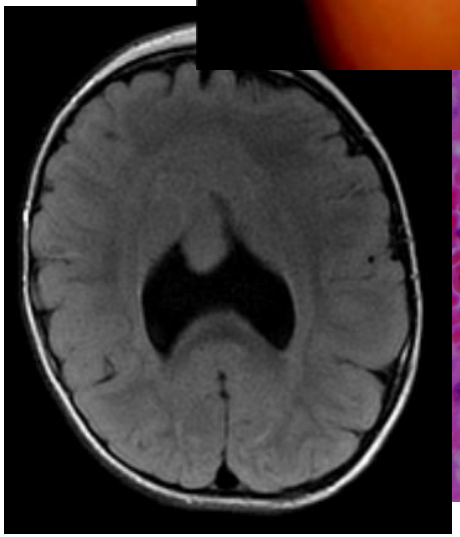
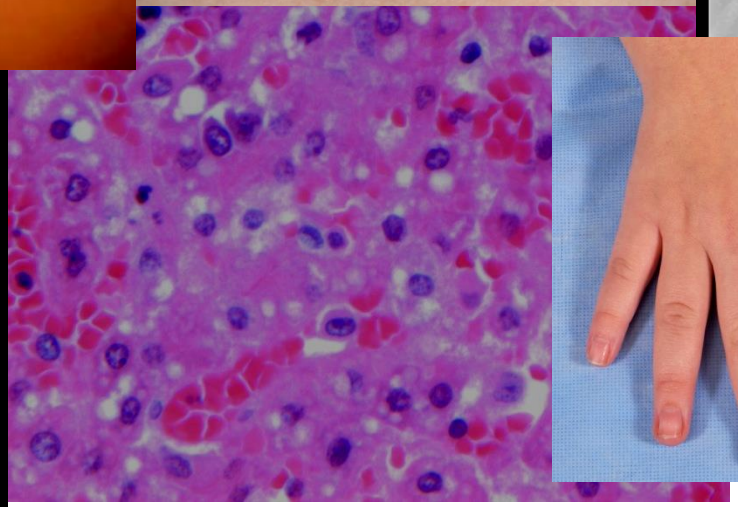
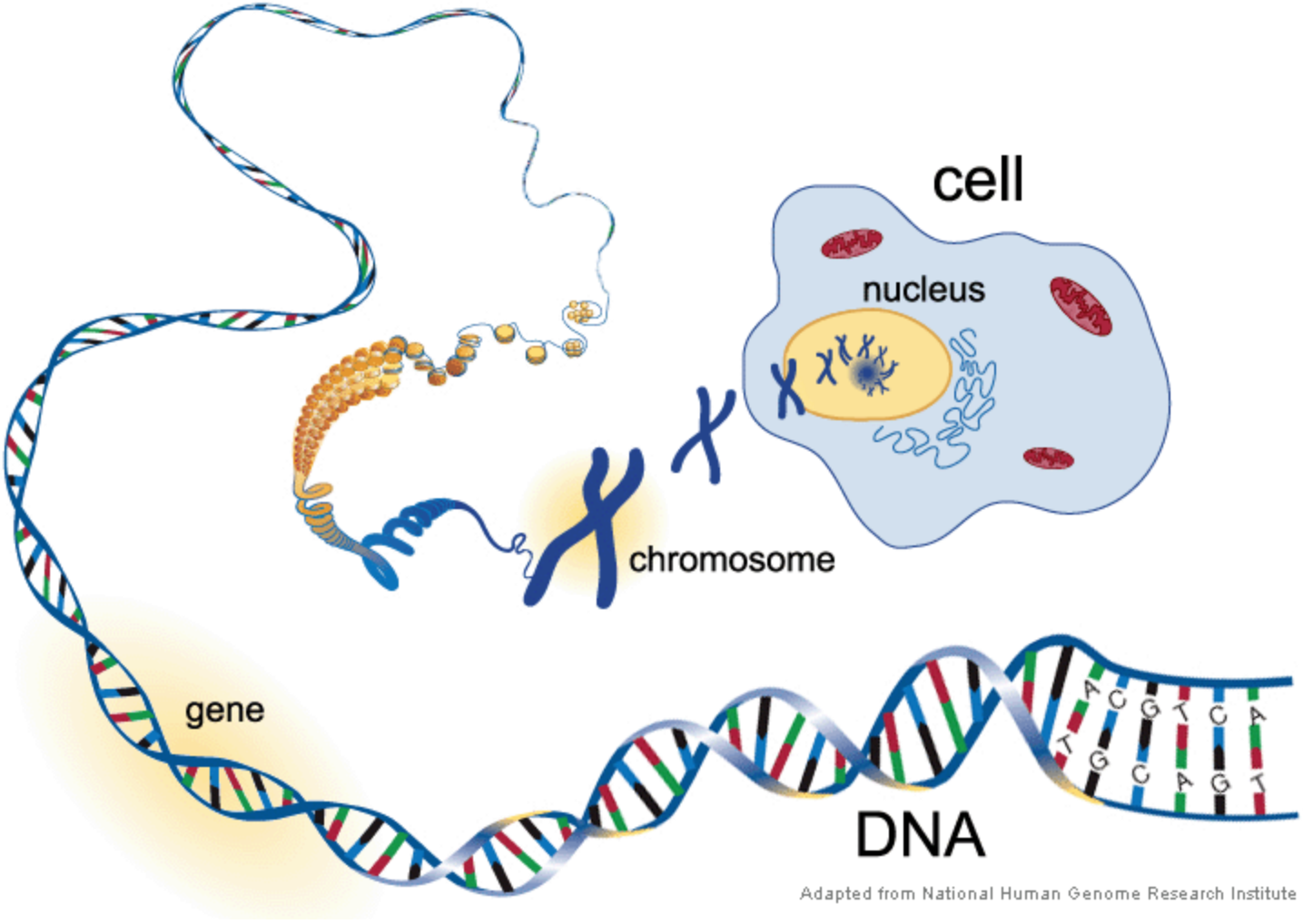
180
190

Don’t Forget “Clinical Tests”!!









Adapted from National Human Genome Research Institute

Alternative variants of genetic information at a specific locus

Allele

Wild Type

- Normal version of the sequence
- Considered the prevailing version

Mutant

- Permanent change in the nucleotide sequence
- Disease-causing

Polymorphism

- "Many forms"
- Locus has at least two relatively common alleles
- Allele frequency ≥ 0.01

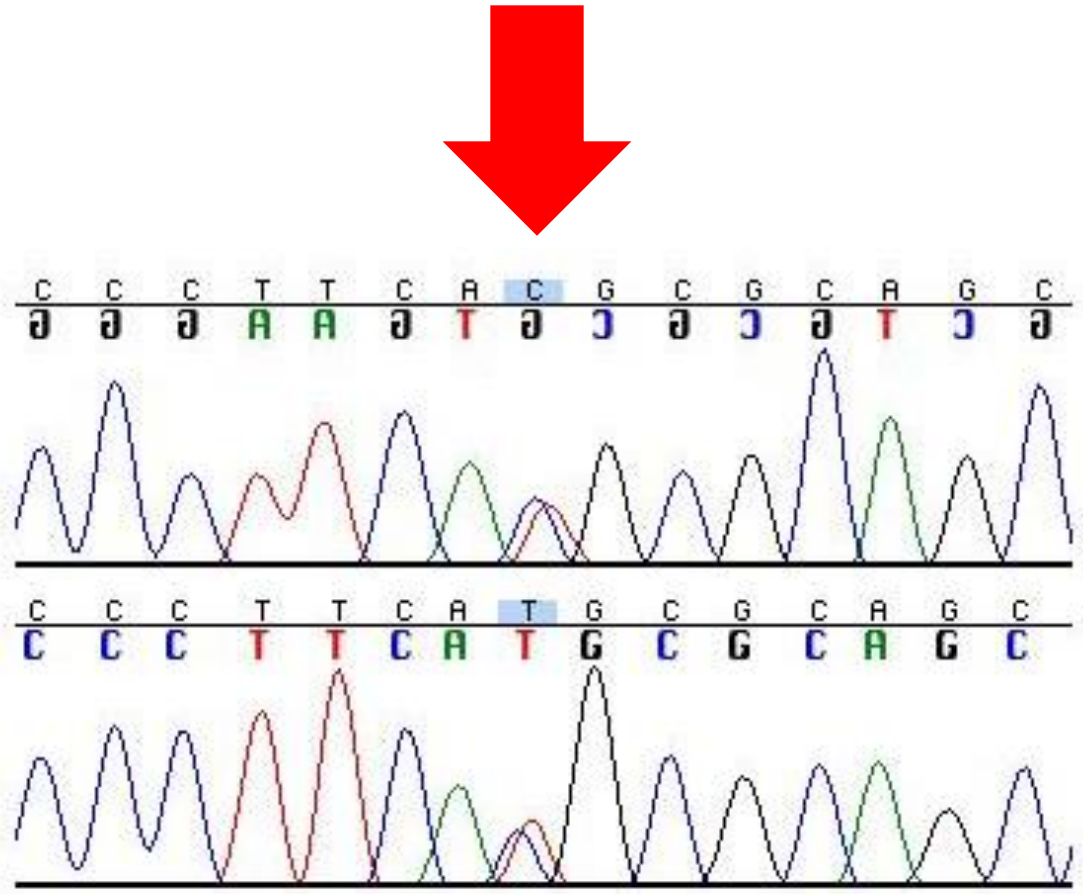
Rare Variant

- Rare allele that is not disease causing
- Allele frequency ≤ 0.01

Name that term!

