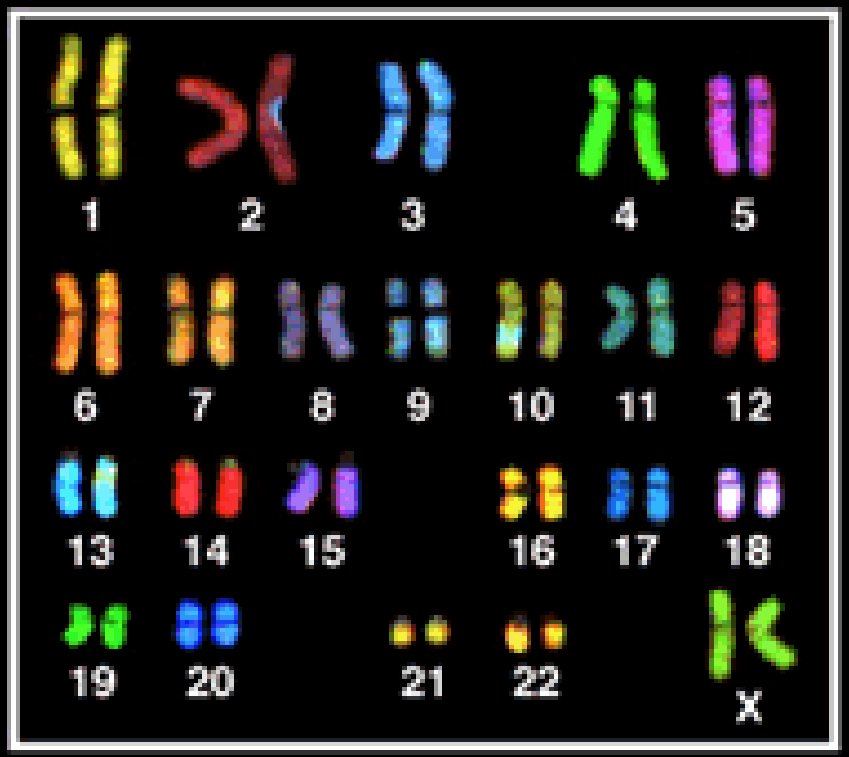
GENETIC

DISORDERS



DISEASES

- GENETIC
- ENVIRONMENTAL
- BOTH

MUTATIONS

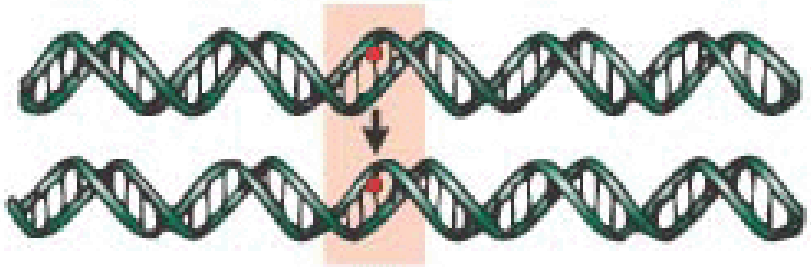
- **PERMANENT change in DNA**

  - **GENE MUTATION: (may, and often, result in a single base error)**
  - **CHROMOSOME MUTATION: (visible chromosome change)**
  - **GENOME MUTATION: (whole chromosome)**

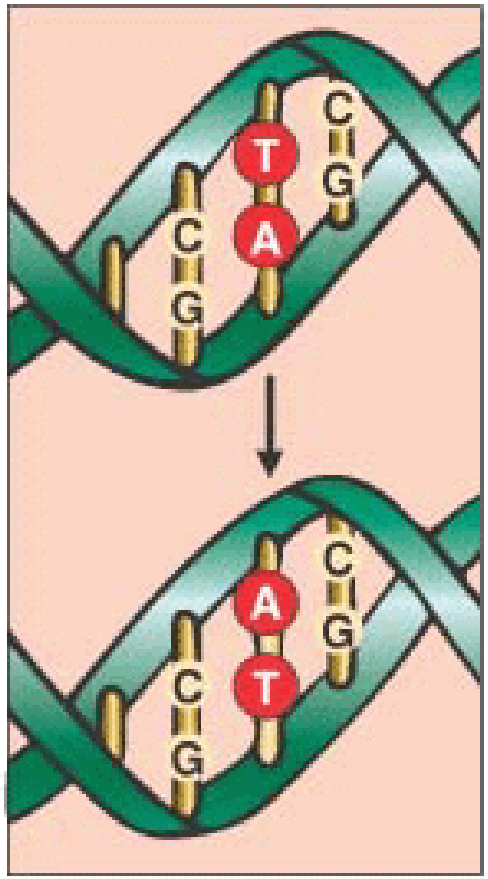
Base pair→ triplet→ gene→ chromosome segment→ whole chromosome→ genome

GENE MUTATION

- **DELETION OF A SINGLE BASE**
- **SUBSTITUTION OF A SINGLE BASE**

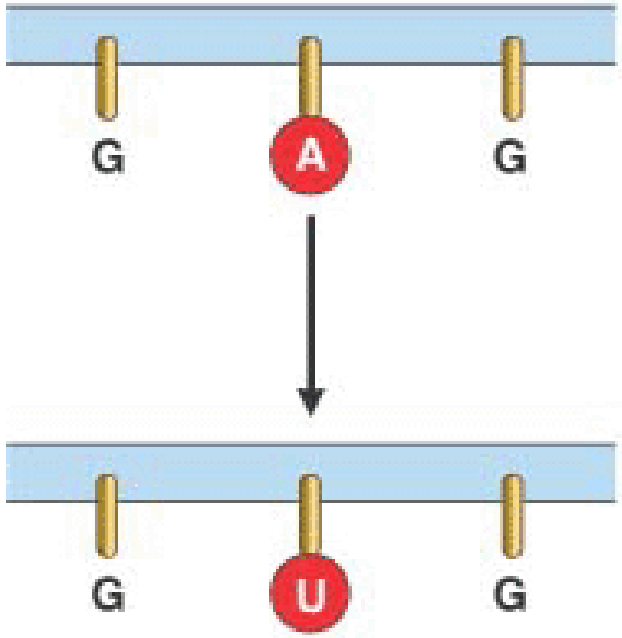


DNA → mRNA → AMINO ACID



β_A chain

β_S chain



GLUTAMIC ACID

VALINE

POINT MUTATION

GENE MUTATION

- **POINT MUTATION** within a coding sequence: VAL-GLU
- **MUTATIONS** in NON-coding sequences→ defective transcription, regulation, apop.
- **DELETIONS/INSERTIONS**→ **"frameshift"** mutation, involvement is NOT a multiple of 3
- Tri-nucleotide **REPEATS**, e.g., CGG repeats many times in fragile X syndrome, CAG in others

GENE MUTATIONS

- **INTERFERE with protein synthesis**
- **SUPPRESS transcription, DNA→RNA**
- **PRODUCE abnormal mRNA**
- **DEFECTS carried over into TRANSLATION**
- **ABNORMAL proteins WITHOUT impairing syntheses**

GENETIC DISORDERS

- **SINGLE** gene mutations, following classical MENDELIAN inheritance patterns the most
- **MULTIFACTORIAL** inheritance
- **CHROMOSOMAL** disorders
- **NON-MENDELIAN** disorders

MENDELIAN inheritance patterns

- AUTOSOMAL DOMINANT
- AUTOSOMAL RECESSIVE
- SEX-LINKED (recessive), involving "X" chromosome

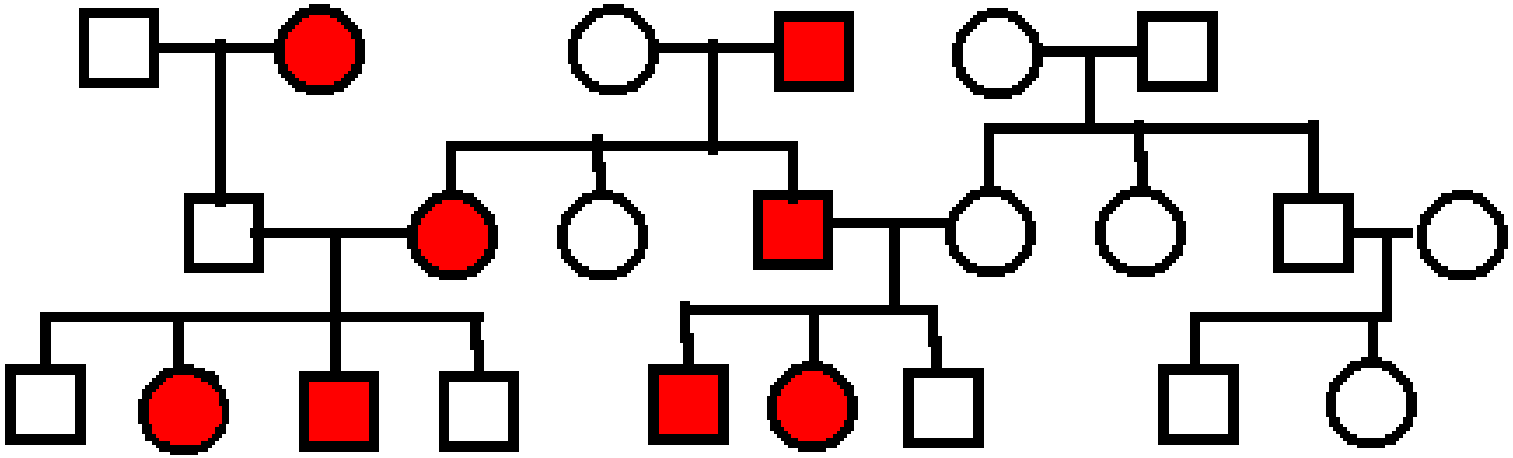
AUTOSOMAL DOMINANT

- Disease is in HETEROZYGOTES
- NEITHER parent may have the disease (NEW mut.)
- **REDUCED PENETRANCE** (environment?, other genes?)
- **VARIABLE EXPRESSIVITY** (environment?, other genes?)
- May have a **DELAYED ONSET**
- Usually result in a **REDUCED PRODUCTION** or INACTIVE protein

AUTOSOMAL DOMINANT

- HUNTINGTON DISEASE
- NEUROFIBROMATOSIS
- MYOTONIC DYSTROPHY
- TUBEROUS SCLEROSIS
- POLYCYSTIC KIDNEY
- HEREDITARY SPHEROCYTOSIS
- VON WILLEBRAND DISEASE
- MARFAN SYNDROME
- EHLERS-DANLOS SYNDROMES (some)
- OSTEOGENESIS IMPERFECTA
- ACHONDROPLASIA
- FAMILIAL HYPERCHOLESTEROLEMIA
- ACUTE INTERMITTENT PORPHYRIA

AUTOSOMAL DOMINANT PEDIGREE



1) BOTH SEXES INVOLVED

2) GENERATIONS **NOT** SKIPPED

AUTOSOMAL RECESSIVE

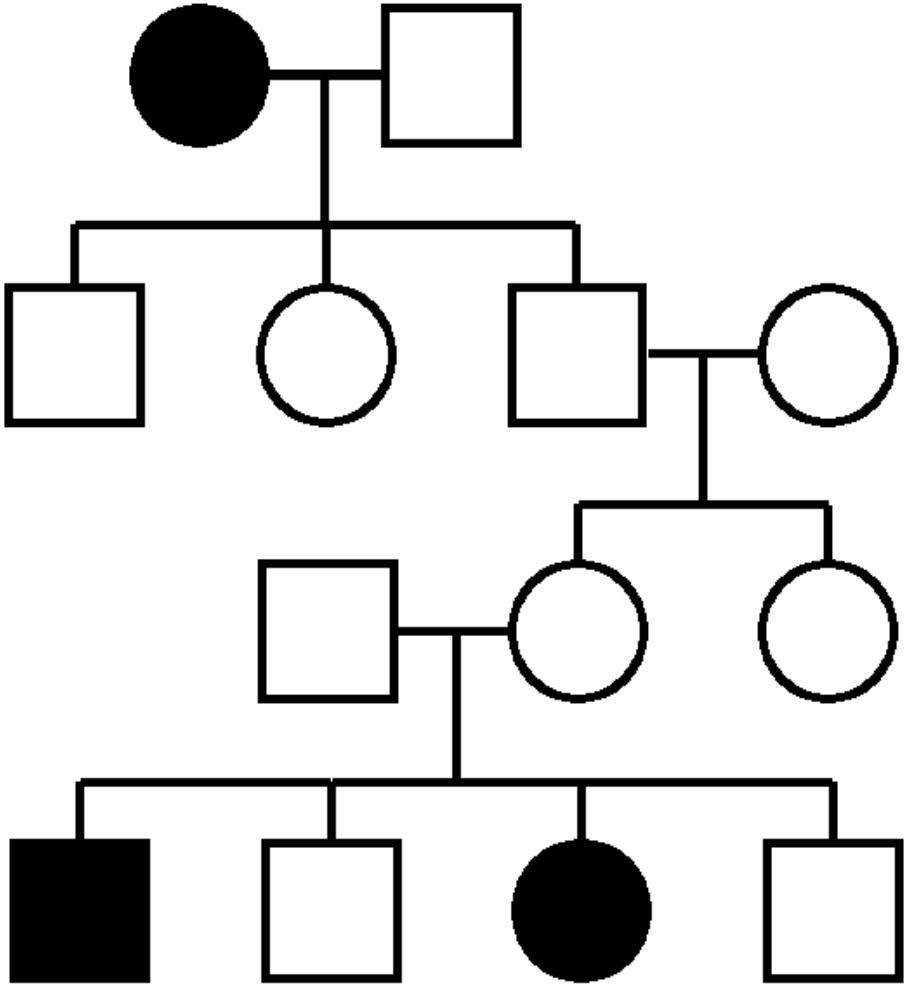
- Disease is in HOMOZYGOTES
- More UNIFORM expression than AD
- Often COMPLETE PENETRANCE
- Onset usually EARLY in life
- NEW mutations rarely detected clinically
- Proteins show LOSS of FUNCTION
- Include ALL inborn errors of metabolism
- MUCH more common that autosomal dominant

