Genetics of Turner syndrome

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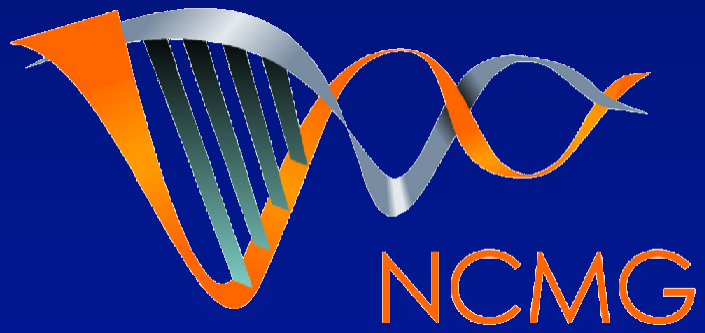
National Centre for Medical Genetics

Clinical Genetics



Cytogenetics

Molecular Genetics

www.genetics.ie

NCMG Clinical Genetic Services

- 4 Consultants

- 3 generic genetic counsellors
- 3 cancer specialist genetic counsellors
- 3 specialist genetic counsellors; Cardiac, CF and NF

- 1 medical registrar

- Genetics clinics in Dublin, Cork, Limerick and Galway

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What is Clinical Genetics?

1. Diagnosis

   Clinical or laboratory Dx of genetic condition

   Estimation of risks to patient

   Estimation of risks to relatives

2. Advice

   Communicate information about condition and its consequences for the whole family

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What is Clinical Genetics?

3. Support

To patient
To family
Non-directive counselling

4. Register of Genetic Disorders

Follow-up of appropriate individuals
Dissemination of new information

5. Research

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Genetic Counselling

Genetic counselling is a communication process that deals with the human problems associated with the occurrence, or the risk of recurrence, of a genetic disorder in a family.

ASHG 1975

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Genetic Counselling

3 Elements of genetic counselling

1) Comprehension of medical facts about a disorder, including diagnosis, natural history, and available management

2) Appreciation of the contribution of heredity to the disorder, and the chance of recurrence in relatives

3) Explore the impact of the genetic elements of a disorder both on individuals and on their family

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Gene

- An inherited element which gives a person a particular trait
- A stretch of DNA which codes for a particular protein
- We all have 30,000 to 40,000 genes
- Genes are present in every cell in our body
- A person has 2 copies (a pair) of each gene, one from each parent

