

OUTLINE OF HUMAN CLINICAL GENETICS

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"Just as our present knowledge and practice of medicine relies on a sophisticated knowledge of human anatomy, physiology and biochemistry, so will dealing with disease in the future demand a detailed understanding of the molecular anatomy, physiology and biochemistry of the human genome"

Paul Berg. Nobel Prize Lecture, 1980

BACKGROUND

- Gene

- The unit of inheritance

- Triplets of nucleotide bases: Purines

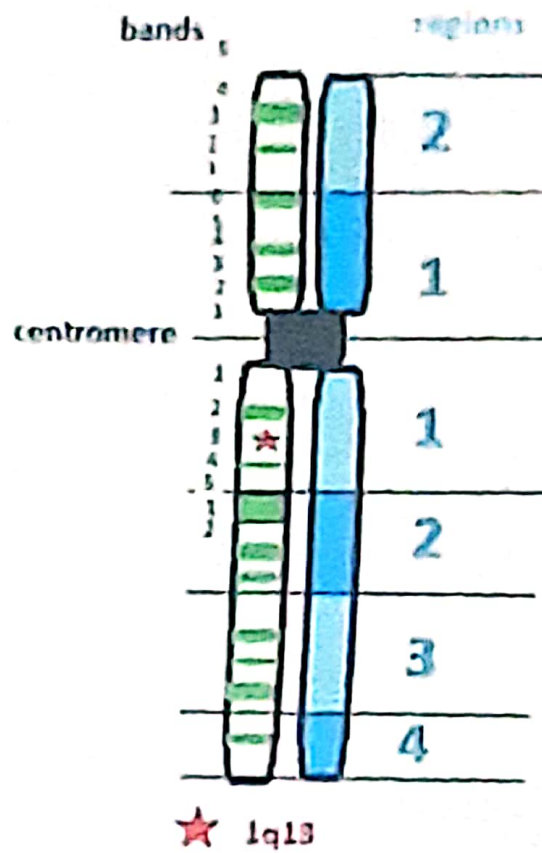
- (A,G) and Pyrimidines (C,T,U)

- Genes form double helix bonds of DNA
- DNA is contained within the CHROMOSOMES
- Chromosomes are found mainly in the cell nuclei, with a few in the mitochondria

Chromosomes Cont....

- Each chromosome has 2 short arms (p) and 2 long arms (q) joined at the centre (centromere)
- Each arm is divided into BANDS, which in turn are grouped into REGIONS
- EUPLOID cells have 46 chromosomes; HAPLOID have 23.
- Multiples of 23 are said to be POLYPLOID; the rest are ANEUPLOID
- Interference with chromosome results in genetic damage leading to abnormality being expressed

Chromosome 1



ETIOLOGY OF GENETIC ABERRATIONS

- Age
- Infections
- Radiation
- Chemicals
- Drugs

Older fathers associated with increased birth risks

From the data of more than 40 million births, scientists at Stanford have linked paternal age to birth risks, and even risks to the mother's health.

A decade of data documenting live births in the United States links babies of older fathers with a variety of increased risks at birth, including low birth weight and seizures, according to a new study by researchers at the [Stanford University School of Medicine](#).

The data even suggest that the age of the father can sway the health of the mother during pregnancy, specifically her risk for developing diabetes.

Advanced paternal age: A man who is age 40 years or older at the time of conception. (There is no universally accepted definition of advanced paternal age but this criterion is often used in [genetic counseling](#).)

Advanced paternal age is associated with an increased risk of new mutations in the offspring. This risk for genetic defects does not increase dramatically at age 40, but rather increases linearly with the age of the father. The risk of genetic defects due to new dominant mutations is 4 to 5 times greater for fathers aged 45 and above than for men in their early twenties.

There are two types of paternal age effects. One relates to the autosomes and the other to the X chromosome. New autosomal mutations for dominant conditions show up in the children. Their diseases are due directly to advanced paternal age.