AUTOSOMAL RECESSIVE

- CF
- PKU
- GALACTOSEMIA
- HOMOCYSTINURIA
- LYSOSOMAL STORAGE
- A-1 ANTITRYPSIN
- WILSON DISEASE
- HEMOCHROMATOSIS
- GLYCOGEN STORAGE DISEASES

Hgb S
THALASSEMIAS
CONG. ADRENAL HYPERPLASIA
EHLERS-DANLOS (some)
ALKAPTONURIA
NEUROGENIC MUSC. ATROPHIES
FRIEDREICH ATAXIA
SPINAL MUSCULAR ATROPHY

AUTOSOMAL RECESSIVE PEDIGREE



1) BOTH SEXES INVOLVED

2) GENERATIONS **SKIPPED**

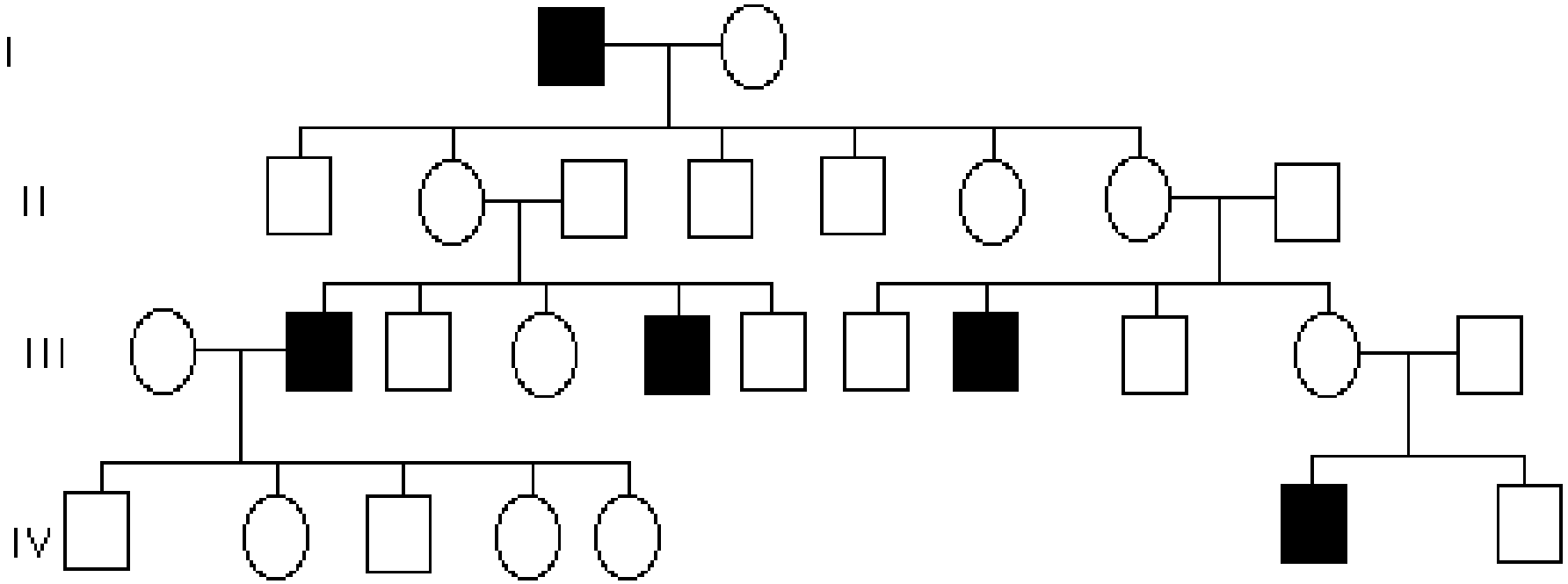
SEX ("X") LINKED

- MALES ONLY
- HIS SONS are OK, right?
- ALL his DAUGHTERS are CARRIERS
- The "Y" chromosome is NOT homologous to the "X", i.e., the classic concept of dominant/recessive has no meaning here
- HETEROZYGOUS FEMALES have no phenotypic expression (carriers)….usually, this means autosomal "recessive", right?

SEX ("X") LINKED

- DUCHENNE MUSCULAR DYSTROPHY
- HEMOPHILIA , A and B
- G6PD DEFICIENCY
- AGAMMAGLOBULINEMIA
- WISKOTT-ALDRICH SYNDROME
- DIABETES INSIPIDUS
- LESCH-NYHAN SYNDROME
- FRAGILE-X SYNDROME

SEX LINKED PEDIGREE



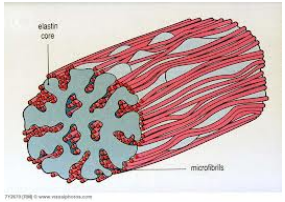
1) MALES ONLY, sons of affected males are OK

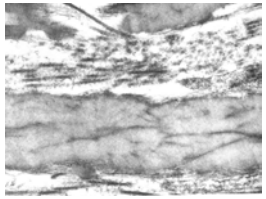
2) GENERATION SKIPPING DOESN'T MATTER

SINGLE GENE DISORDERS

- **ENZYME DEFECT (Most of them, e.g., PKU)**
  - Accumulation of substrate
  - Lack of product
  - Failure to inactivate a protein which causes damage
- **RECEPTOR/TRANSPORT PROTEIN DEFECT (Familial Hypercholesterolemia)**
- **STRUCTURAL PROTEIN DEFECT (Marfan, Ehl-Dan)**
  - Structure
  - Function
  - Quantity
- **ENZYME DEFECT WHICH INCREASES DRUG SUSCEPTIBILITY: G6PD←Primaquine**

STRUCTURAL PROTEIN DEFECTS





- Marfan Syndrome
  - Fibrillin-1 defect (not -2 or -3)
  - Tall, dislocated lens, aortic arch aneurysms, etc.
  - Abraham Lincoln?, Osama bin-Laden?

- Ehlers-Danlos Syndromes (AD, AR)
  - Multiple (6?) different types
  - Classical, Hypermob., Vasc., KyphoSc., ArthChal., Derm
  - Various collagen defects
  - Hyperelastic skin, hyperextensible joints

RECEPTOR PROTEIN DEFECTS

- FAMILIAL HYPERCHOLESTEROLEMIA
  - LDL RECEPTOR defect
  - Cholesterol TRANSPORT across liver cell impaired
  - ergo,→ CHOLESTEROL BUILDUP IN BLOOD
- "Scavenger System" for CHOL kicks in, i.e., MACROPHAGES
- YOU NOW KNOW THE REST OF THE STORY
- YOU NOW KNOW WHY MACROPHAGES are "FOAMY"

ENZYME DEFICIENCIES

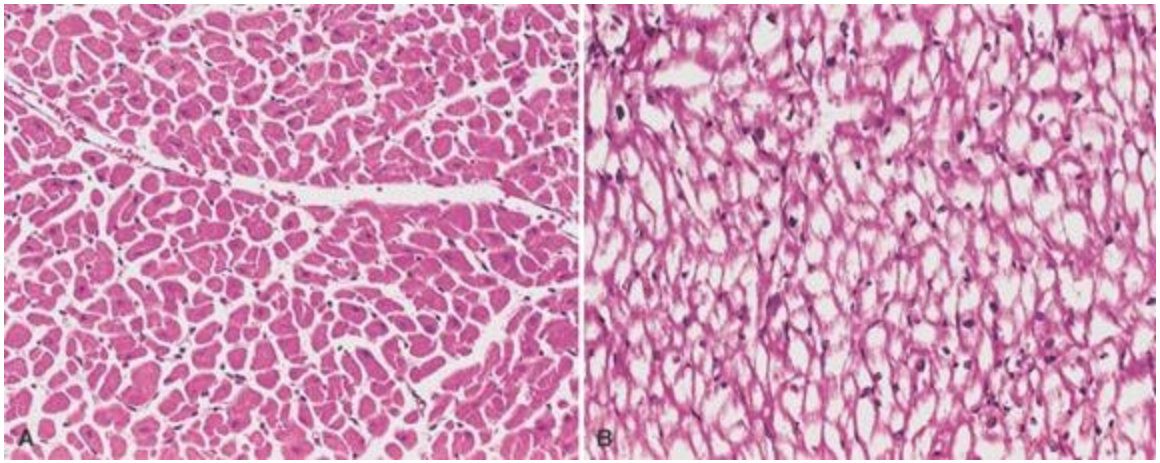
- BY FAR, THE LARGEST KNOWN CATEGORY
  - SUBSTRATE BUILDUP
  - PRODUCT LACK
  - SUBSTRATE could be HARMFUL
- LYSOSOMAL STORAGE DISEASES comprise MOST of them

LYSOSOMAL STORAGE DISEASES

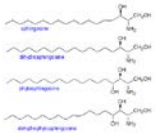
- GLYCOGEN STORAGE DISEASES
- SPHINGOLIPIDOSES (Gangliosides)
- SULFATIDOSES
- MUCOPOLYSACCHARIDOSES
- MUCOLIPIDOSES
- OTHER
  - Fucosidosis, Mannosidosis, Aspartylglycosaminuria
  - WOLMAN, Acid phosphate deficiency

GLYCOGEN STORAGE DISEASES

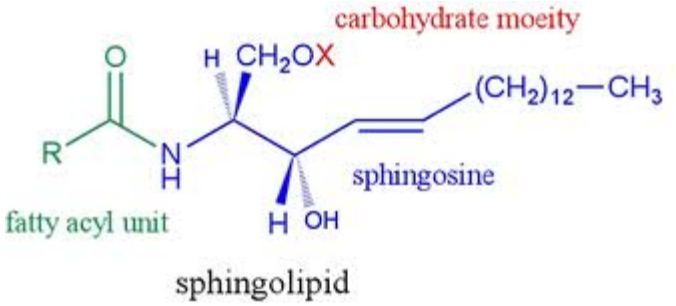
- MANY TYPES (at least 13)
- Type 2 Pompe (acid-α-glucosidase) , von Gierke (Glu-6P-ase), McArdle (phosphorylase), most studied and discussed, and referred to
- Storage sites: Liver, Striated Muscle (Skel + Ht)



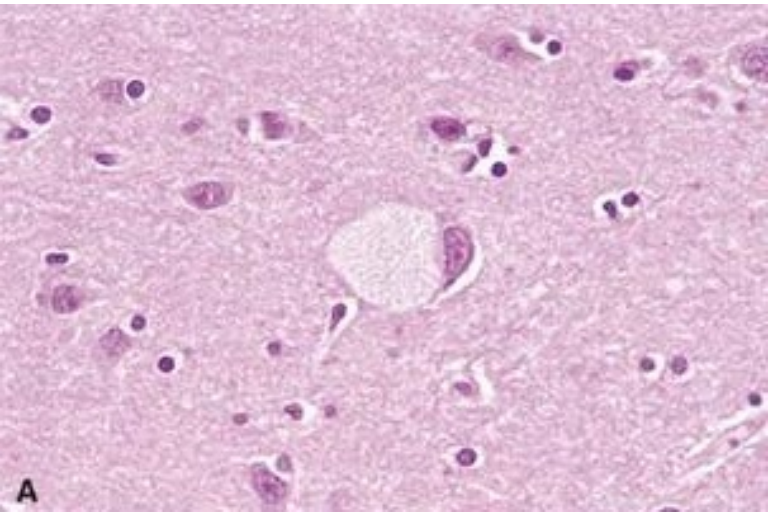
SPHINGOLIPIDOSES

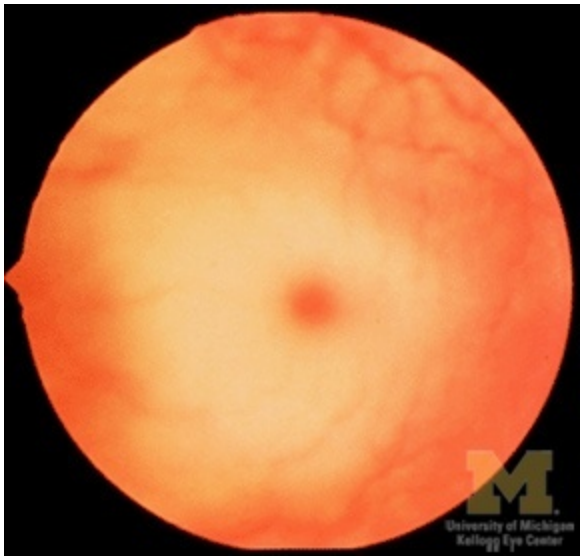


- MANY types, Tay-Sachs most often referred to
  - GANGLIOSIDES are ACCUMULATED
  - Ashkenazi Jews (1/30 are carriers)
  - CNS neurons a site of accumulation
  - CHERRY RED spot in Macula
  - Usually fatal by age 4