Genotype

Set of alleles that make up a person's genetic constitution, usually at a single locus (rarely the word is used for all loci)



FGF8: c.653C>T, resulting in p.Thr229Met

Name that term!

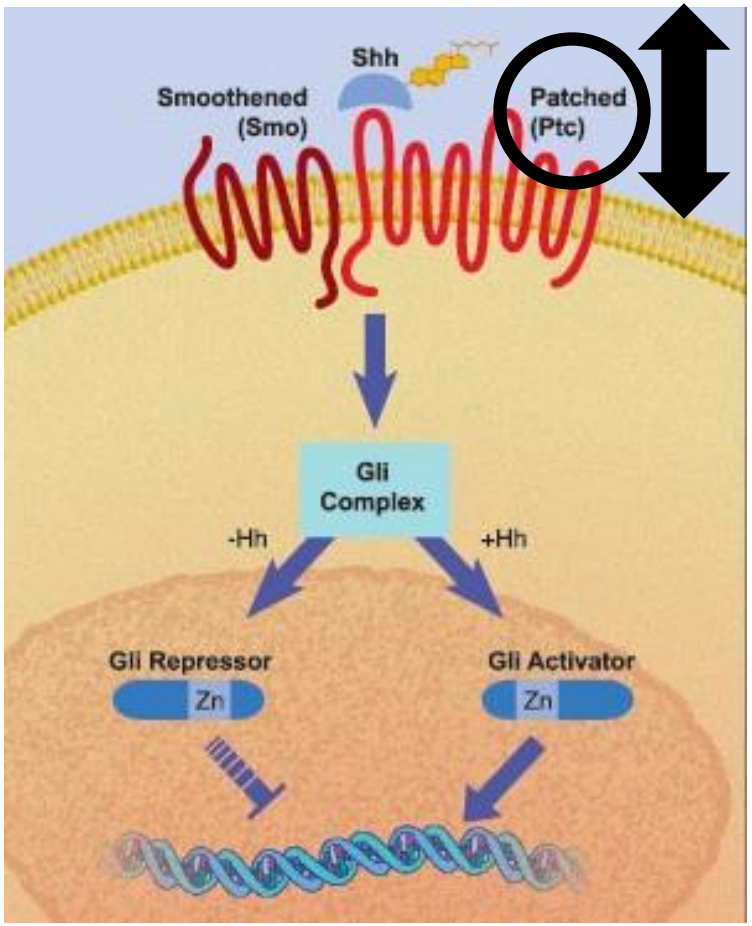
Phenotype

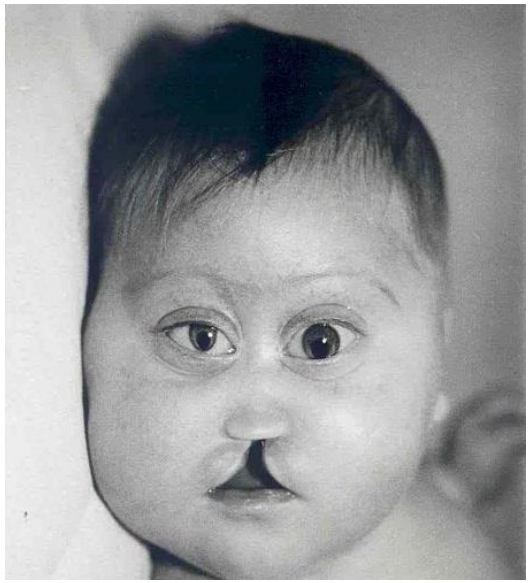
Observable expression of a genotype as a trait (can be morphological, clinical, biochemical, etc.)

Genotype  Phenotype

- “Genotype-Phenotype” correlations
- Frequently not (yet) possible
- Some interesting exceptions

It depends on the type of mutation





Name that term!

de novo

Term for a mutation that appears in a proband (and does not appear to be present in the parents)

Single gene disorder

Determined by alleles at a single locus

Individual or Genotype

Homozygote

An individual with the same allele in each locus

Heterozygote

An individual with different alleles in each locus (a wild type allele, a mutant allele)

Compound Heterozygote

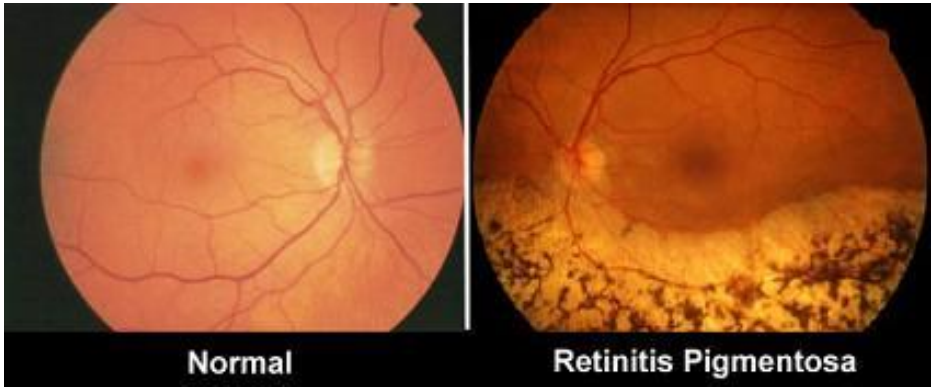
An individual with 2 different mutant alleles of the same gene

Heterogeneity

Locus (Genetic) Heterogeneity

Disorders can be caused by mutations in different genes, or by different mechanisms

Examples: Retinitis Pigmentosa, Noonan syndrome, *MANY* more…



Locus Heterogeneity

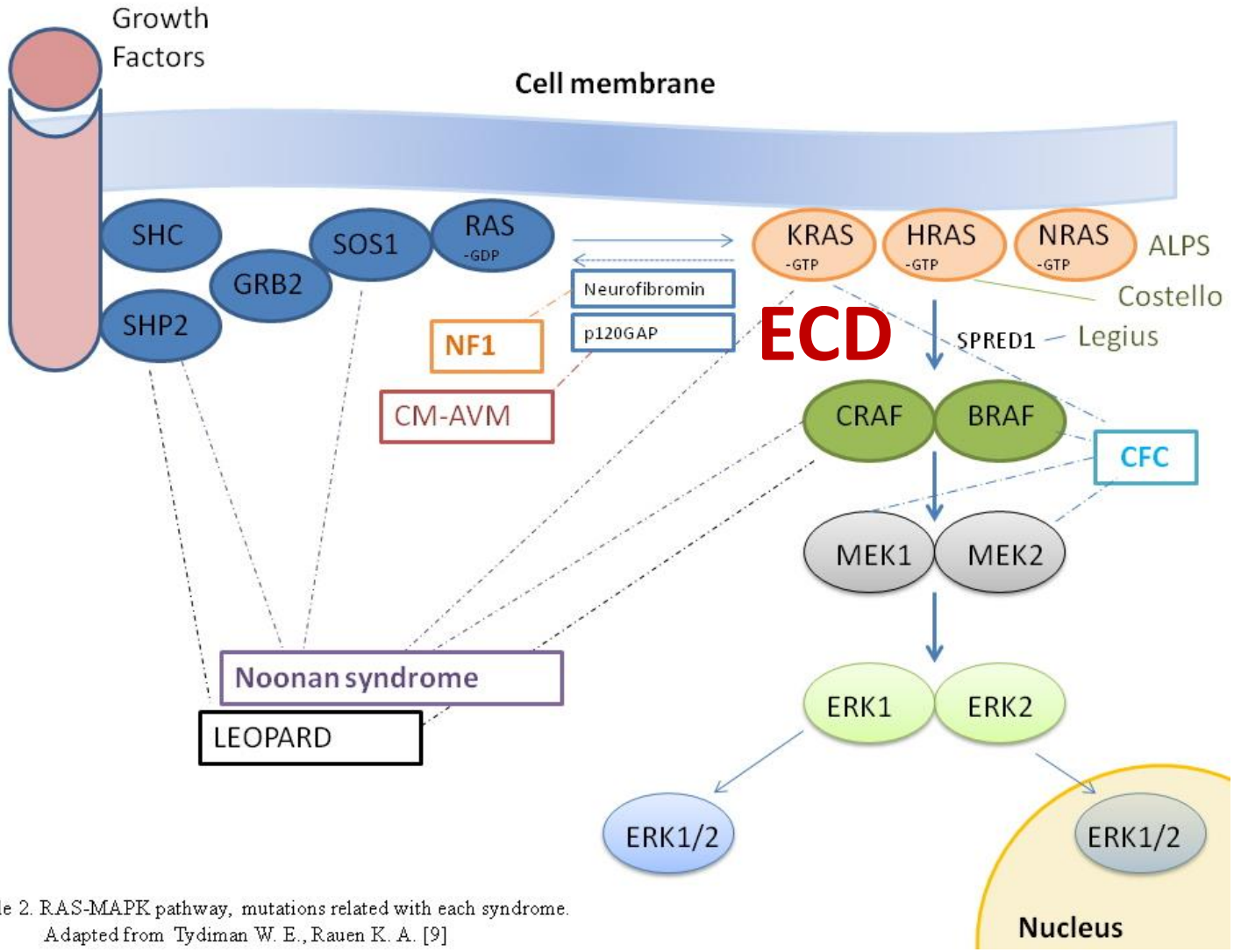


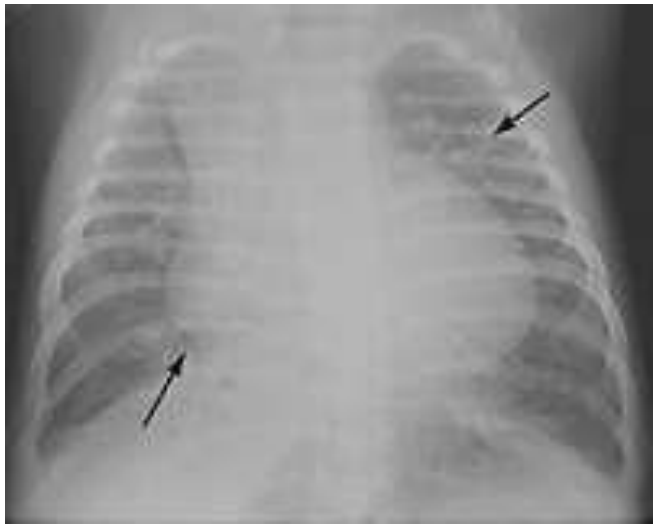
Table 2. RAS-MAPK pathway, mutations related with each syndrome.
Adapted from Tydiman W. E., Rauen K. A. [9]