New mutations on the X chromosome are usually not evident in the children. They are transmitted to daughters who are at risk for having sons with X-linked diseases. This is an indirect paternal age effect; it is the effect of the age of the maternal grandfather.

Examples of autosomal dominant conditions associated with advanced paternal age include [achondroplasia](#), neurofibromatosis, [Marfan syndrome](#), [Treacher Collins syndrome](#), Waardenburg syndrome, thanatophoric dysplasia, osteogenesis imperfecta, and Apert syndrome.

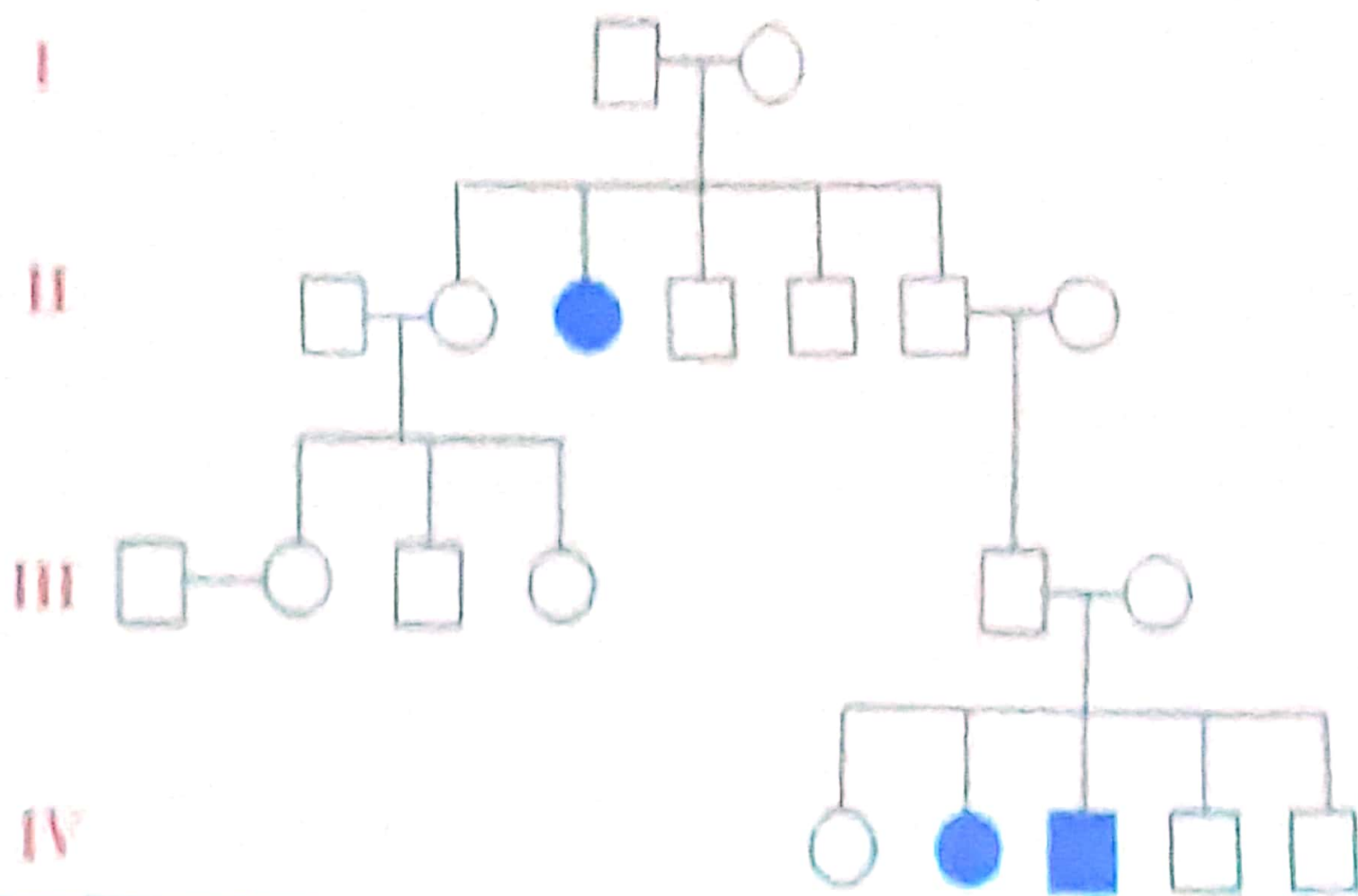
Examples of X-linked conditions associated with increased maternal grandfather's age include fragile X, [hemophilia A](#) (factor VIII deficiency), hemophilia B (factor IX deficiency), Duchenne muscular dystrophy, incontinentia pigmenti, Hunter syndrome, Bruton-type agammaglobulinemia, and [retinitis pigmentosa](#).