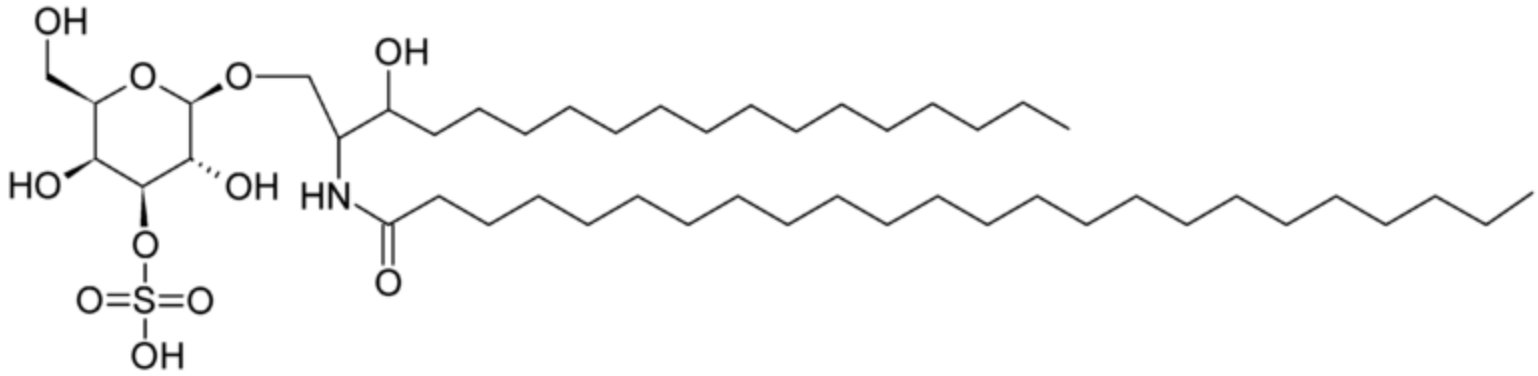


sphingolipid



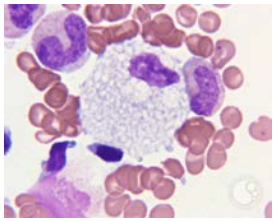


SULFATIDOSES

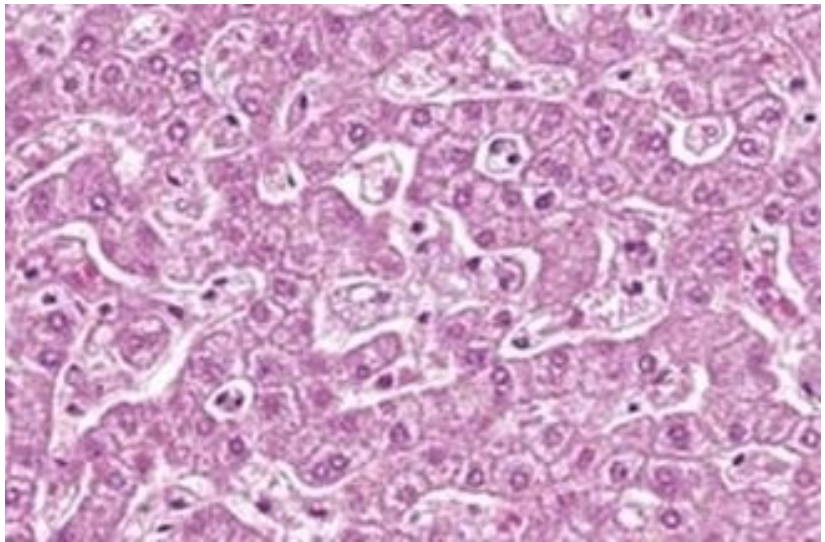


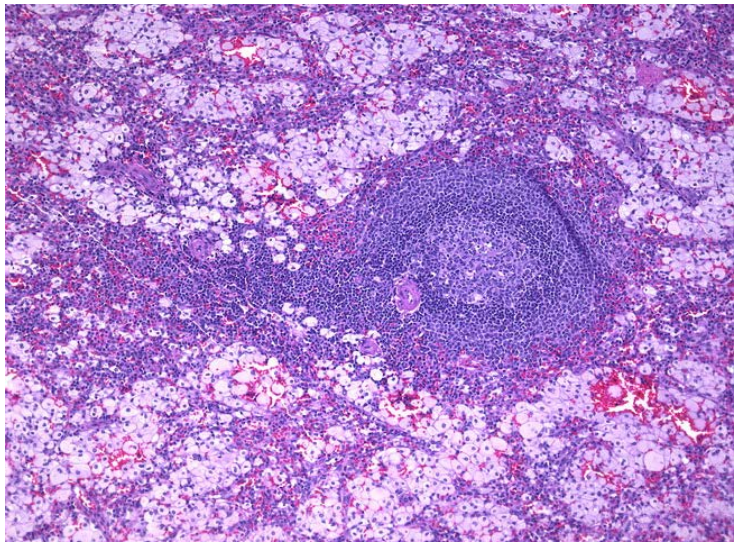
- MANY types, but the metachromatic leukodystrophies (CNS), Krabbe, Fabry, Gaucher, and Niemann-Pick (A and B) are most commonly referred to
- SULFATIDES, CEREBROSIDES, SPHINGOMYELIN are the accumulations

NIEMANN-PICK



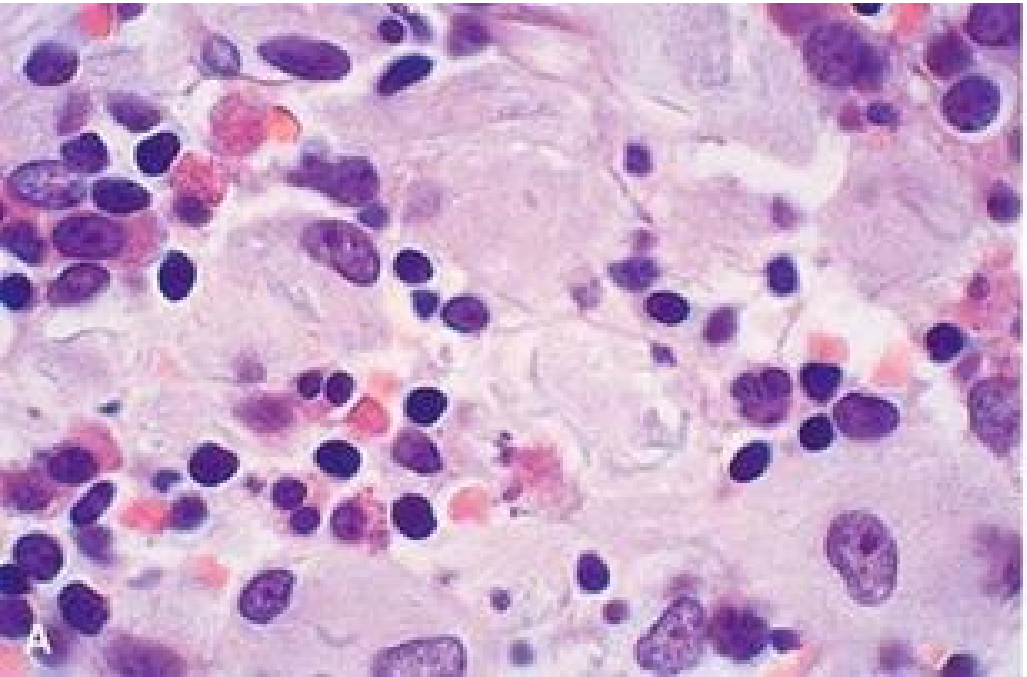
- TYPES A, B, C
- SPHINGOMYELIN BUILDUP
- Sphingomyelinase (ASM), is the missing enzyme
- MASSIVE SPLENOMEGALY
- ALSO in ASHKANAZI JEWS
- OFTEN FATAL in EARLY LIFE, CNS, ORGANOMEGALY

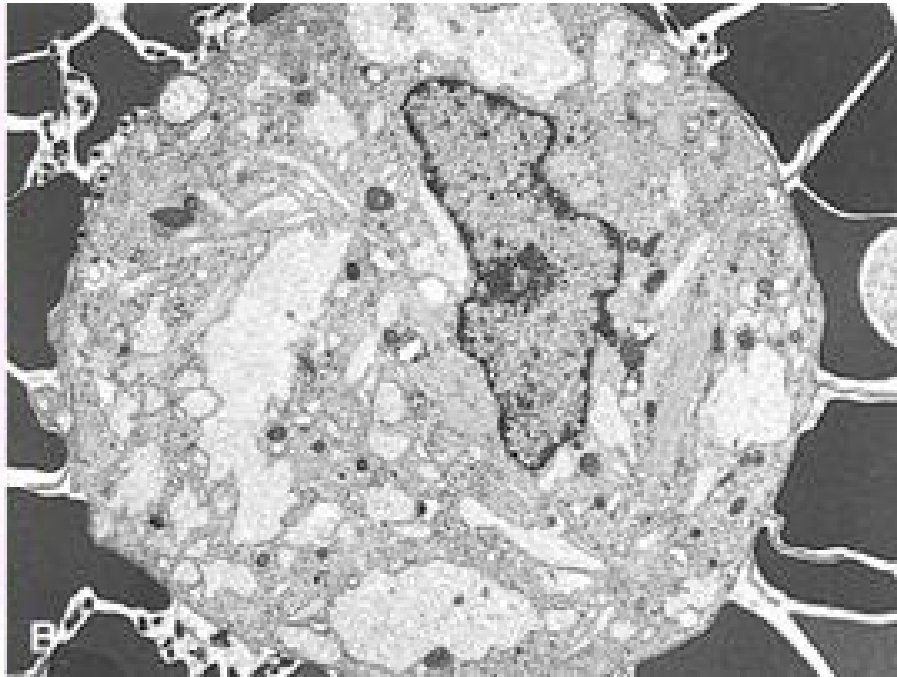




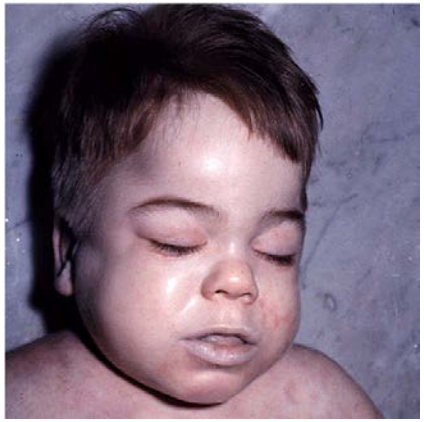
GAUCHER DISEASE

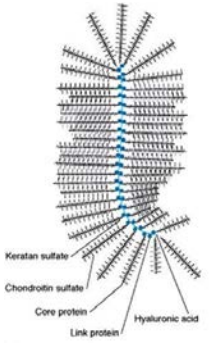
- GLUCOCEREBROSIDE BUILDUP
- 99% are type I, NO CNS involvement
- ALL MACROPHAGES, liv, spl, nodes, marrow





MUCOPOLYSACCHARIDOSES





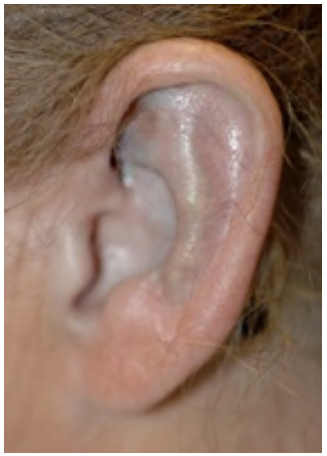
- HURLER/HUNTER, for I and II, respectively, 14 types
- DERMATAN sulfate, HEPARAN sulfate buildup, respectively
  - coarse facial features
  - clouding of the cornea
  - joint stiffness
  - mental retardation
  - URINARY EXCRETION of SULFATES COMMON