Heterogeneity

Phenotypic Heterogeneity/ Pleiotropy

Changes in a single gene influences multiple phenotypic traits

Example: Holt-Oram syndrome (*TBX5*)

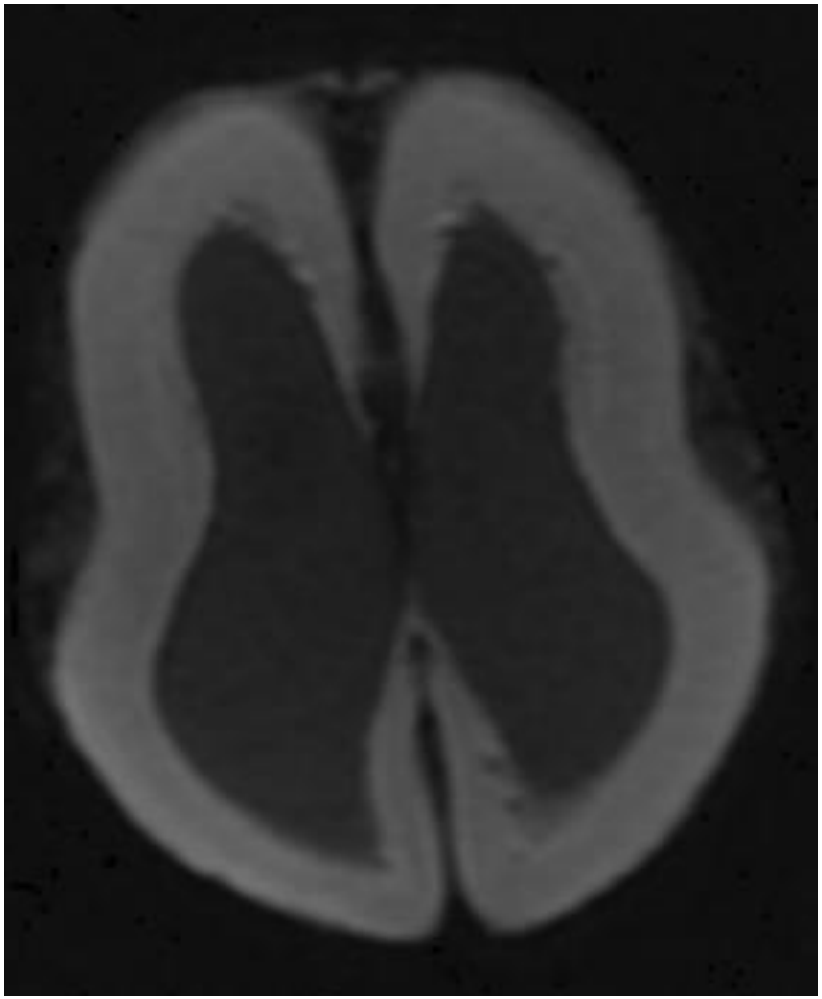


Congenital vs. Genetic

- Congenital: present at birth
- Genetic: determined by genes
- A condition can be both congenital and genetic

Miller-Dieker Syndrome

- Deletion of 17p13.3
- *LIS1*
- Severe neurological compromise, seizures, organ anomalies



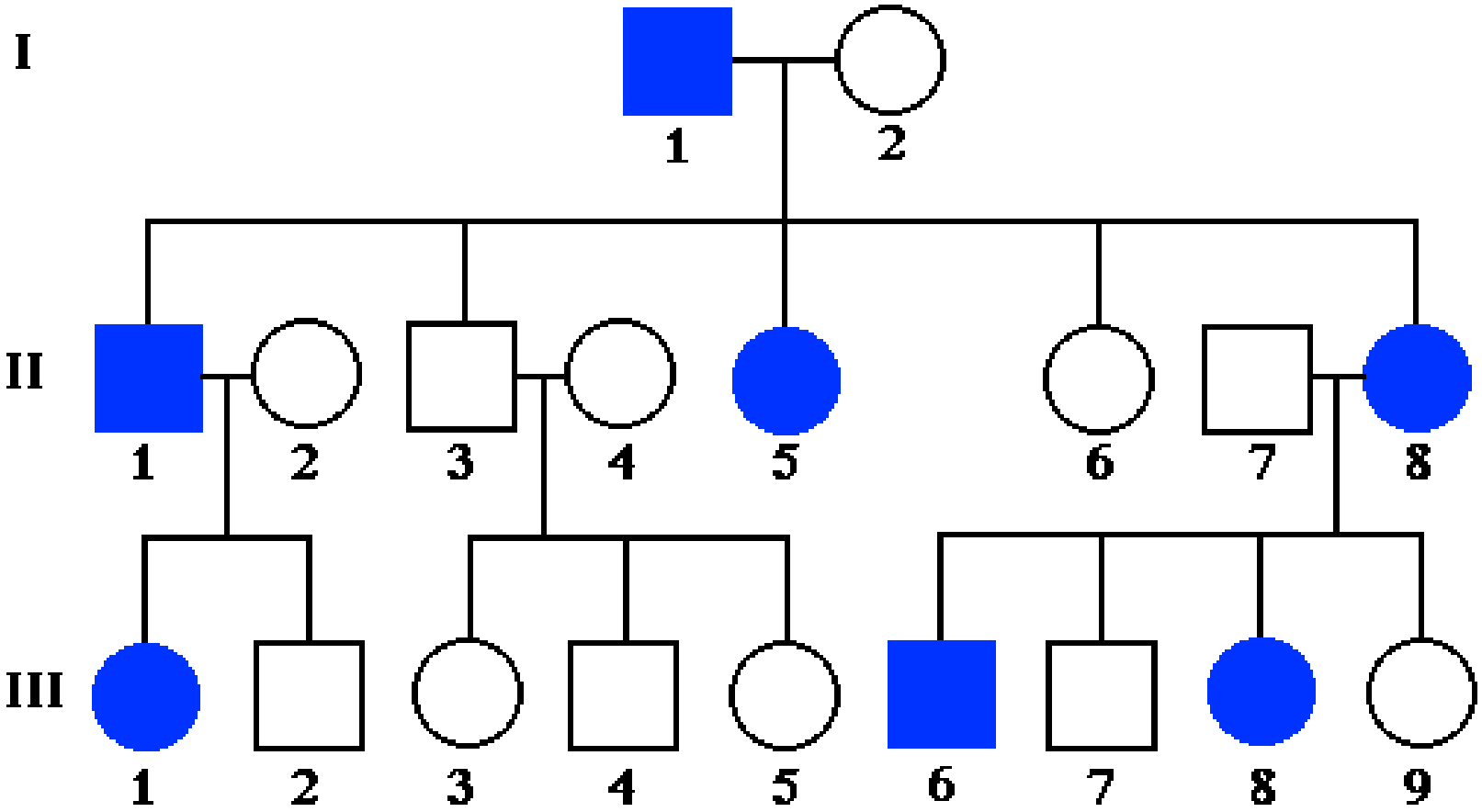
III. Inheritance Patterns

Goal:

Familiarity with basic patterns of human heredity

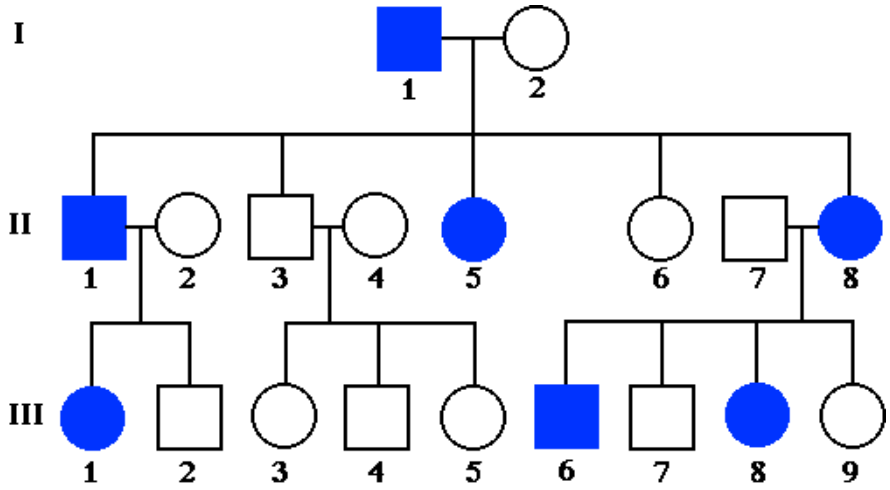
“Mendelian” disorders

Autosomal Dominant

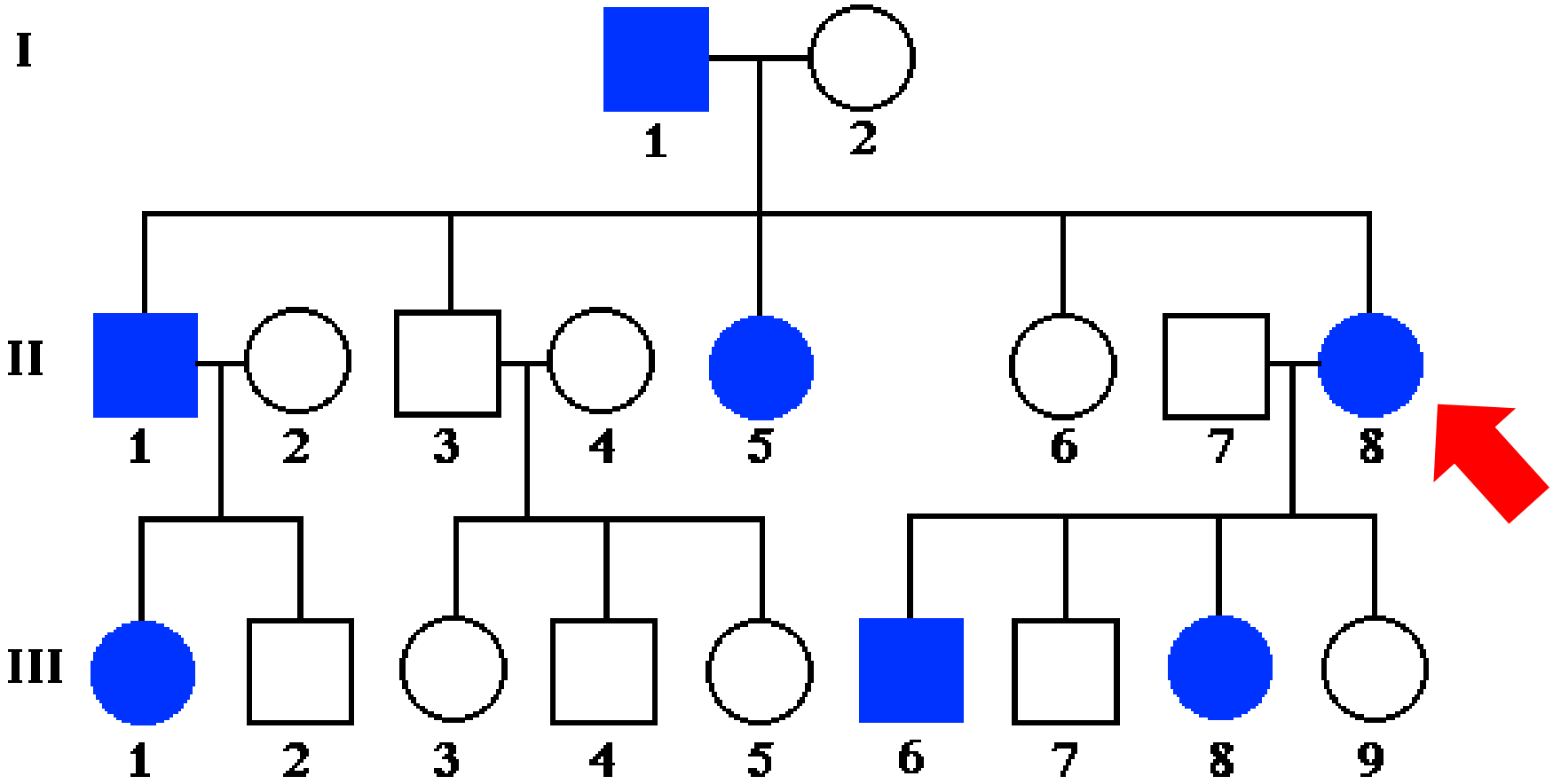


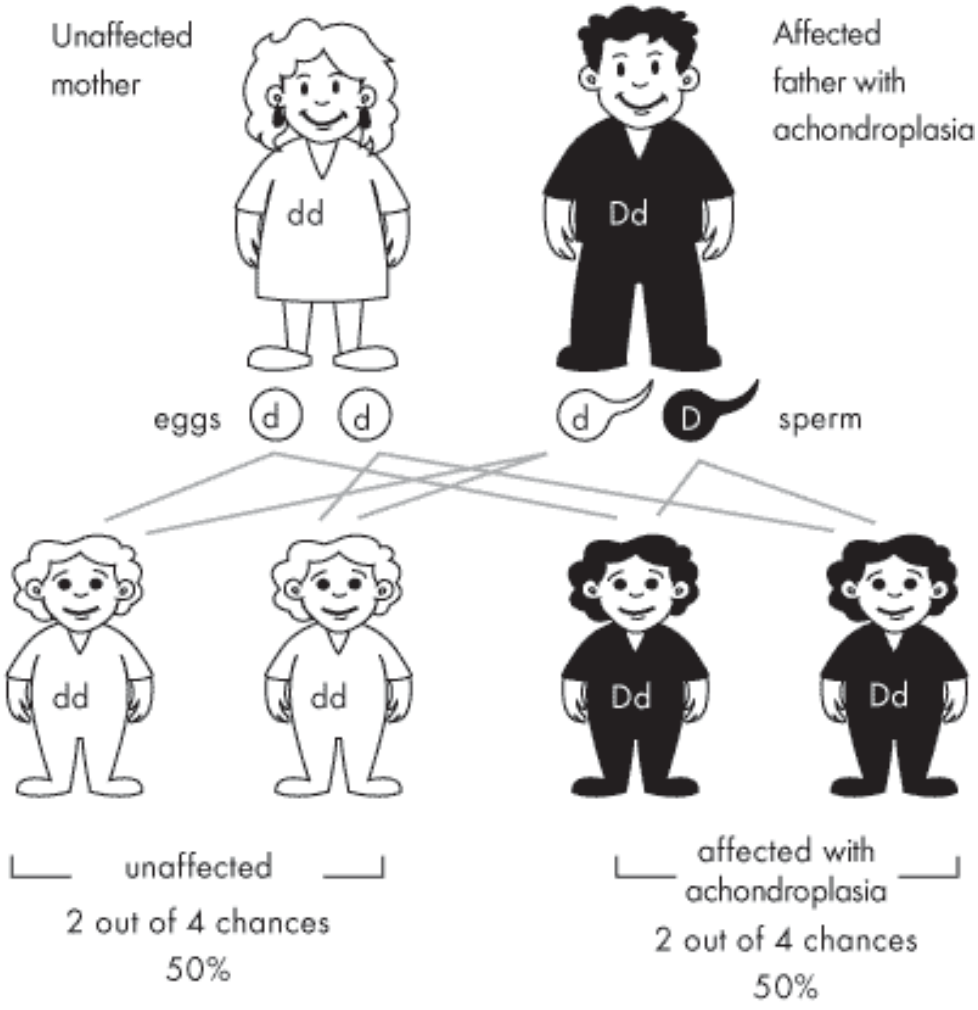
Autosomal Dominant

- “Phenotype seen in heterozygotes”
- Males and females equally affected
- Every affected person (usually) has an affected parent
- Unaffected parents (usually)don’t have affected children



Autosomal Dominant: Recurrence Risk




Unaffected
mother
dd
Affected
father with
achondroplasia
Dd
eggs
d
d
d
D
sperm
dd
dd
Dd
Dd
unaffected
2 out of 4 chances
50%
affected with
achondroplasia
2 out of 4 chances
50%

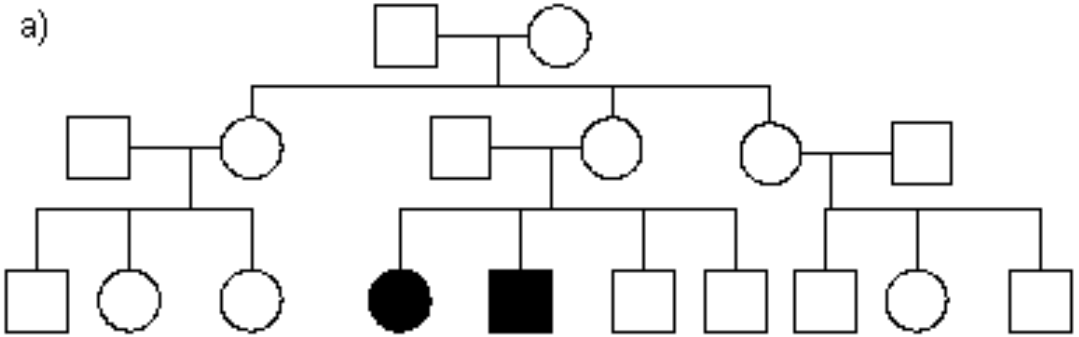

51

NF-1

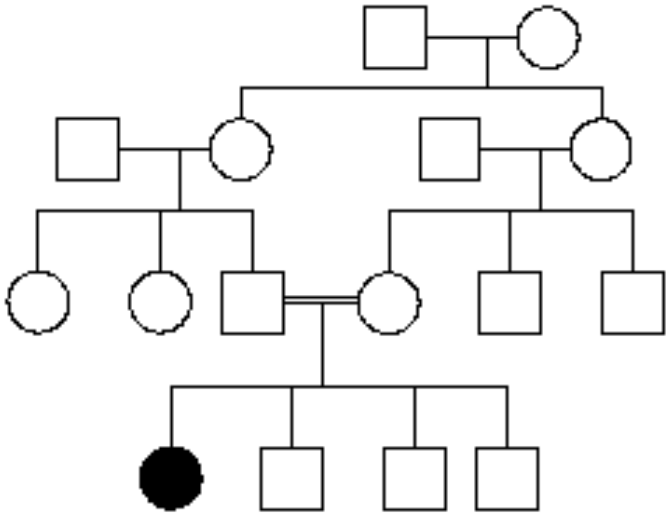
Tuberous Sclerosis

Autosomal Recessive

a)