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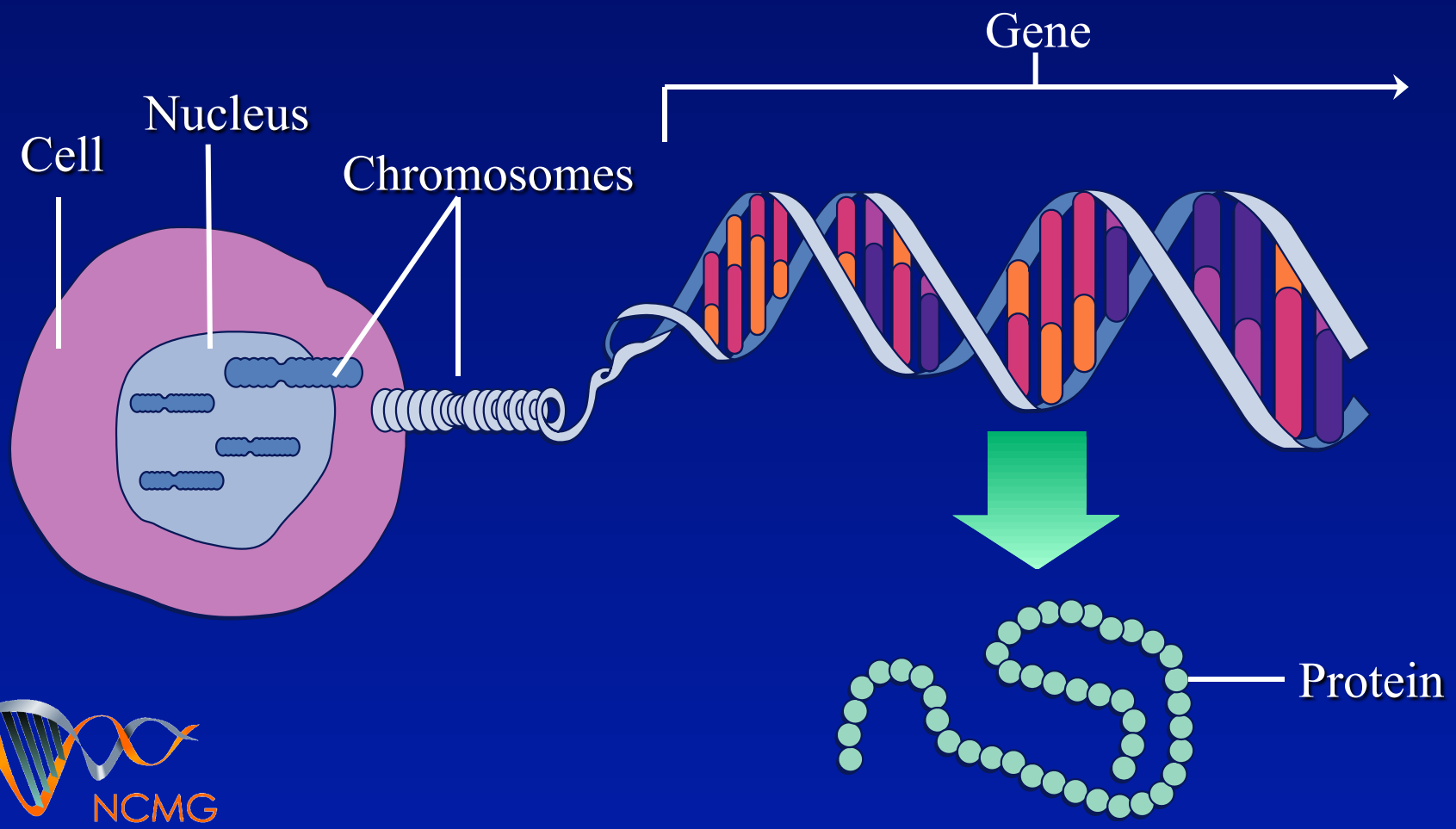
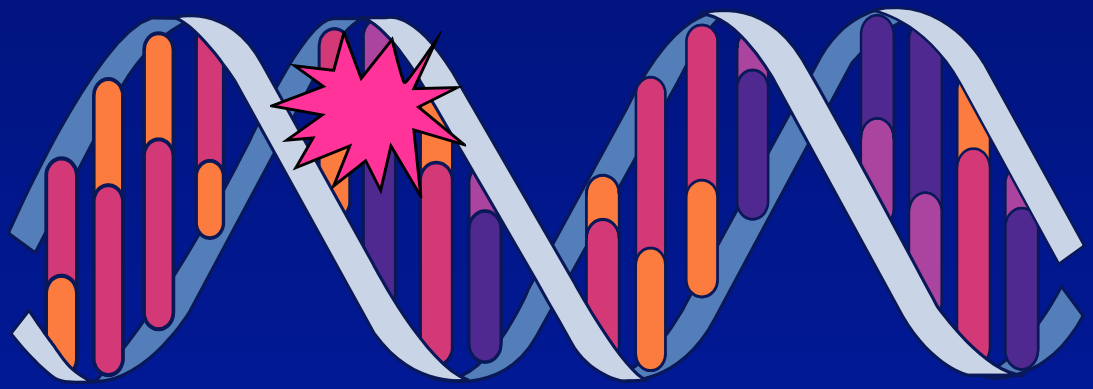
Chromosomes, DNA, and Genes



Disease-Associated Mutations

A mutation is a change in the normal base pair sequence



Commonly used to define DNA sequence changes that alter protein function

Chromosome

The human chromosome number is 46
(44 autosomes and 2 sex chromosomes)
46 chromosomes is the diploid number
23 chromosomes is the haploid number