MECHANISMS OF GENETIC ABNORMALITIES

- SINGLE GENE
 - Mendelian
 - Non Mendelian
 - Multifactorial
- CHROMOSOMAL NUMERICAL ABNORMALITY
- CHROMOSOMAL STRUCTURAL ABNORMALITY
- DYSMORPHOLOGY

Single Gene: Mendelian

- Autosomal or X-linked
- Can be RECESSIVE (abnormality only seen if both alleles abnormal) or DOMINANT if single abnormal allele expresses itself
- Pattern of inheritance can be drawn up in a family "tree" in a predictable manner (PEDIGREE)



Autosomal Recessive

- May skip generations
- Both sexes affected equally
- Individuals with single abnormal gene are CARRIERS
- Two carrier parents have 25% risk affected child, 50% of carriers and 25% chance of normal child
- Consanguinity frequent
- Eg most inborn errors of metabolism, SCA

Autosomal Dominant

- De Novo mutations frequent
- Expresses in all individuals with abnormal gene
- Both sexes affected equally
- Eg Marfans syndrome; neurofibromatosis

X linked Recessive

- Females are carriers and do not express the disorder
- Transmission is from mother to son
- All males with the abnormal gene express it
- Eg

Hemophilia

Duchenne muscular dystrophy

X linked Dominant

Both sexes express P for dominant gene

Eg. Vit D resistance rickets

Single Gene, Non Mendelian

Shady Day, Muscular Dystrophy

Example:

Phenotype

Genotype

Single Gene, Multifactorial

Longevity, detection of the eye

Genetic factor (allele)