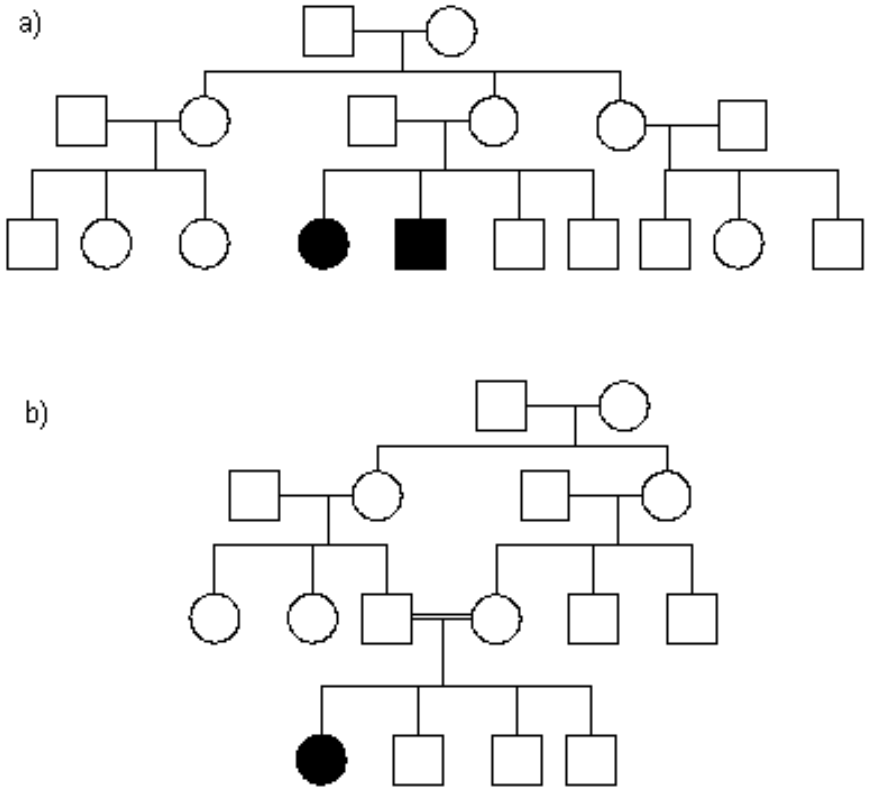


b)



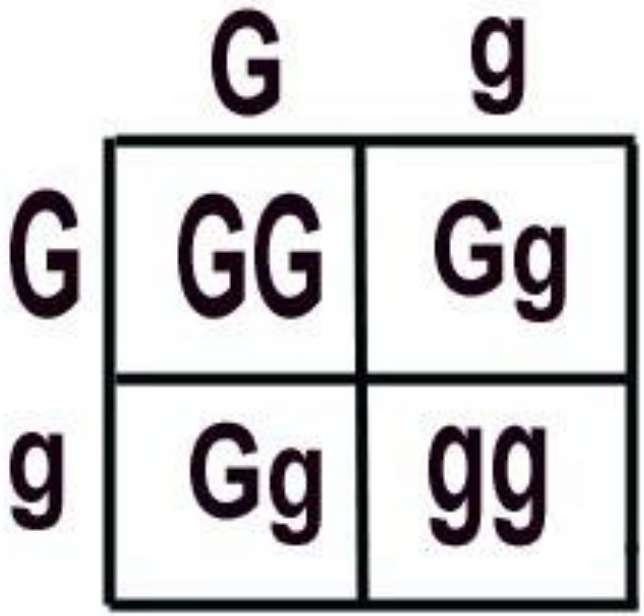
Autosomal Recessive

- “Phenotype only in homozygotes”
- Males and females equally affected
- Affected people have unaffected parents
- Affected people have unaffected children