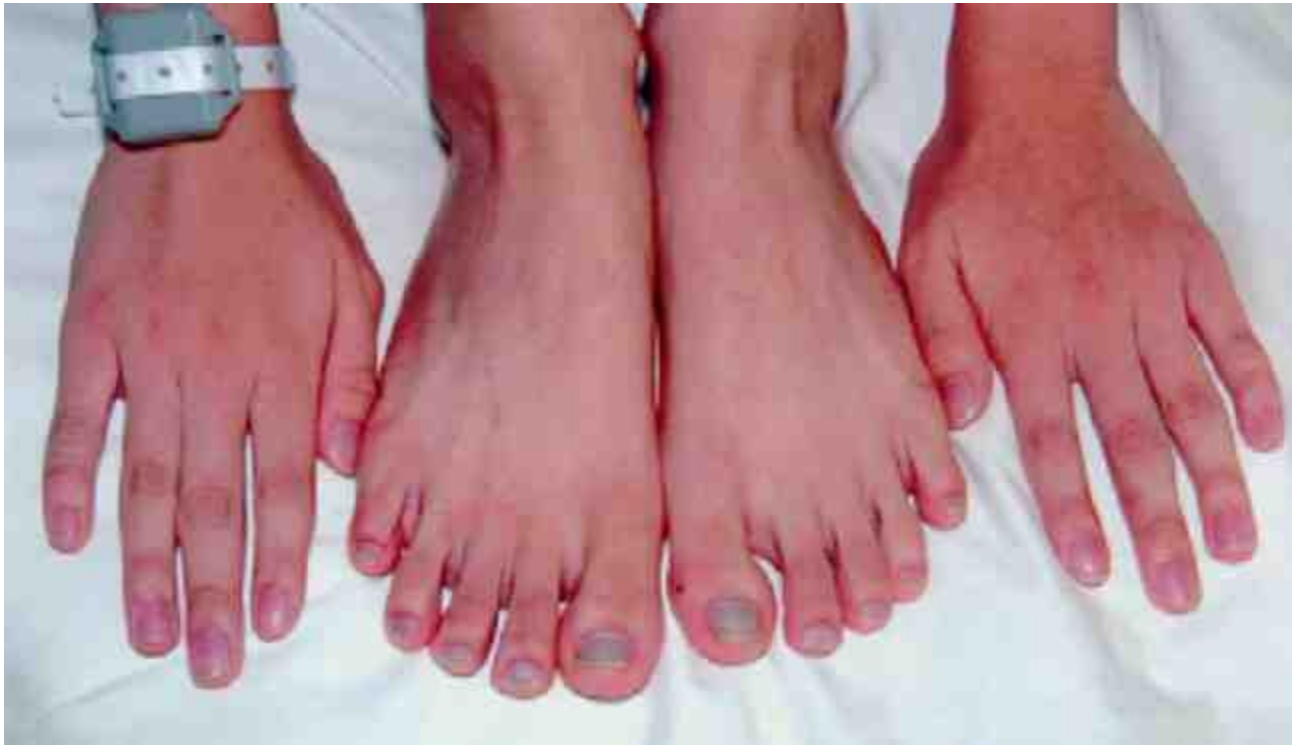
OTHER LYSOSOMAL STORAGE DIS.

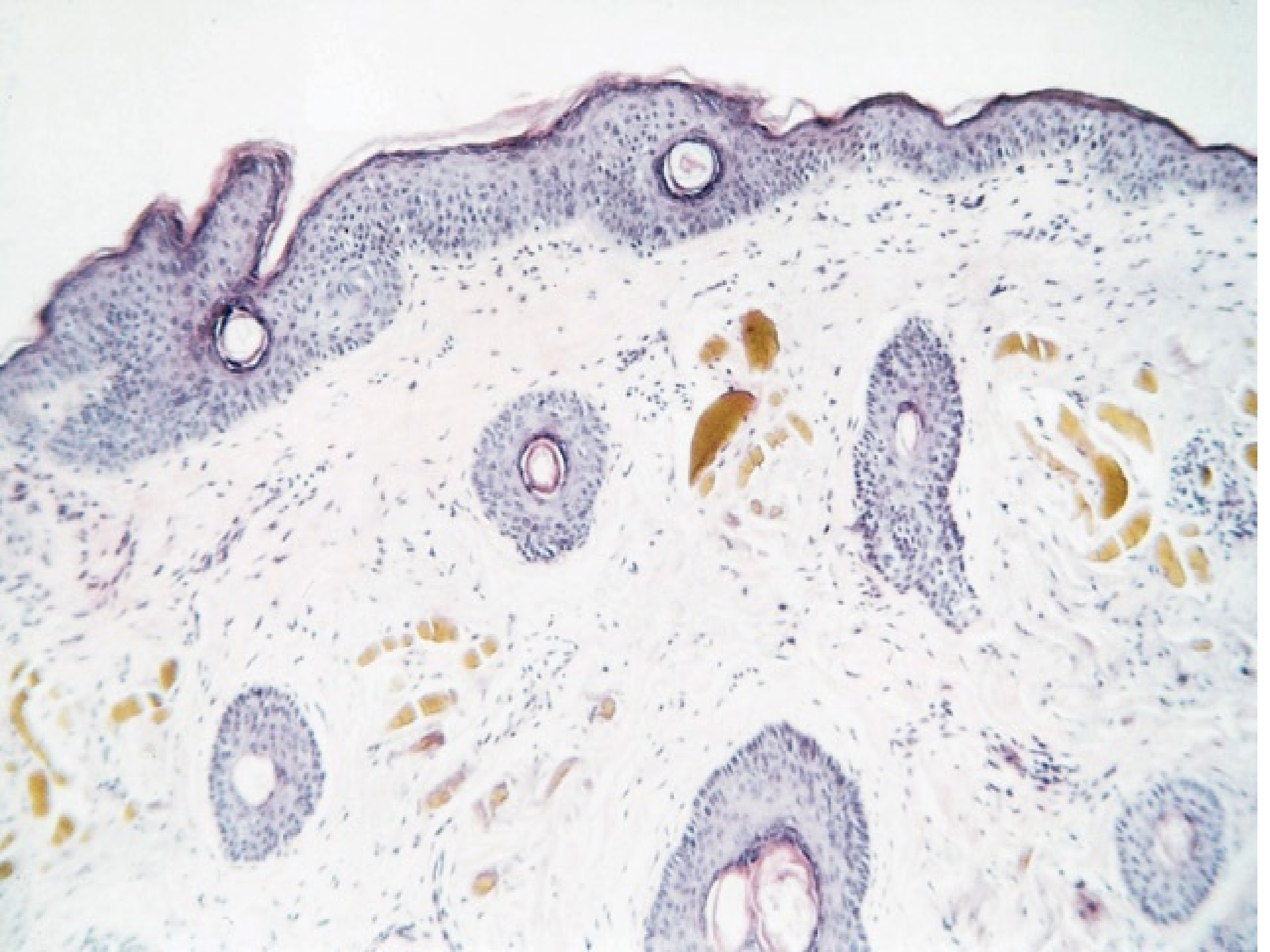
- FUCOSIDOSIS
- MANNOSIDOSIS
- ASPARTYLGLYCOSAMINURIA
- WOLMAN (CHOL., TRIGLYCERIDES)
- ACID PHOSPHATE DEFICIENCY (PHOS. ESTERS)

ALCAPTONURIA

- NOT a LYSOSOMAL ENZYME DISEASE
- FIRST ONE TO BE DESCRIBED
- HOMOGENTISIC ACID
- HOMOGENTISIC ACID OXIDASE
  - –**BLACK** URINE
  - –**BLACK** NAILS (OCHRONOSIS), SKIN
  - –**BLACK** JOINT CARTILAGE (SEVERE ARTHRITIS)

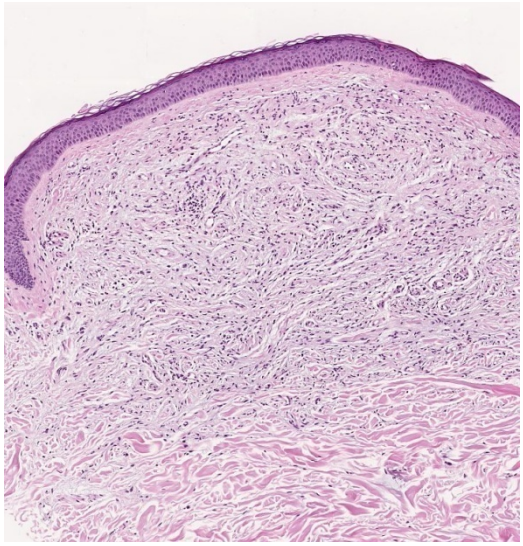




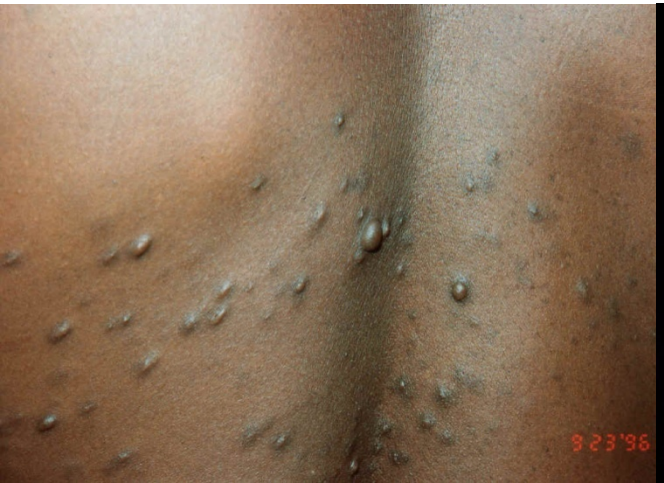


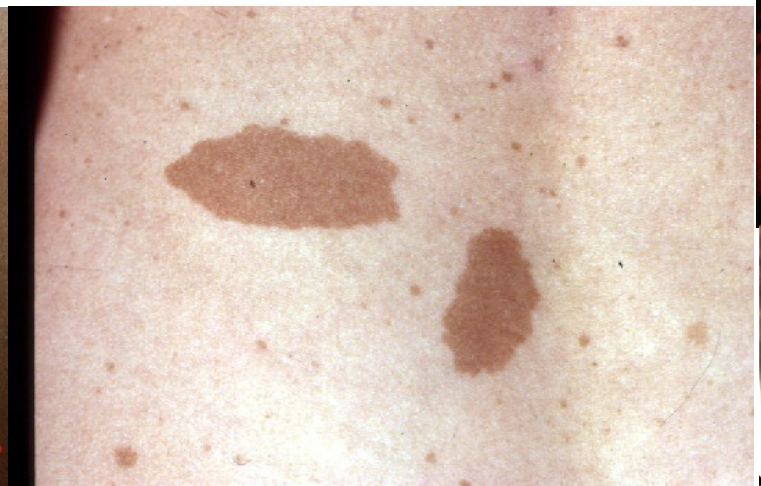
NEUROFIBROMATOSIS

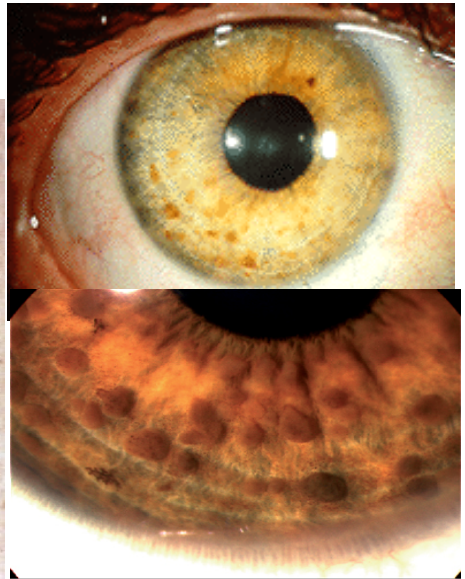
- 1 and 2
  - 1-von Recklinghausen
  - 2- “acoustic” neurofibromatosis



- 1
  - Neurofibromas, café-au-lait, Lisch nodules







NEUROFIBROMATOSIS

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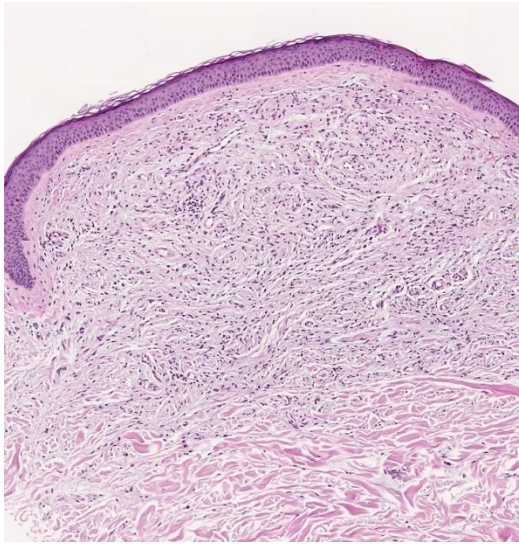
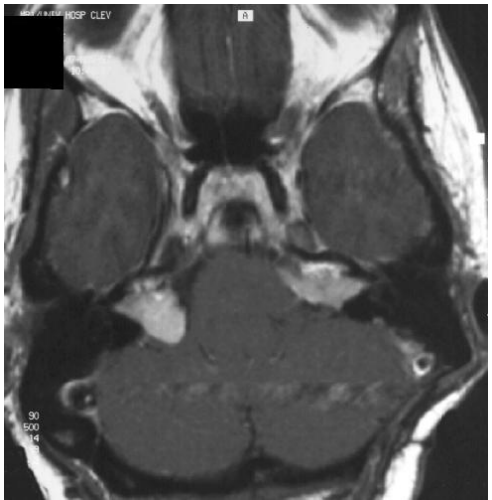
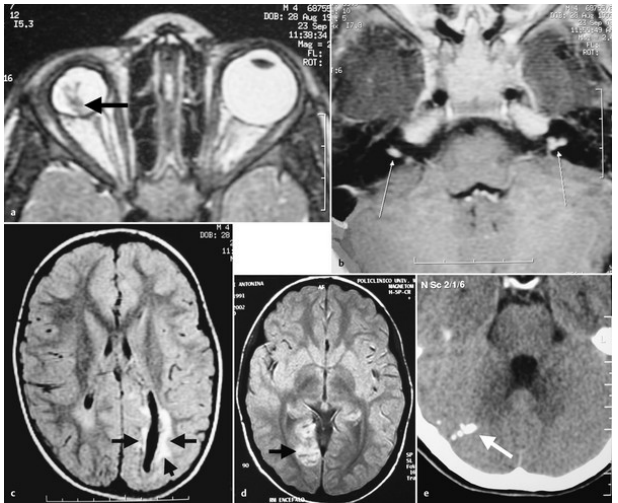