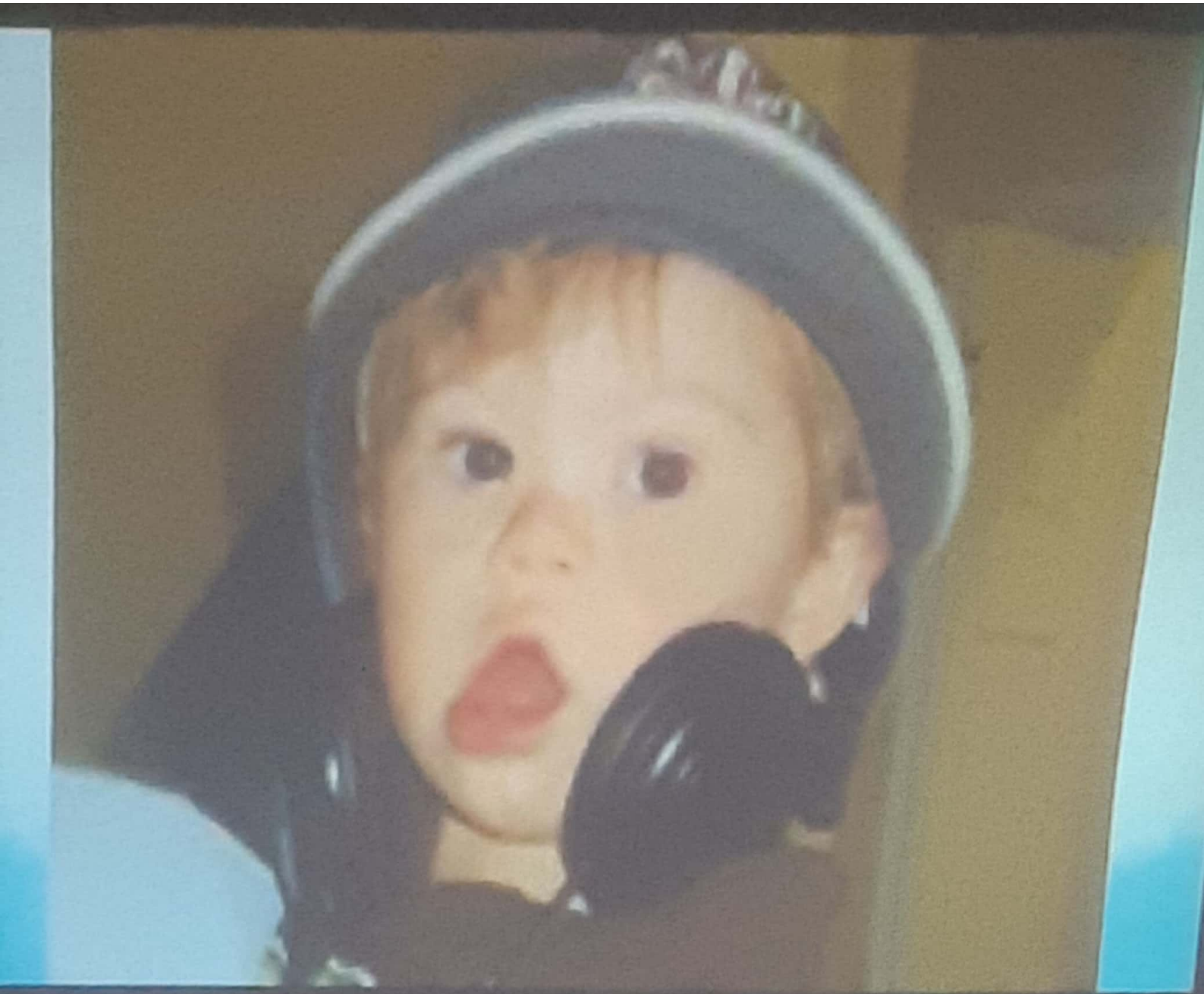
Environment

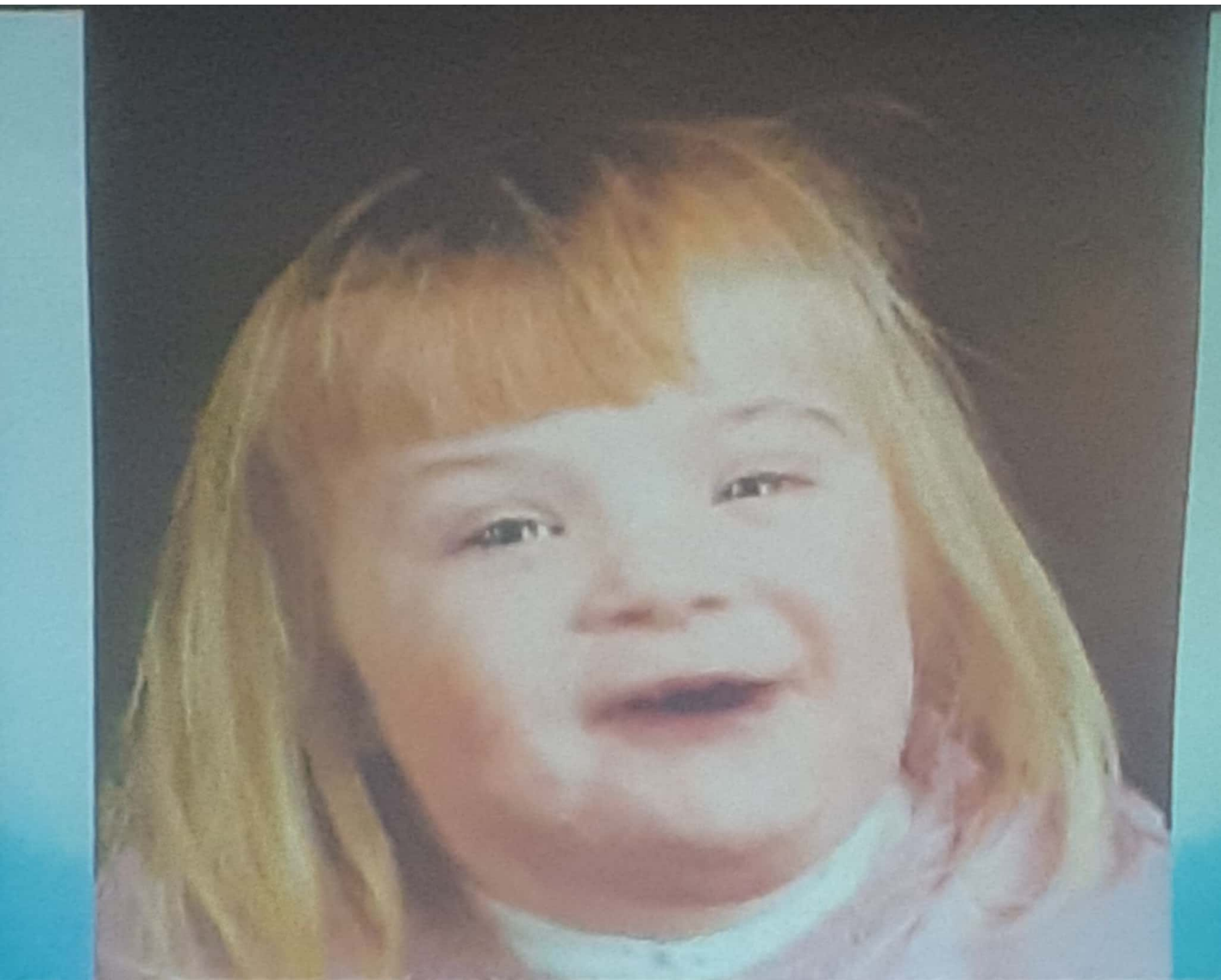