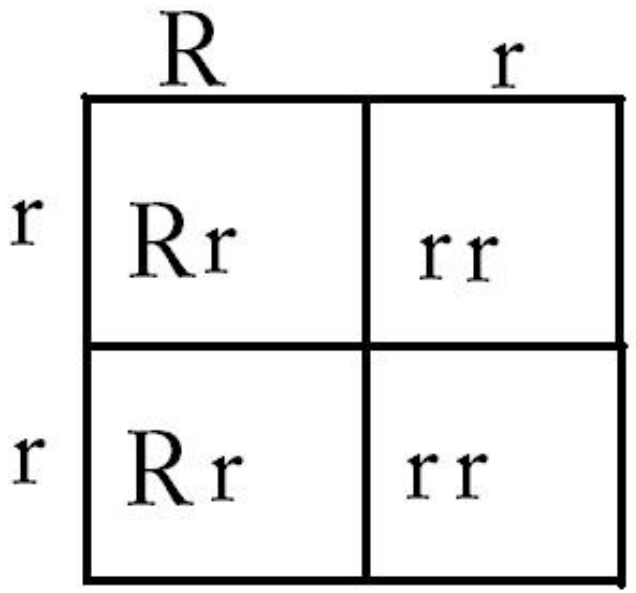


Autosomal Recessive

Gg x Gg

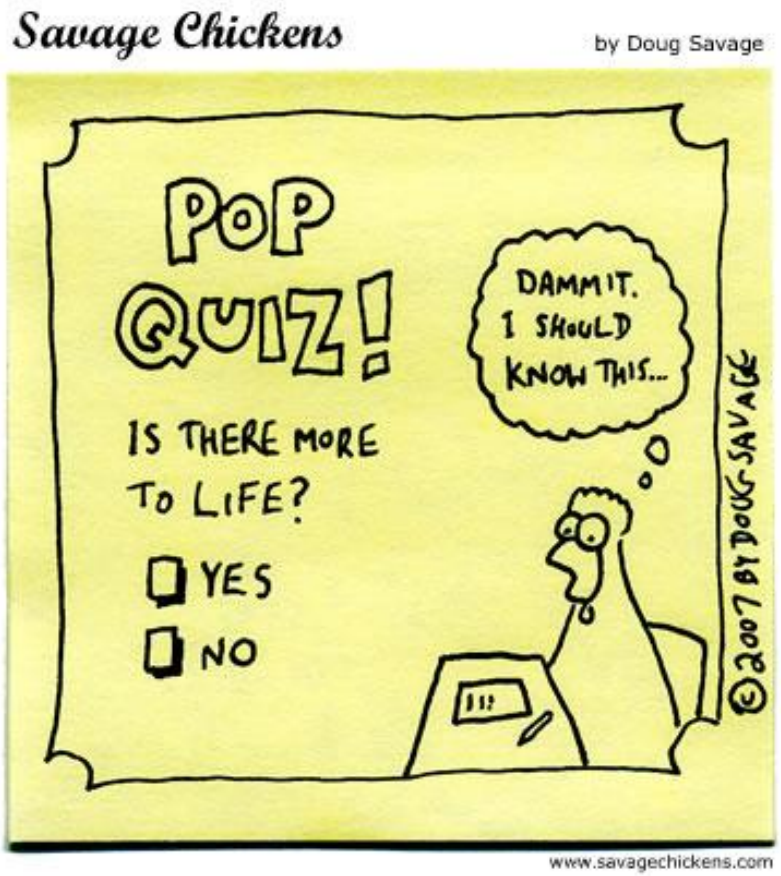


Rr x rr

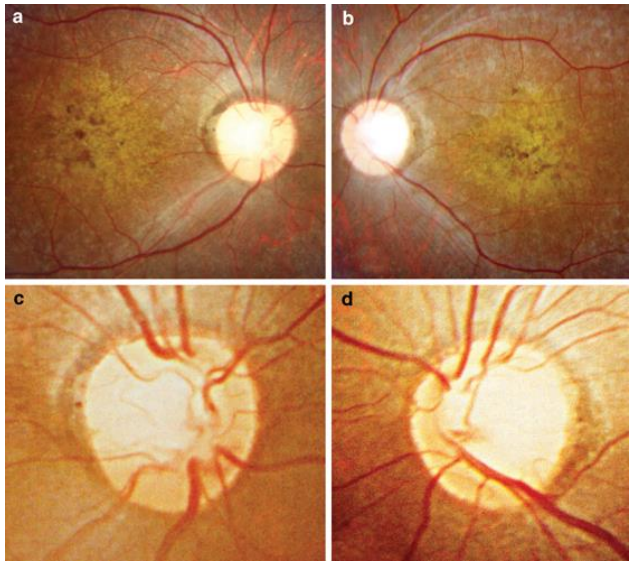


Autosomal Recessive

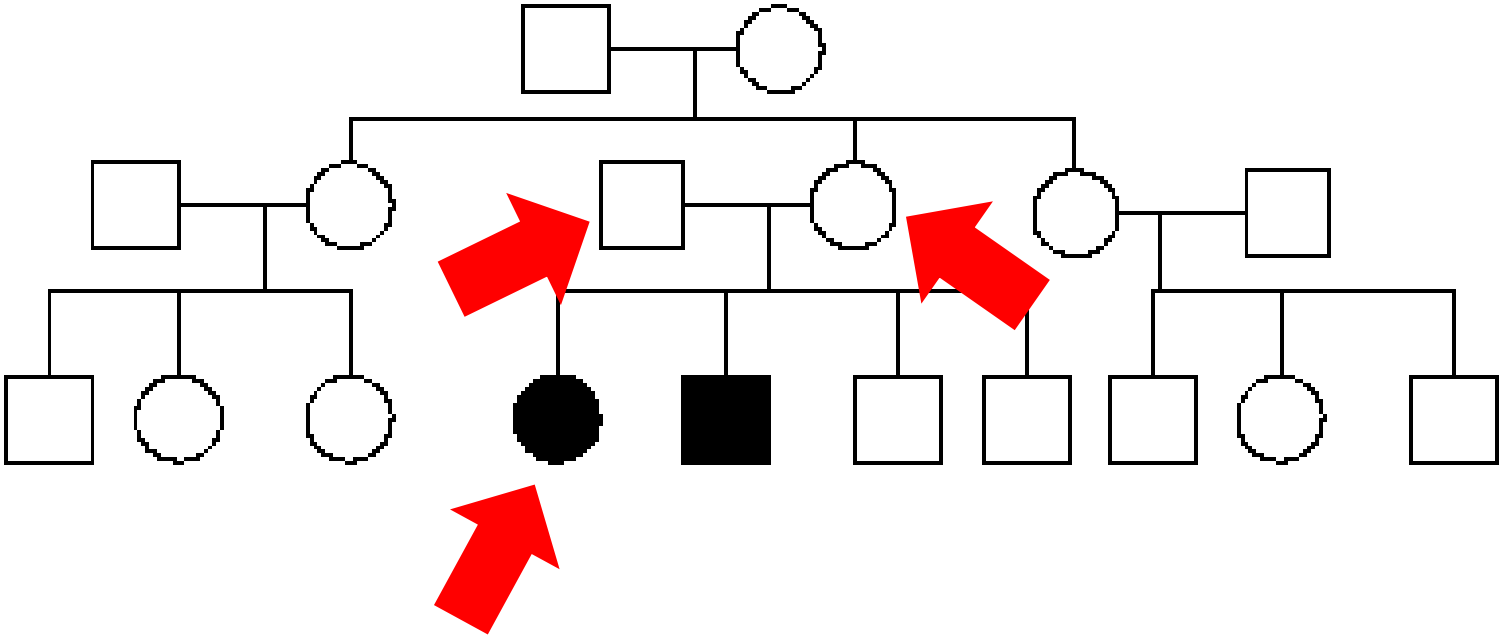
- We all are carriers of ~8-10 recessive mutations
- Certain alleles are more common in specific populations
- Usually, new mutation rate < carrier rate



Bardet-Biedl syndrome

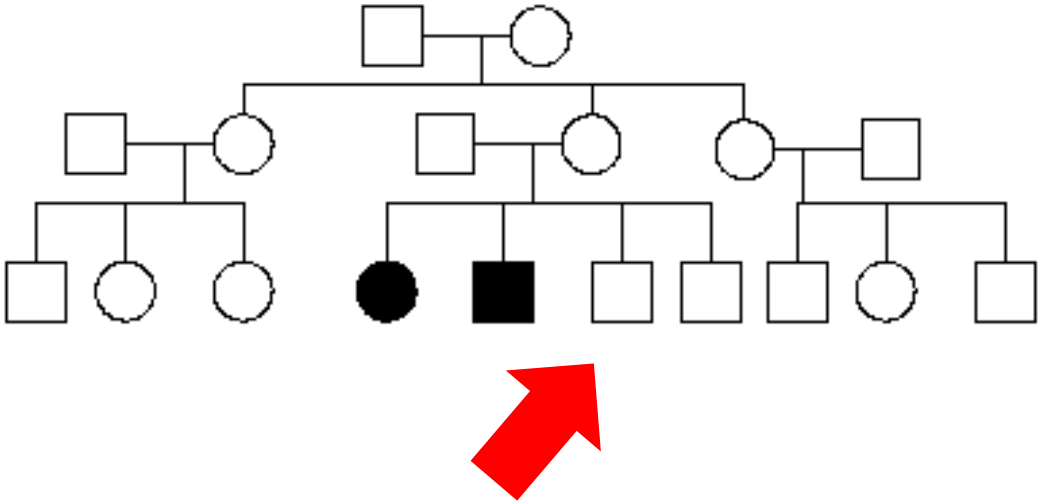


Autosomal Recessive: Recurrence Risk



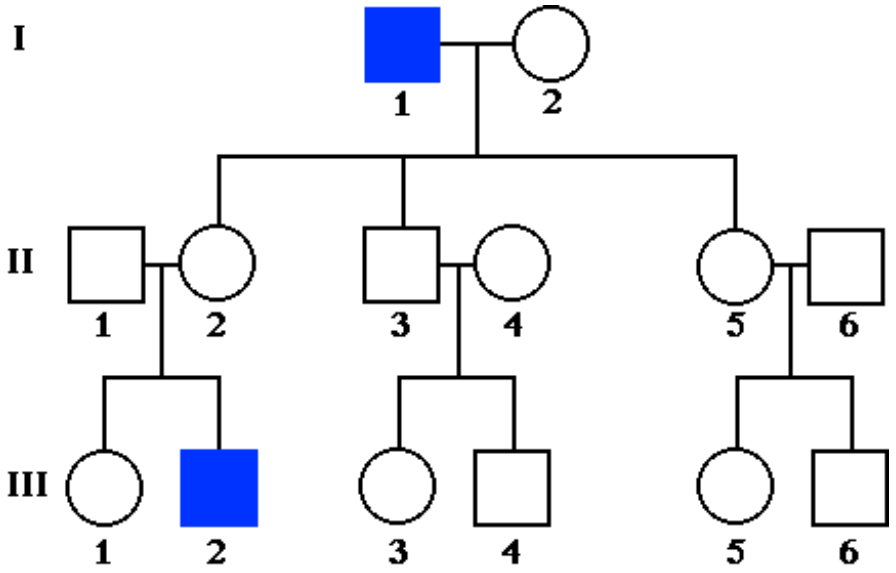
Autosomal Recessive

	G	g
G	GG	Gg
g	Gg	gg



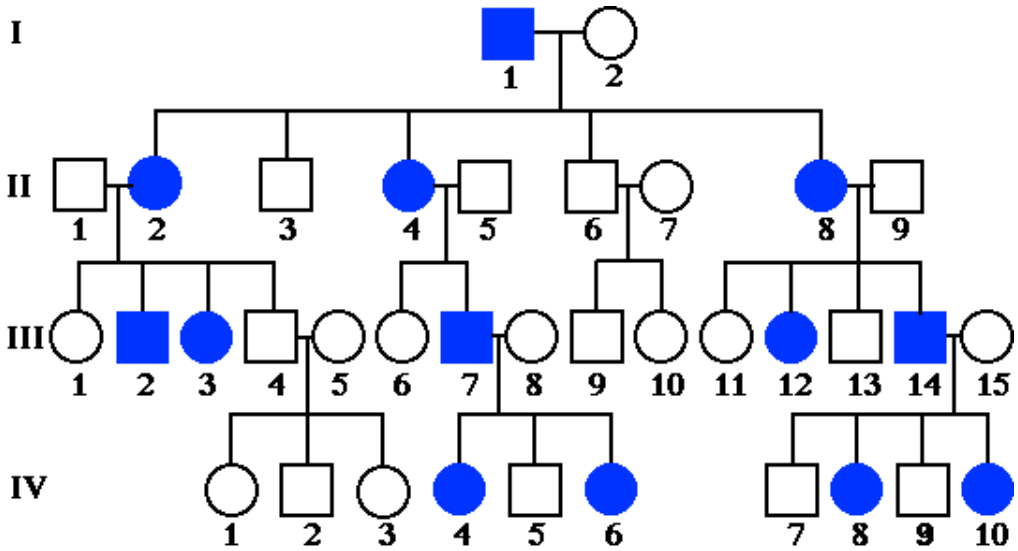
X-linked “Recessive”

- Males predominantly affected
- Female “carriers” may show some disease signs
- Condition never transmitted from father to son
- “Carrier” female can have affected sons

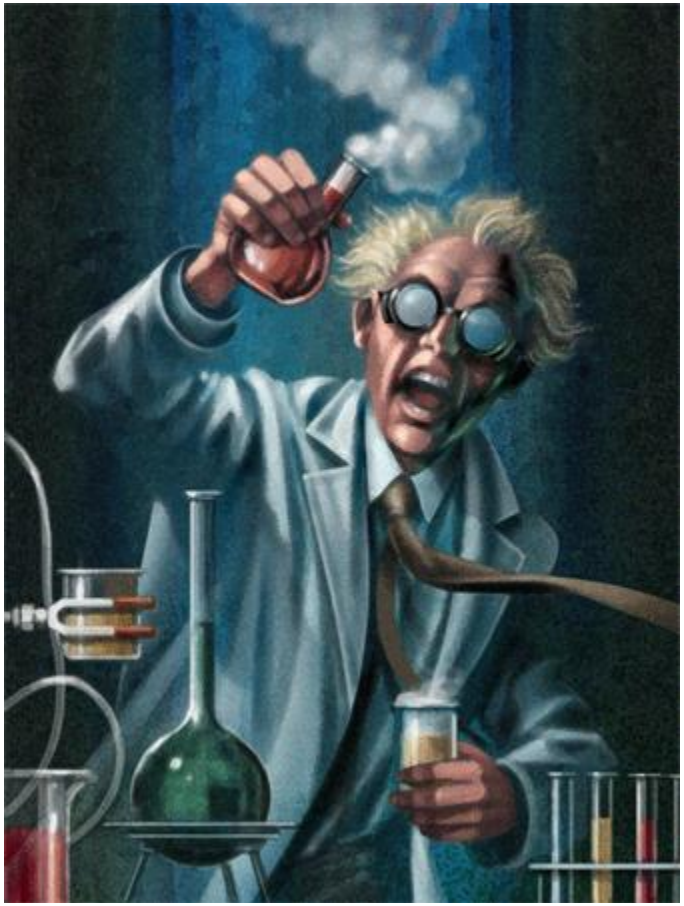


X-linked “Dominant”