- 2
  - Bilateral acoustic neuromas and multiple meningiomas





MULTIFACTORIAL INHERITANCE

- Multi-"FACTORIAL", not just multi-GENIC
- "SOIL" theory
- Common phenotypic expressions governed by "multifactorial" inheritance
  - Hair color
  - Eye color
  - Skin color
  - Height
  - Intelligence
  - Diabetes, type II

FEATURES of multifactorial inheritance

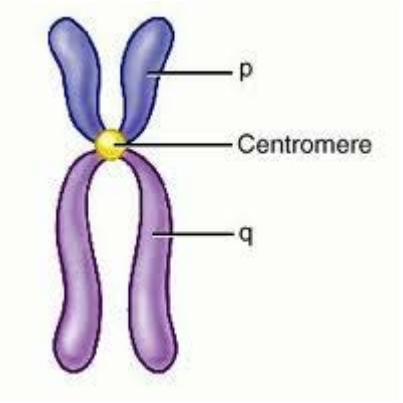
- Expression determined by NUMBER of genes
- Overall 5% chance of 1st degree relatives having it
- Identical twins >>>5%, but WAY less than 100%
- This 5% is increased if more children have it
- Expression of **CONTINUOUS** traits (e.g., height) vs. DISCONTINUOUS traits (e.g., diabetes)

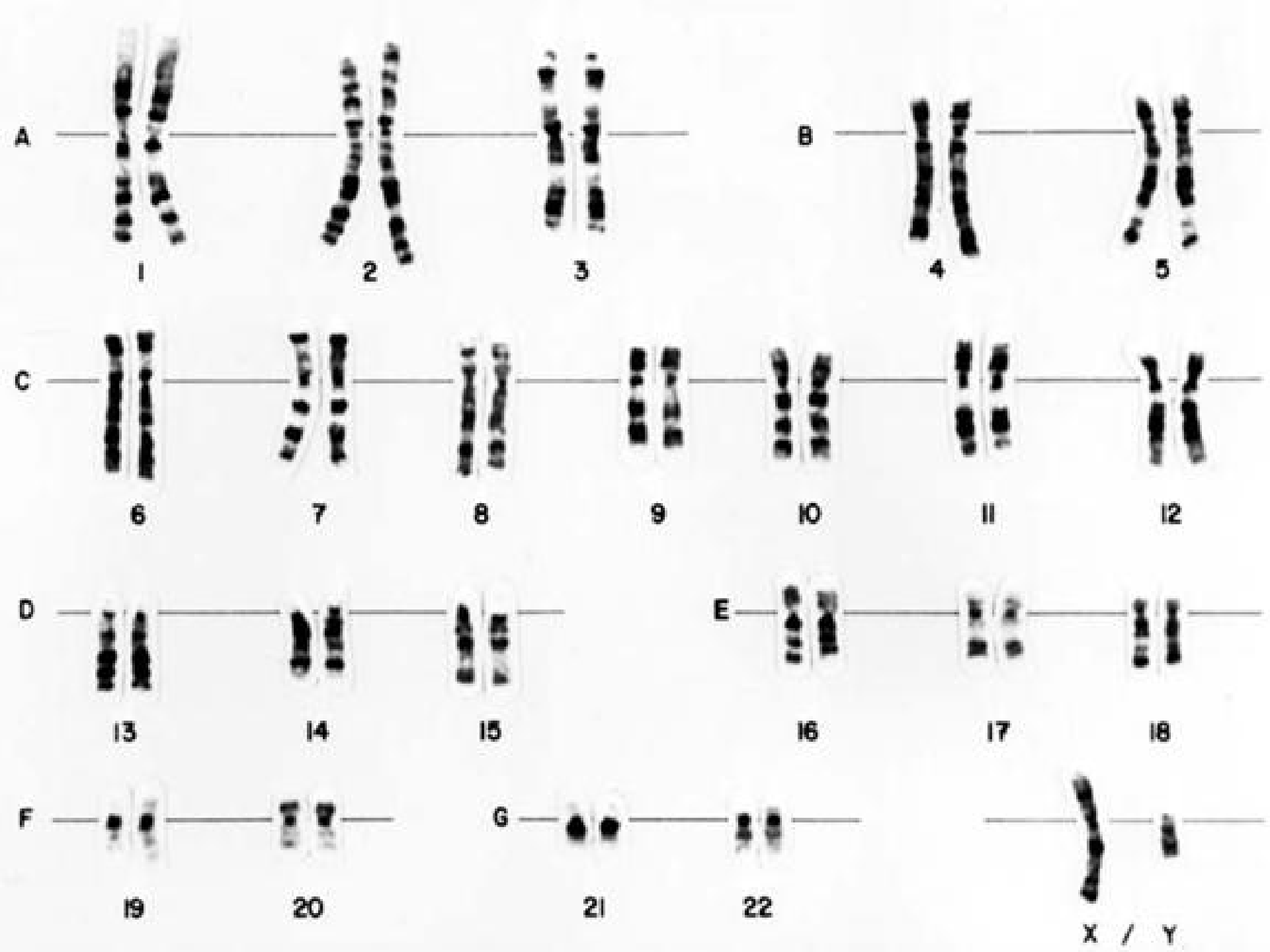
"MULTIFACTORIAL" DISORDERS

- Cleft lip, palate
- Congenital heart disease
- Coronary heart disease
- Hypertension
- Gout
- Diabetes
- Pyloric stenosis
- MANY, MANY, MANY, MANY MORE…..

KARYOTYPING

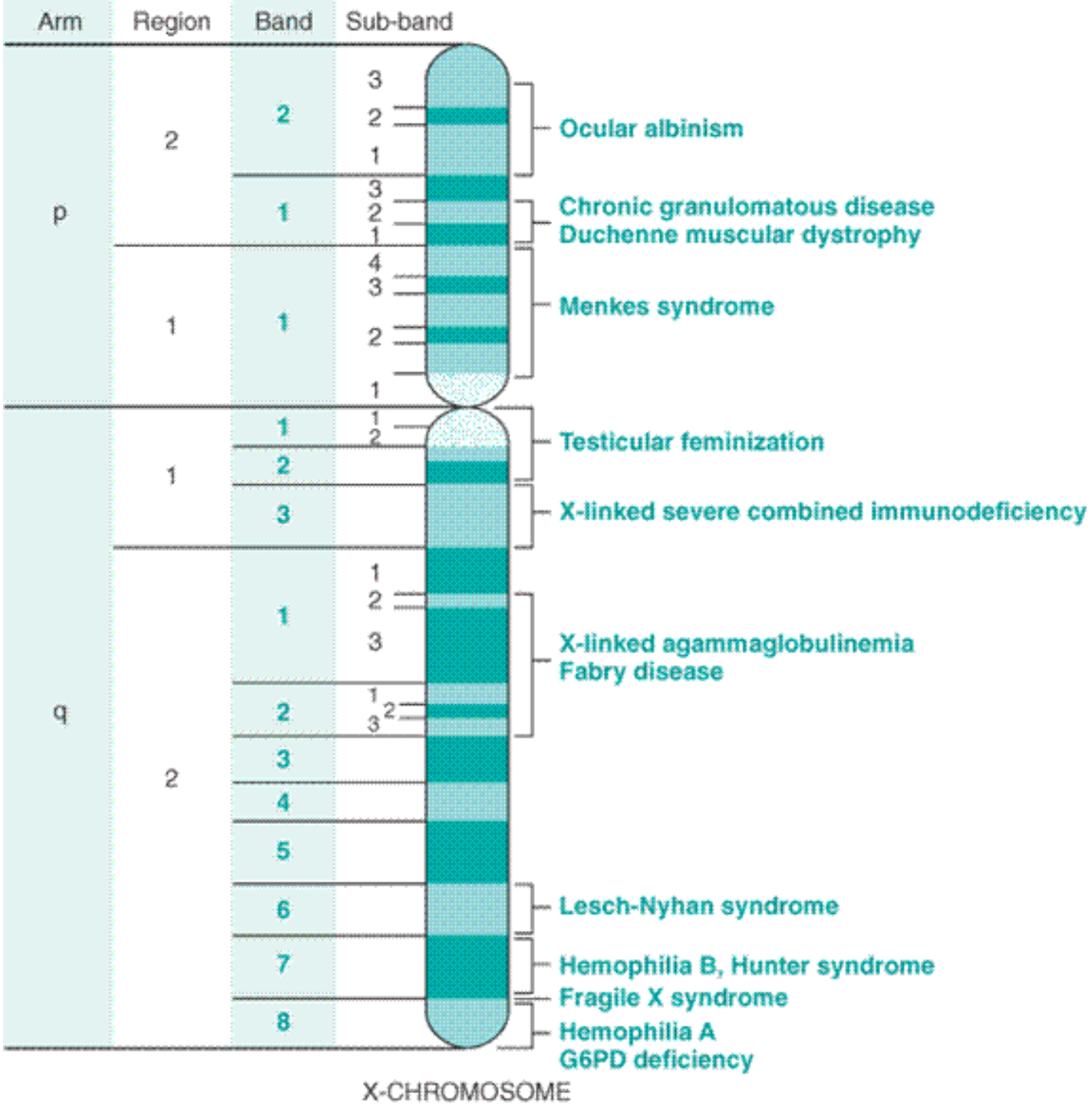
- Defined as the study of CHROMOSOMES
- 46 = (22x2) + X + Y
- Conventional notation is “46,XY” or “46,XX”
- G(iemsa)-banding, 500 bands per haploid recognizable 
- Short (“p”-etit) arm = p, other (long) arm = q




A
1
2
3
B
4
5
C
6
7
8
9
10
11
12
D
13
14
15
E
16
17
18
F
19
20
G
21
22
X / Y

More KARYOTYPING info

- A,B,C,D,E,F,G depends on chromosome length
  - A longest
  - G shortest
- Groups within these letters depend on the p/q ratio
- ARM→REGION→BAND→Sub-BAND, numbering from the centromere progressing distad


Arm
Region
Band
Sub-band
p
q
2
1
2
1
1
2
3
1
2
3
1
2
3
4
5
6
7
8
Ocular albinism
Chronic granulomatous disease
Duchenne muscular dystrophy
Menkes syndrome
Testicular feminization
X-linked severe combined immunodeficiency
X-linked agammaglobulinemia
Fabry disease
Lesch-Nyhan syndrome
Hemophilia B, Hunter syndrome
Fragile X syndrome
Hemophilia A
G6PD deficiency
X-CHROMOSOME

F.I.S.H. (gene "probes")