Chromosomal Numerical Abnormalities

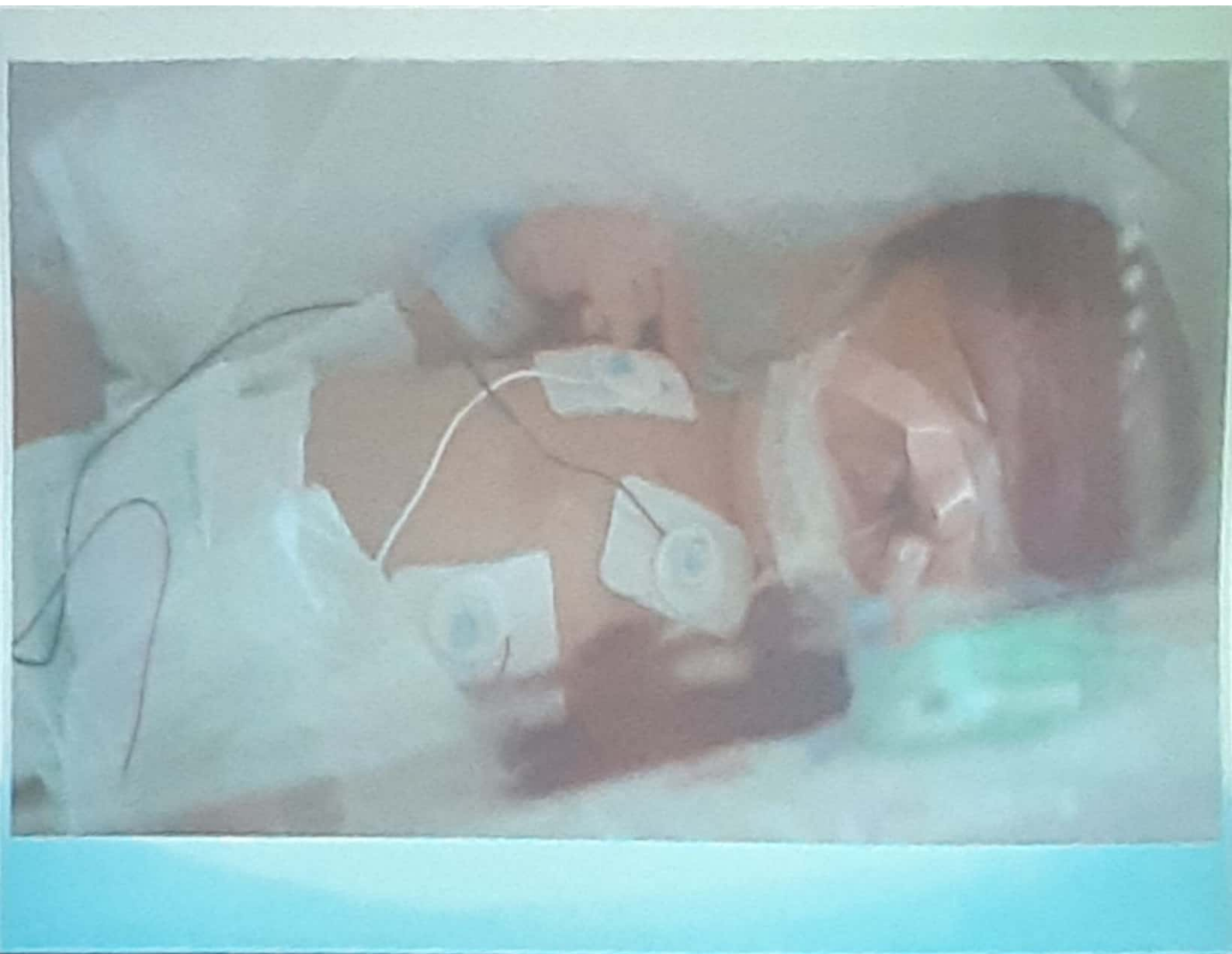
- Usually as a result of TRANSLOCATION or NON DYSJUNCTION