- Affected males have no affected sons
- Affected males have all affected daughters
- What can it look like?
- Autosomal dominant
- Don’t forget “pseudo-autosomal” conditions

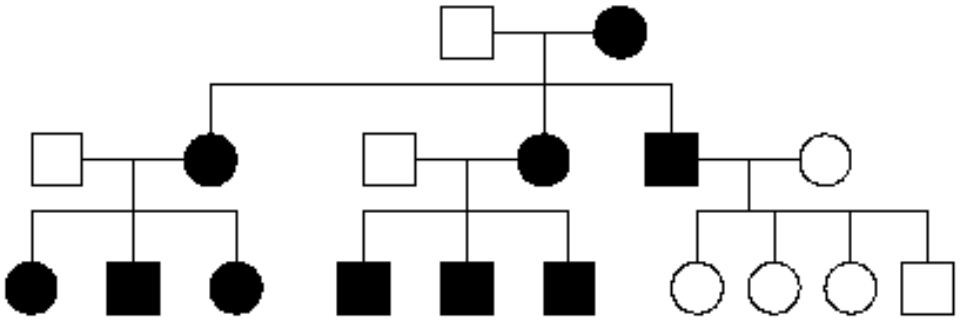


Other Modes of Inheritance



Mitochondrial

- ~16.5 kb DNA
- Maternal inheritance
- Incomplete penetrance
- Heteroplasmy
- Threshold effect
- Can be tissue-specific
- (Remember: some mitochondrial disorders are recessive)
- A diagnostic challenge!



Mosaicism

- An individual or tissue with multiple genetically different cell lines derived from a single zygote
- Pre vs. postnatal
- Somatic vs. germline

Mosaicism

Complex/Multifactorial

Neural tube defects

Multiple Sclerosis

ADHD

Hypertension

DIABETES MELLITUS

ASTHMA

Longevity

Obesity

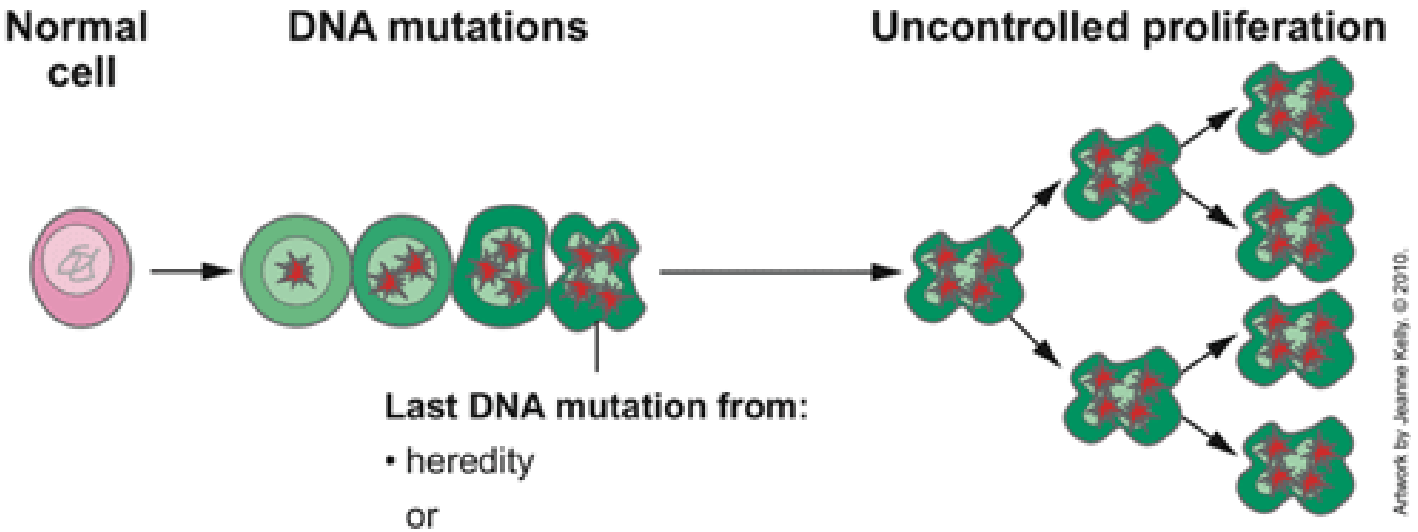
Schizophrenia

Kawasaki's disease

Cancer Genetics

- **Cancer: A Genetic Disease**
- **Oncogenes**
- **Tumor Suppressor Genes**
- **Genetic Pathways to Cancer**

Cancer Arises From DNA Mutations in Cells



NATIONAL CANCER INSTITUTE

Cancer and Genes

- **Oncogenes** are genes that, when mutated, actively promote cell proliferation.

- **Tumor suppressor genes** are genes that, when mutated, fail to repress cell division.

Genetic Pathways to Cancer

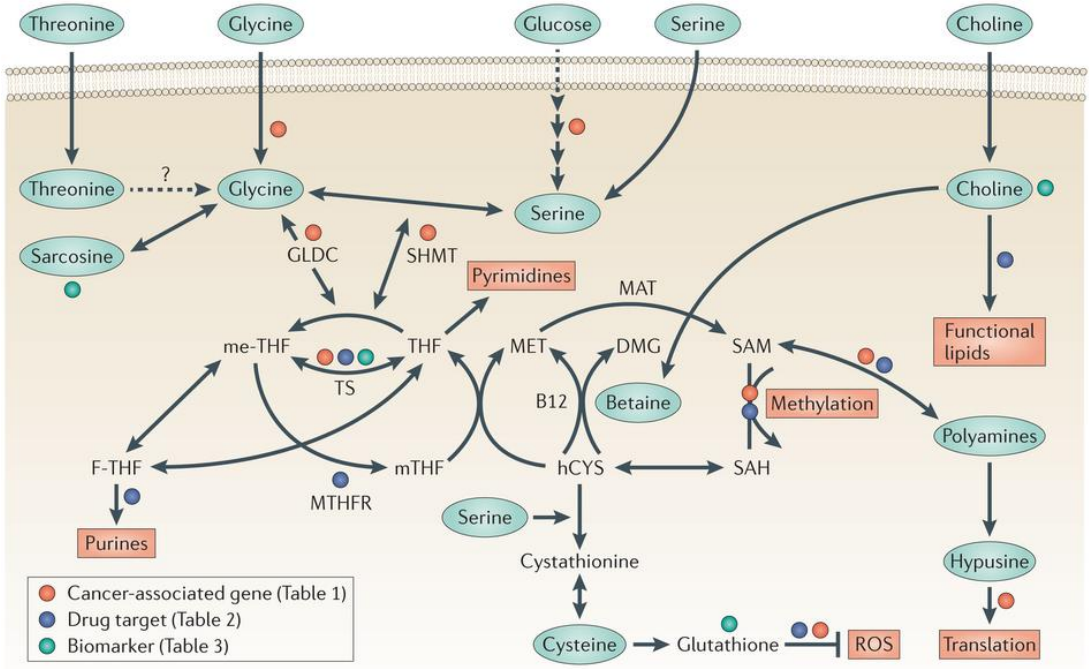
- Most malignant tumors cannot be attributed to mutation of a single gene.
- Tumor formation, growth, and metastasis depend on the accumulation of mutations in several different genes.
- The genetic pathways to cancer are diverse and complex.

Somatic Mutation and Cancer

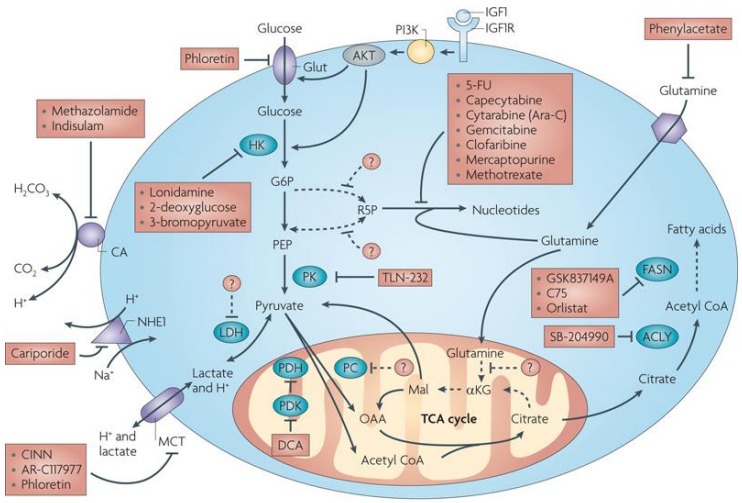
- Somatic mutation is the basis for the development and progression of all types of cancer.

- As mutations accumulate and cells become unregulated, genetic instability increases the likelihood that the cells will develop the hallmarks of cancer.

Pathways and Cancer.