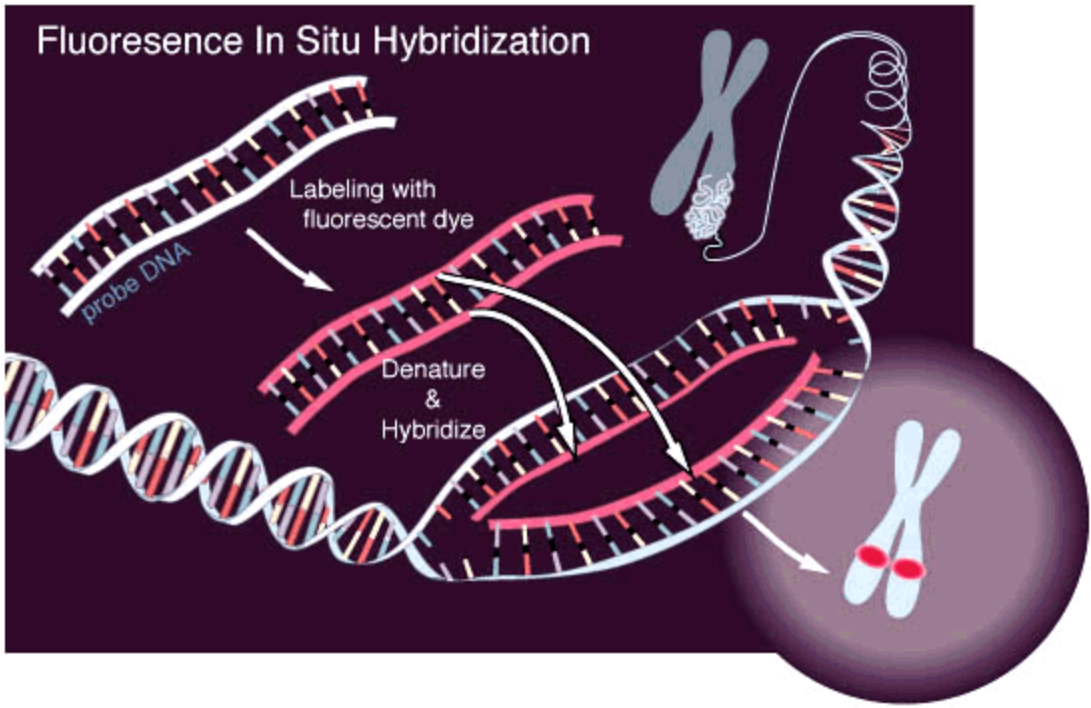
greatly enhances G-banding

- **F**luorescent **I**n-

  Situ

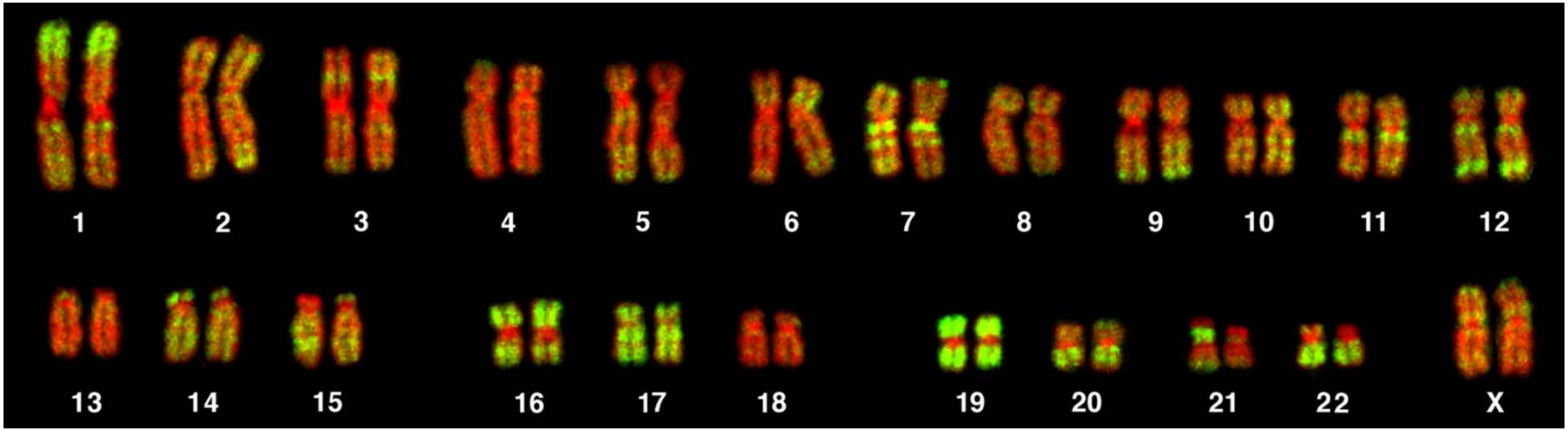
  Hybridization

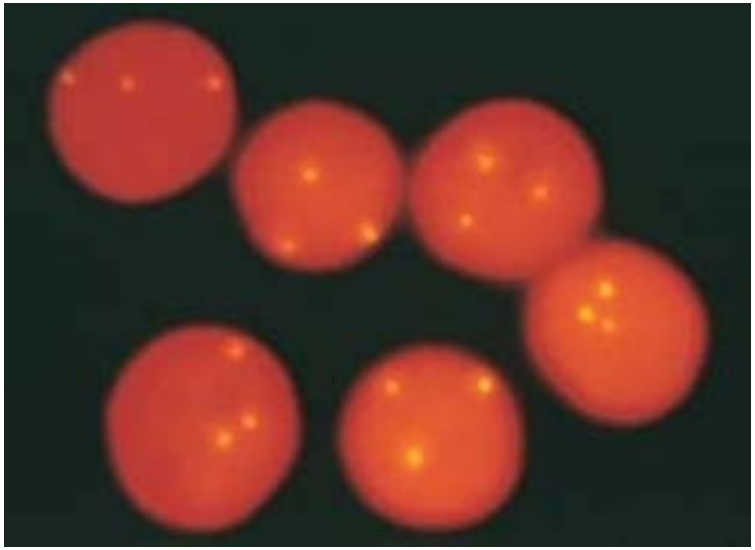
- **Uses fluorescent labelled DNA fragments, ~10,000 base pairs, to bind (or not bind) to its complement**



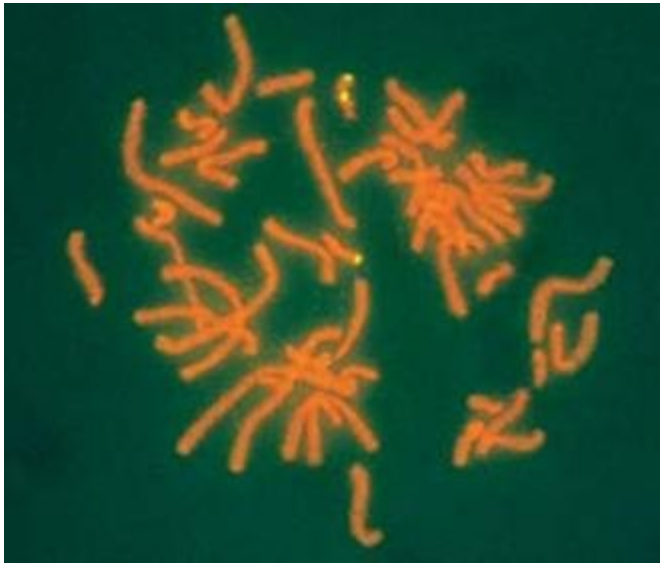
FISH

- SUBTLE MICRODELETIONS
- COMPLEX TRANSLOCATIONS
- AND TELOMERE ALTERATIONS



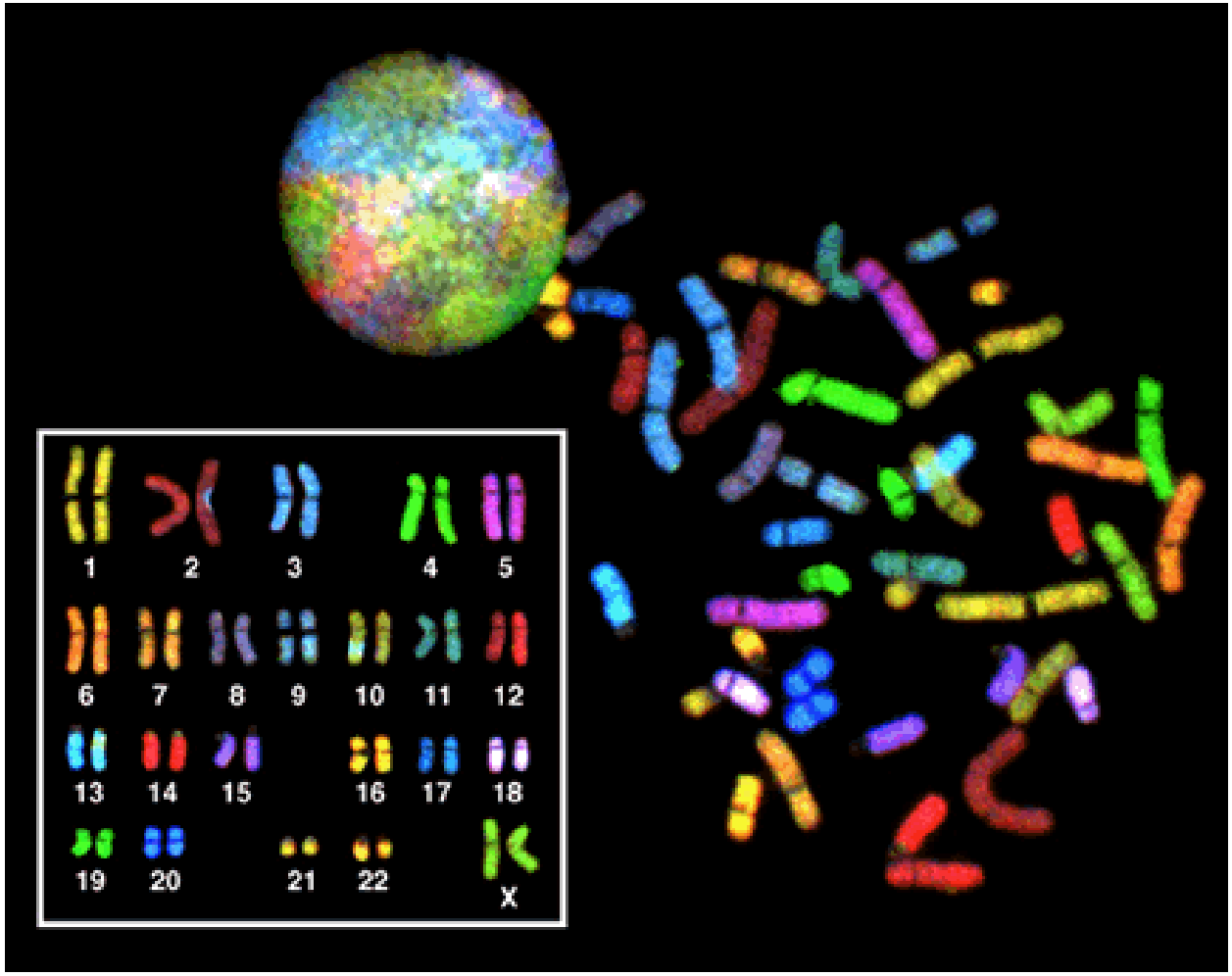


TRIPLE CHROMOSOME #20



A DELETION in
CHROMOSOME #22

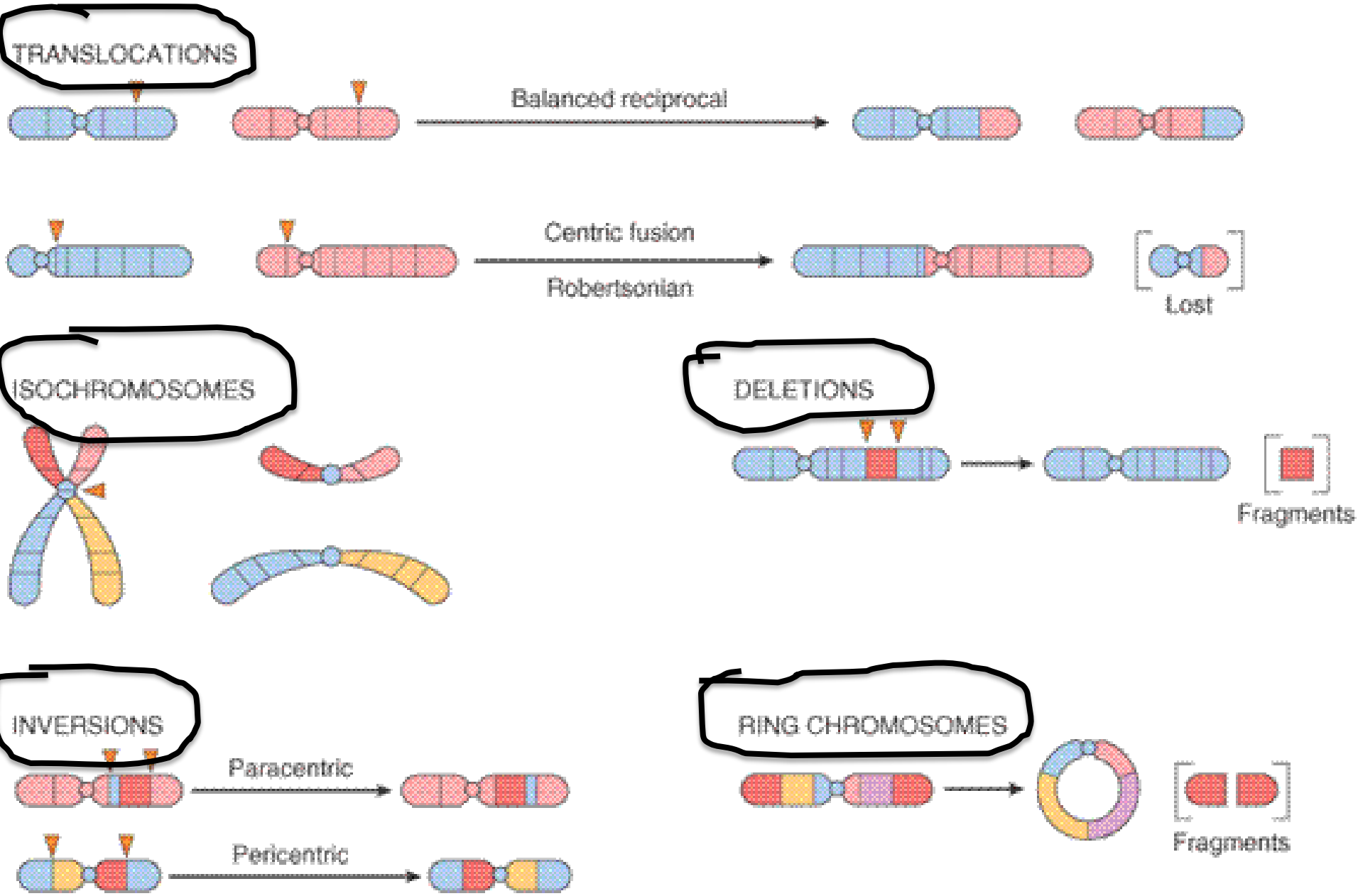
SPECTRAL KARYOTYPING



CYTOGENETIC DISORDERS

- DEFINITIONS:
  - EUPLOID (46XX or 46XY)
  - ANEUPLOID (NOT AN EXACT MULTIPLE OF 23)
    - MONOSOMY, AUTOSOME OR SEX
    - TRISOMY, AUTOSOME OR SEX
  - DELETION
  - BREAKAGE