Examples

- Trisomies 21, 13, 18 etc
- Monosomies 45XO
- Klinefelter's syndrome



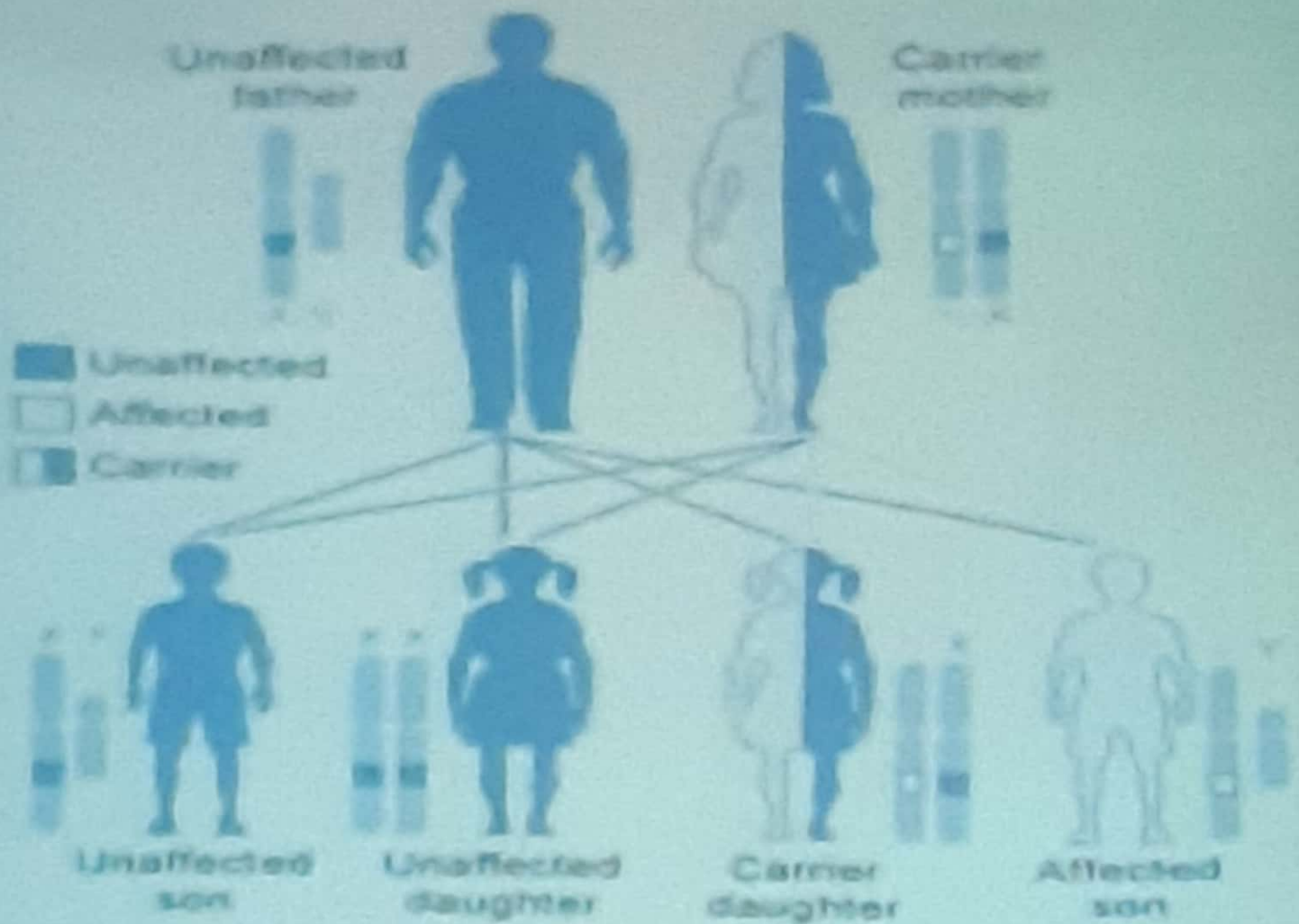




Chromosomal Structural Abnormalities

- Usually due to chromosomal deletions, insertions or unstable chromosomes (also called "chromosomal breakage syndromes")
- Examples of deletions
5p-, 4p-, 15q11- to 15q13-, Xq27-
- Examples of breakage syndromes
Bloom syndrome, ataxia telangiectasia,
xeroderma pigmentosa

X-linked recessive, carrier mother



U.S. National Library of Medicine

DYSMORPHOLOGY

- Some abnormalities have no clear cut pattern of genetic inheritance
- They appear to be due to interference with the processes of cell differentiation and organogenesis in early life
- Majority of them present with recognizable syndromic patterns
- The recurrence rate tends to be about 5%

- Examples

Apert , Pierre Robin, osteogenesis

Imperfecta

Modern Application of Genetics

- Use of molecular genetics in the production of therapeutic agents eg insulin, growth hormone, Hepatitis B vaccine
- Understanding the role of genes in cancer causation and applying this to cancer therapy (oncogenetics)
- Applying molecular genetics in treating single gene disorders
- Application of "cloning" technique to solve a myriad of genetic problems in the future
- Human Genome Project (1990-2005) has opened a wide range of genetic application