Nature Reviews | Cancer



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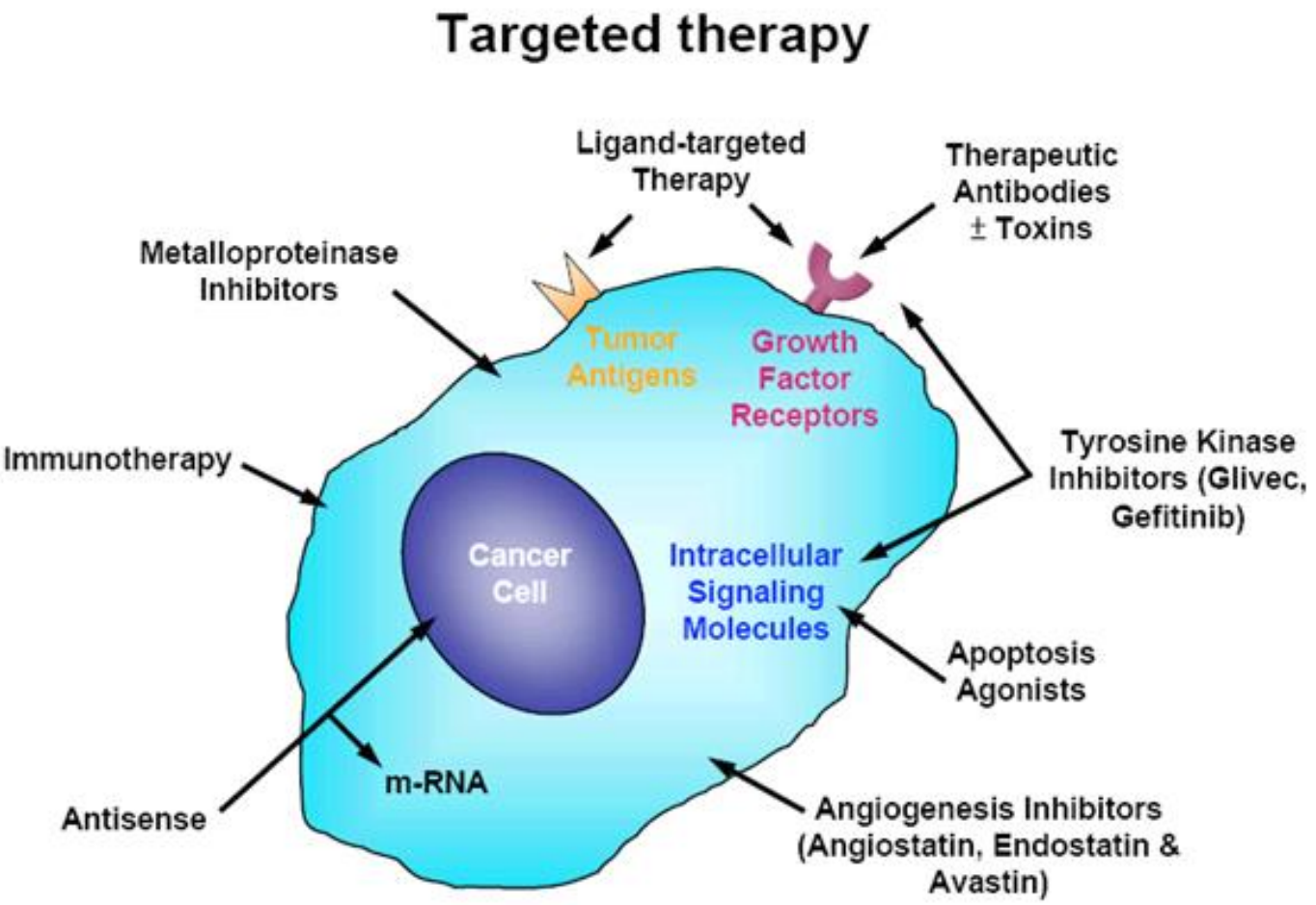
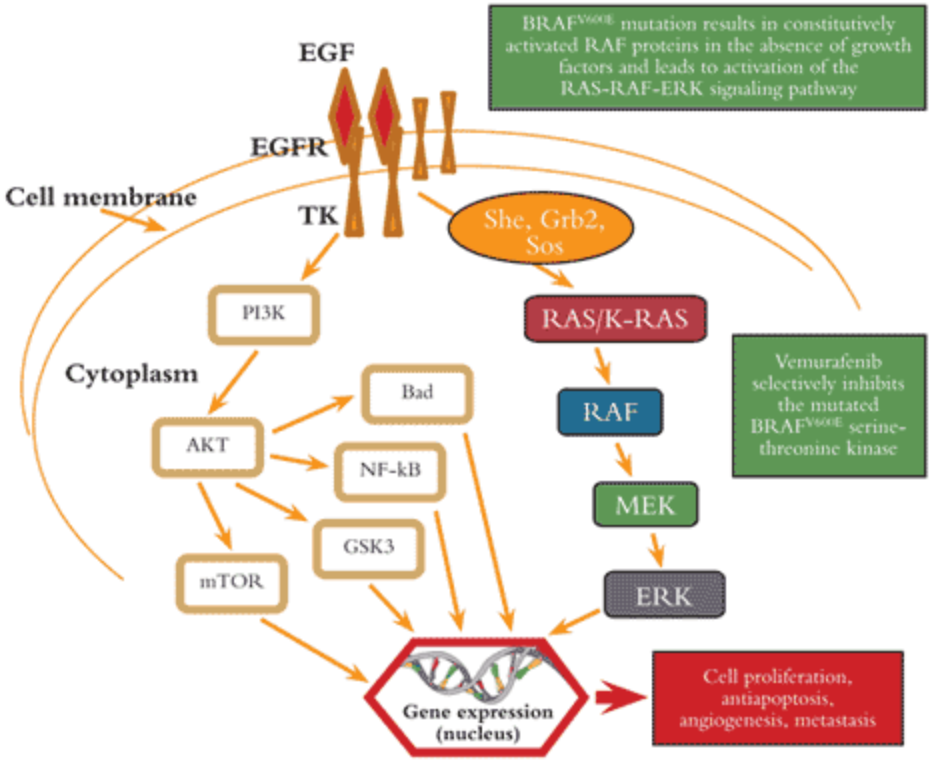
Cancer Targeted Therapy.



Cancer Targeted Therapy.

Figure 2. $BRAF^{V600E}$ Mutation and RAS-RAF-MEK-ERK Signal Transduction Cascade



AKT: v-akt murine viral oncogene; Bad: Bcl-2-associated death promoting protein; EGF: epidermal growth factor; EGFR: EGF receptor; ERK: extracellular signal-regulated kinase; Grb2: growth factor receptor-bound protein 2 adaptor protein; GSK3: glycogen synthase kinase 3; K-RAS: v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue; MEK: MAPK/ERK kinase; mTOR: mammalian target of rapamycin; NF-kB: nuclear factor kB; PI3K: phosphoinositide 3-kinase; RAF: proto-oncogene serine/threonine kinase; RAS: rat sarcoma subfamily of guanosine triphosphate-binding proteins (GTPases); She: Src homology 2 domain; Sos: "Son of sevenless" guanine nucleotide exchange protein; TK: tyrosine kinase.

Cancer Targeted Therapies – FDA Approved.

- Adenocarcinoma of the stomach or gastroesophageal junction: Trastuzumab (Herceptin®)
- Basal cell carcinoma: Vismodegib (Erivedge™)
- Brain cancer: Bevacizumab (Avastin®), Everolimus (Afinitor®)
- Breast cancer: Everolimus (Afinitor®), tamoxifen, toremifene (Fareston®), Trastuzumab (Herceptin®), fulvestrant (Faslodex®), anastrozole (Arimidex®), exemestane (Aromasin®), lapatinib (Tykerb®), letrozole (Femara®), pertuzumab (Perjeta™), ado-trastuzumab emtansine (Kadcyla™)
- Colorectal cancer: Cetuximab (Erbitux®), Panitumumab (Vectibix®), Bevacizumab (Avastin®), Ziv-aflibercept (Zaltrap®), Regorafenib (Stivarga®)
- Dermatofibrosarcoma protuberans: Imatinib mesylate (Gleevec®)

- Head and neck cancer: Cetuximab (Erbitux®)
- Gastrointestinal stromal tumor: Imatinib mesylate (Gleevec®), Sunitinib (Sutent®), Regorafenib (Stivarga®)
- Giant cell tumor of the bone: Denosumab (Xgeva®)
- Kaposi sarcoma: Alitretinoin (Panretin®)
- Kidney cancer: Bevacizumab (Avastin®), Sorafenib (Nexavar®), Sunitinib (Sutent®), Pazopanib (Votrient®), Temsirolimus (Torisel®), Everolimus (Afinitor®), Axitinib (Inlyta®)
- Leukemia: Tretinoin (Vesanoid®), Imatinib mesylate (Gleevec®), Dasatinib (Sprycel®), Nilotinib (Tasigna®), Bosutinib (Bosulif®), Rituximab (Rituxan®), Alemtuzumab (Campath®), Ofatumumab (Arzerra®), Obinutuzumab (Gazyva™)
- Liver cancer: Sorafenib (Nexavar®)

- Soft tissue sarcoma: Pazopanib (Votrient®)
- Stomach cancer: Ramucirumab (Cyramza™)
- Systemic mastocytosis: Imatinib mesylate (Gleevec®)
- Thyroid cancer: Cabozantinib (Cometriq™), Vandetanib (Caprelsa®), Sorafenib (Nexavar®)

Thank you!

"It's not my fault I got all the good genes.
Nobody told me you'd be coming."