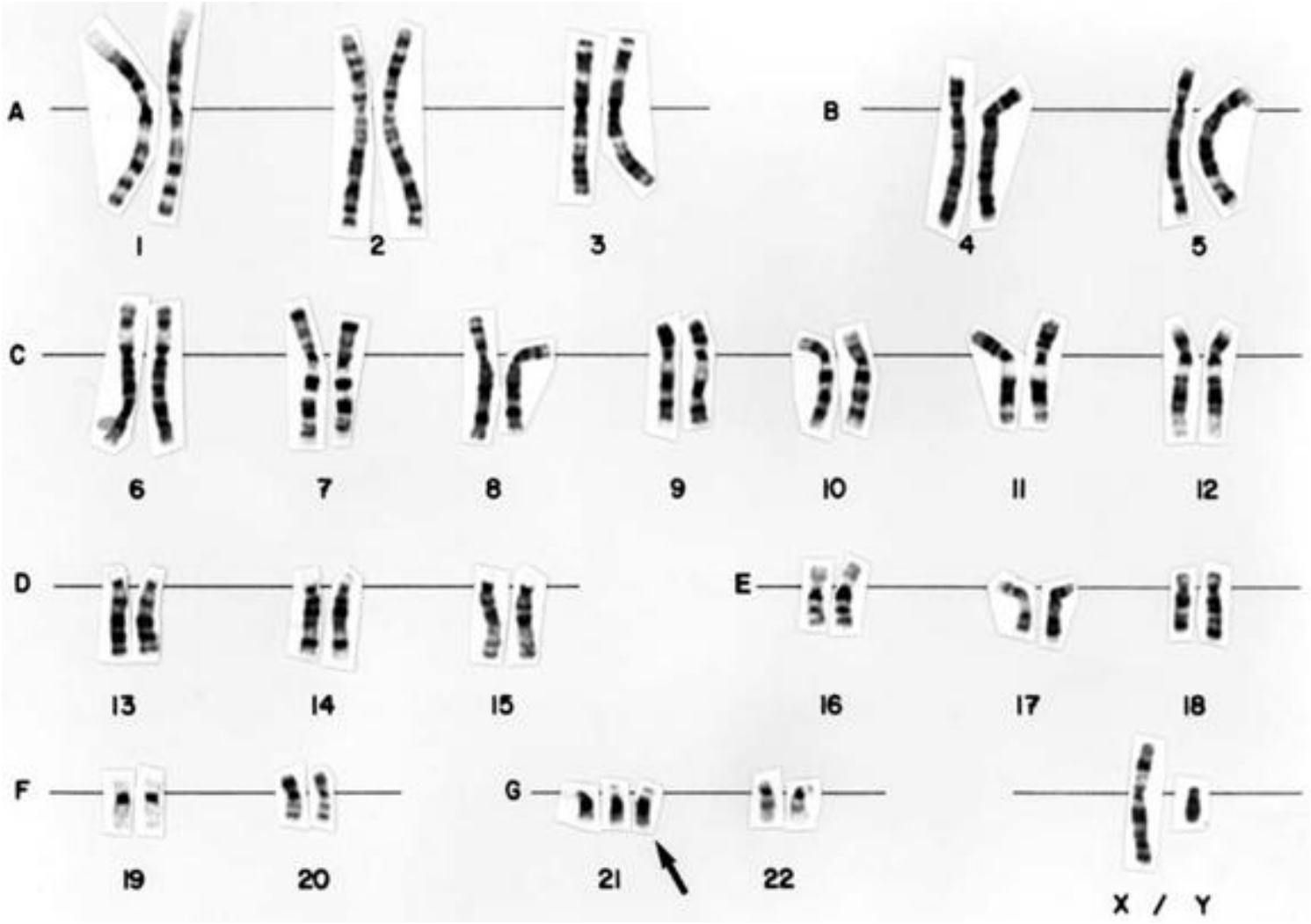
MORE DEFINITIONS



COMMON CYTOGENETIC DISEASES

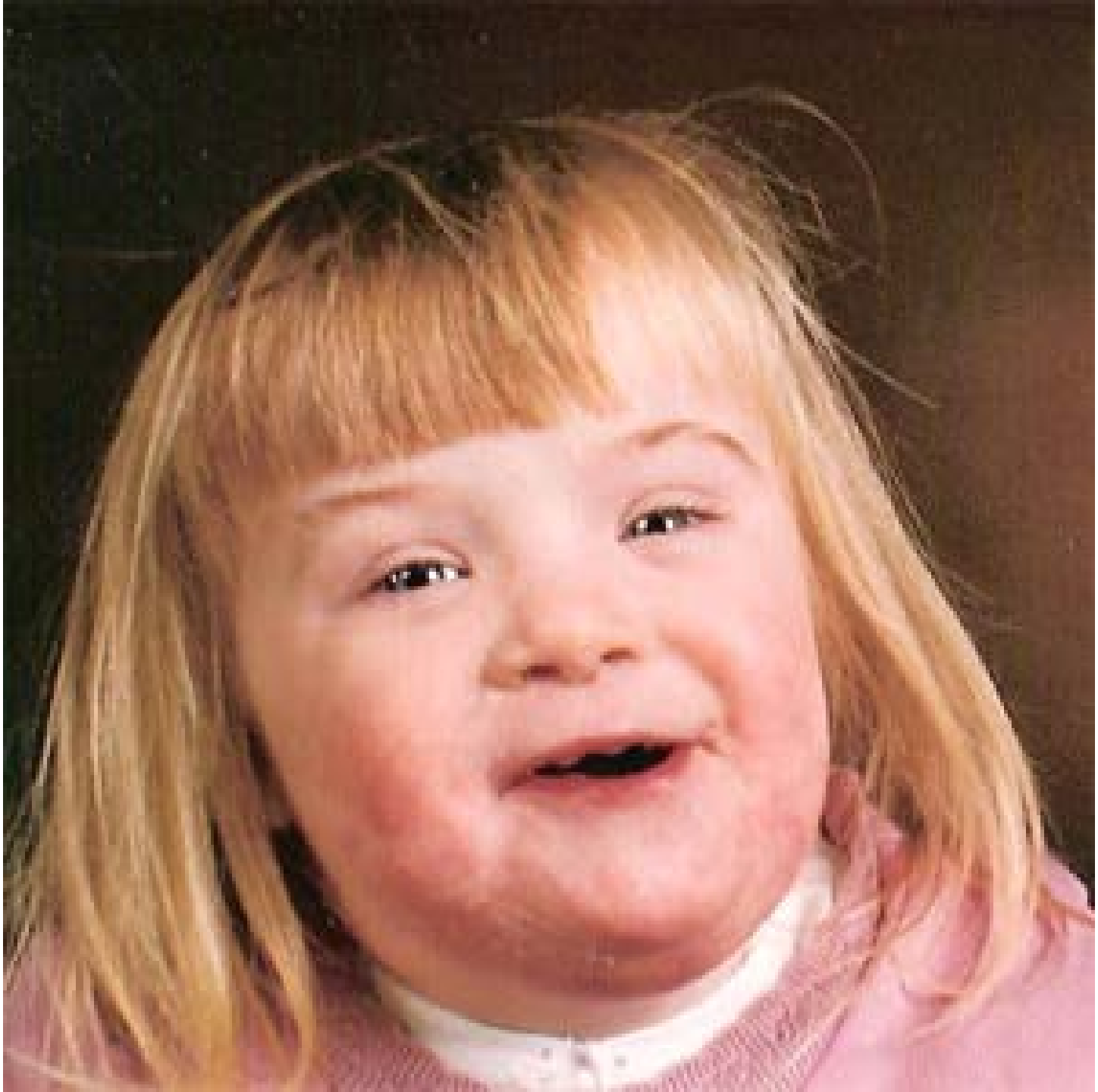
- AUTOSOMES
  - TRISOMY-21 (DOWN SYNDROME)
  - 8, 9, 13 (Patau), 18 (Edwards), 22
  - 22q.11.2 deletion
- SEX CHROMOSOMES
  - KLINEFELTER: XXY, XXXY, etc.
  - TURNER: XO

TRISOMY-21



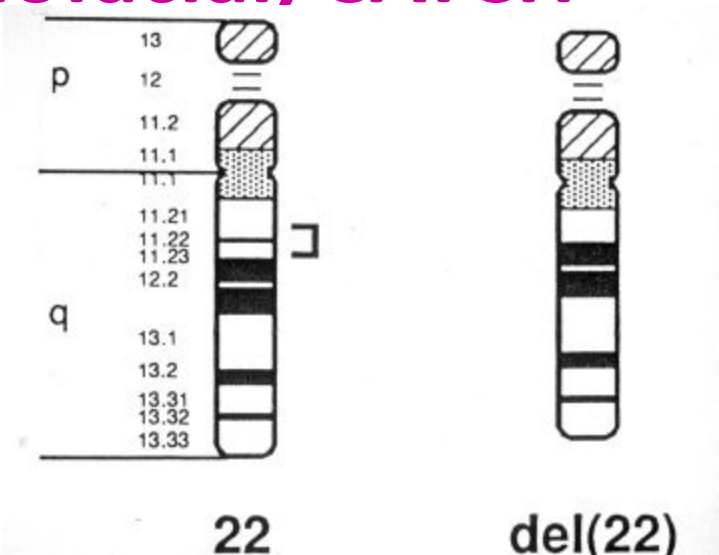
TRISOMY-21

- Most trisomies (monosomies, aneuploidy) are from maternal non-disjunction
- (non-disjunction or anaphase lag are BOTH possible)
- **#1 cause of mental retardation**
- Maternal age related
- Congenital Heart Defects, risk for acute leukemias, GI atresias
- Most LOVABLE of all God's children

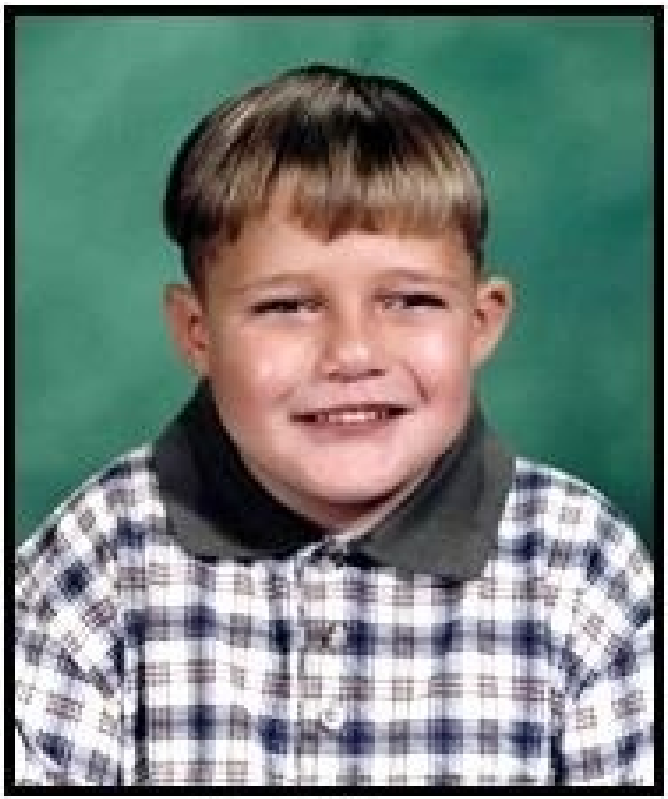


Chromosome 22q11.2 Deletion Syndrome

- Because of a DELETION, this cannot be detected by standard karyotyping and needs FISH
- Cardiac defects, DiGeorge syndrome, velocardiofacial, CATCH*



Velocardiofacial Syndrome/ DiGeorge Syndrome



Daniel Avram

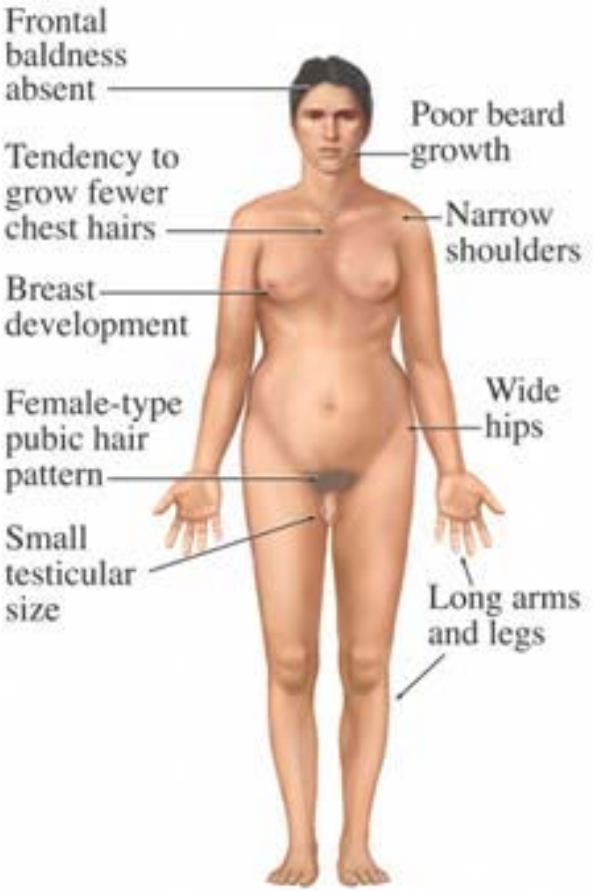
Keri Reigle

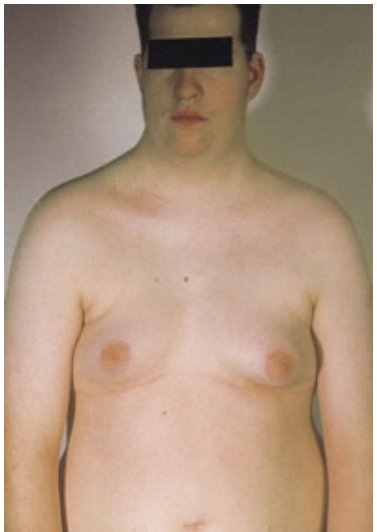
SEX CHROMOSOME DISORDERS

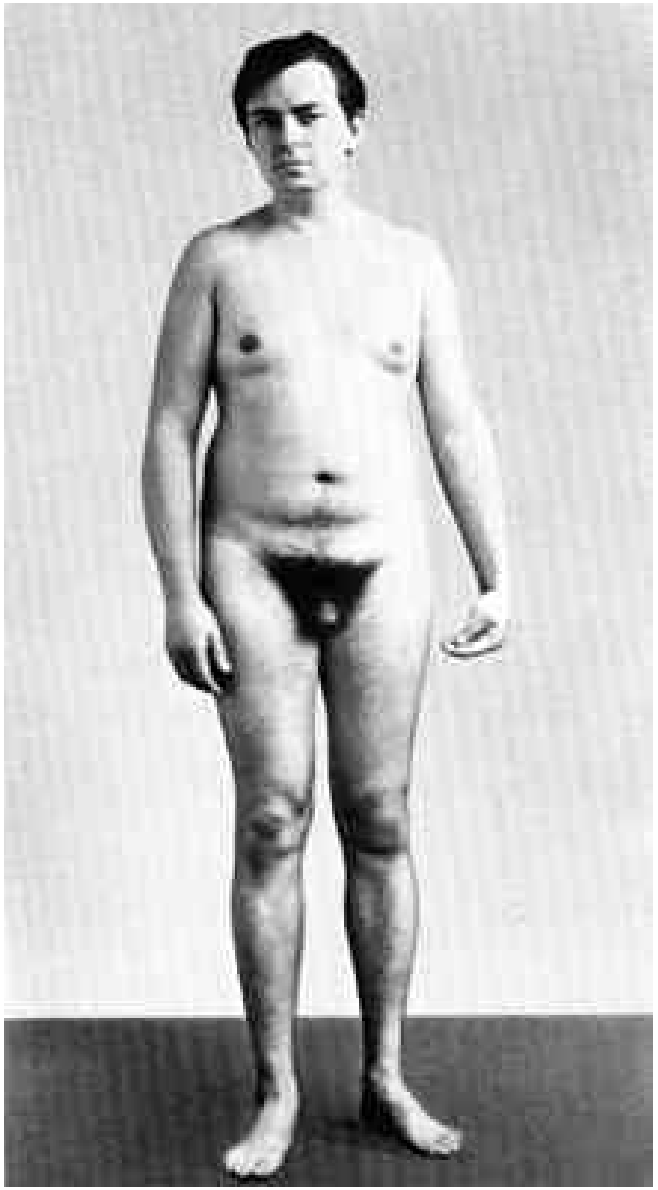
- Problems related to sexual development and fertility
- Discovered at time of puberty
- Retardation related to the number of X chromosomes
- If you have at least ONE “Y” chromosome, you are male

KLINEFELTER (XXY, XXXY, etc.)

- Hypogonadism found at puberty
- **#1 cause of male infertility**
- NO retardation unless more X's
- 47, XXY 82% of the time
- L----O----N----G legs, atrophic testes, small penis


Frontal baldness absent
Poor beard growth
Tendency to grow fewer chest hairs
Narrow shoulders
Breast development
Wide hips
Female-type pubic hair pattern
Small testicular size
Long arms and legs





TURNER (XO)

- 45, X is the “proper” designation
- Mosaics common
- Often, the WHOLE chromosome is not missing, but just part
- **NECK “WEBBING”**
- EDEMA of HAND DORSUM
- CONGENITAL HEART DEFECTS most FEARED
- “STREAK” OVARIES

Short stature

Low hairline

Shield-shaped thorax

Widely spaced nipples

Shortened metacarpal IV

Small finger nails

Brown spots (nevi)

Characteristic facial features

Fold of skin

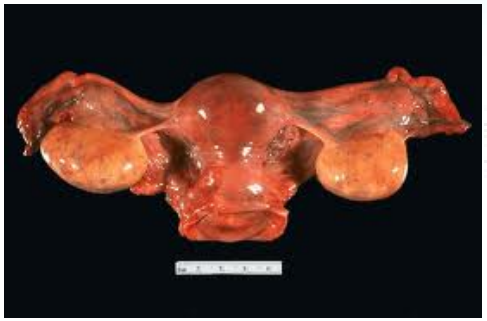
Constriction of aorta

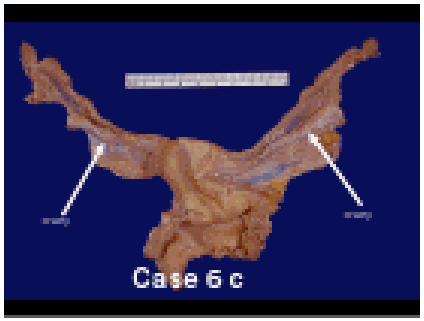
Poor breast development

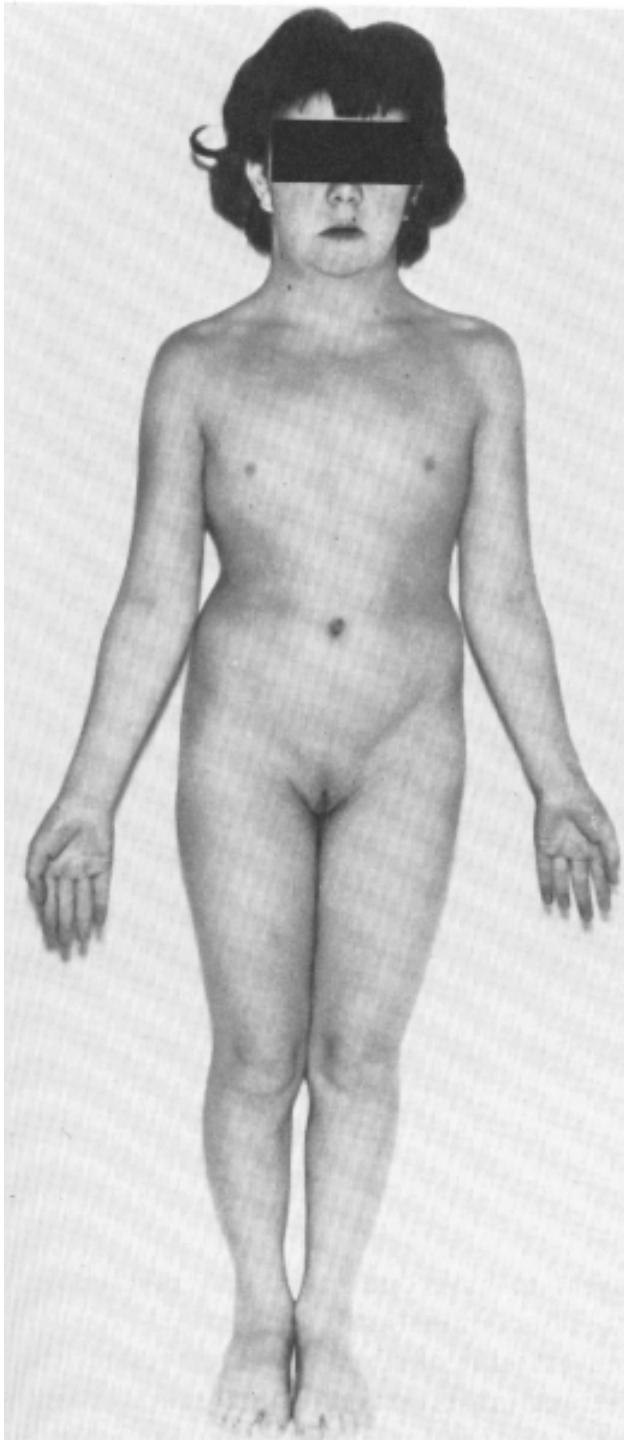
Elbow deformity

Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)

No menstruation







HERMAPHRODITES

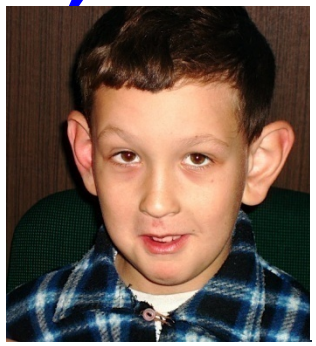
♂

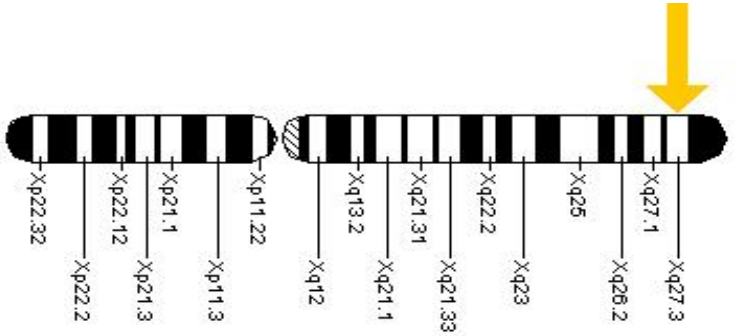
♀

- **GENETIC SEX is determined by the PRESENCE or ABSENCE of a "Y" chromosome, but there is also, GONADAL (phenotypic), and DUCTAL sex**
- **TRUE HERMAPHRODITE: OVARIES AND TESTES, often on opposite sides (VERY RARE)**

- **PSEUDO-HERMAPHRODITE:**
  - **MALE: TESTES with female characteristics (Y-)**
  - **FEMALE: OVARIES with male characteristics (XX)**

SINGLE GENE, NON-Mendelian





- **Triplet repeats**
  - **Fragile X (CGG)**
  - **Others: ataxias, myotonic dystrophy**
- **Mitochondrial Mutations: (maternal)**

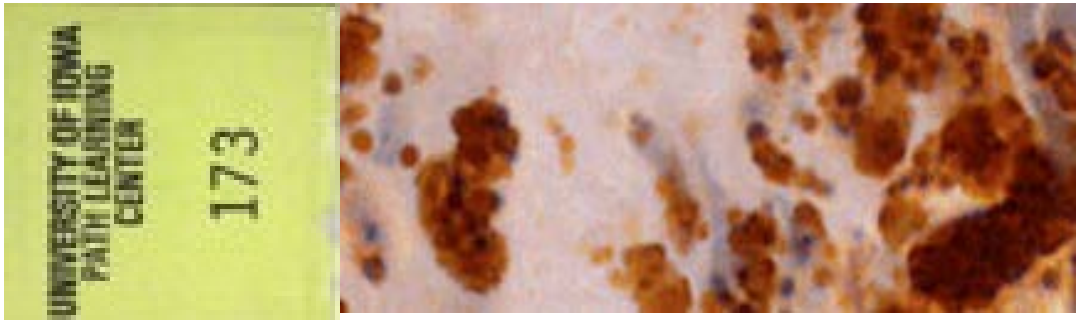
  (LEBER HEREDITARY OPTIC NEUROPATHY)
- **Genomic "IMPRINTING": (Inactivation of maternal or paternal allele, contradicts Mendel)**
- **Gonadal "MOSAICISM": (only gametes have mutated cells)**

MOLECULAR DX by DNA PROBES

- BIRTH DEFECTS, PRE- or POST- NATAL
- TUMOR CELLS
- CLASSIFICATIONS of TUMORS
- IDENTIFICATION of PATHOGENS
- DONOR COMPATIBILITY
- PATERNITY
- FORENSIC

H&E tissue structures

Immuno-Antigen Proteins



GENES that MAKE those PROTEINS