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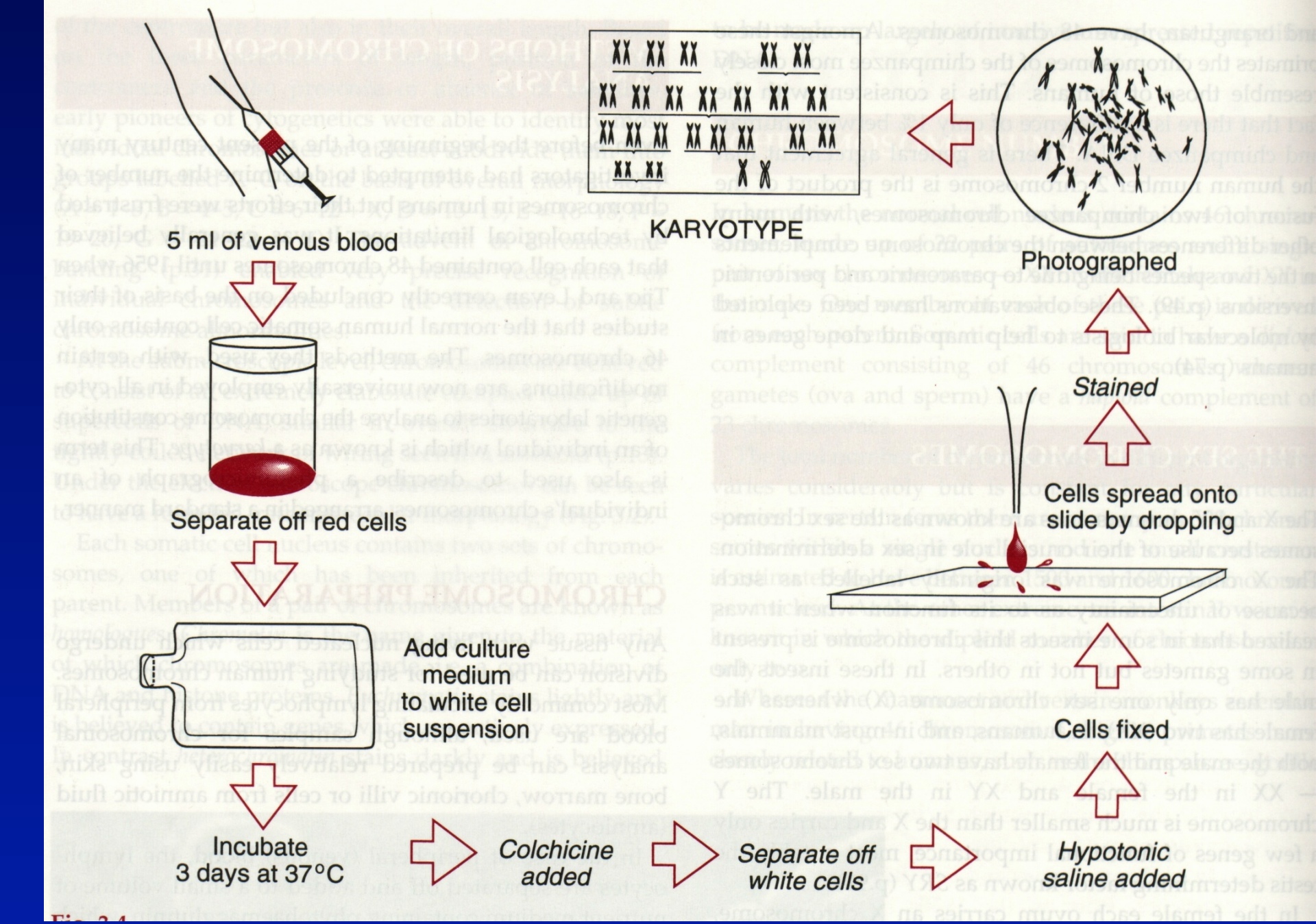
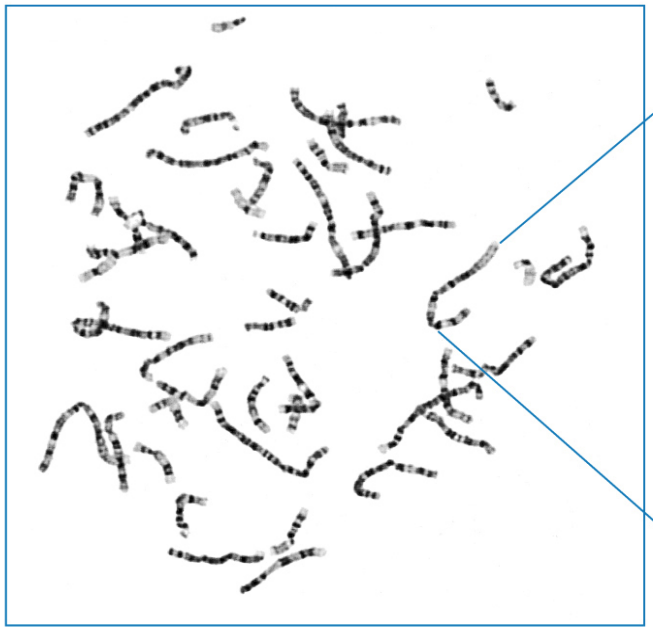

5 ml of venous blood
Separate off red cells
Add culture medium to white cell suspension
Incubate 3 days at 37°C
Colchicine added
Separate off white cells
Hypotonic saline added
Cells fixed
Cells spread onto slide by dropping
Stained
Photographed
KARYOTYPE

Metaphase Spread

Anatomy of a Chromosome

CHROMOSOME SPREAD



Chromosome

Idiogram Karyotype

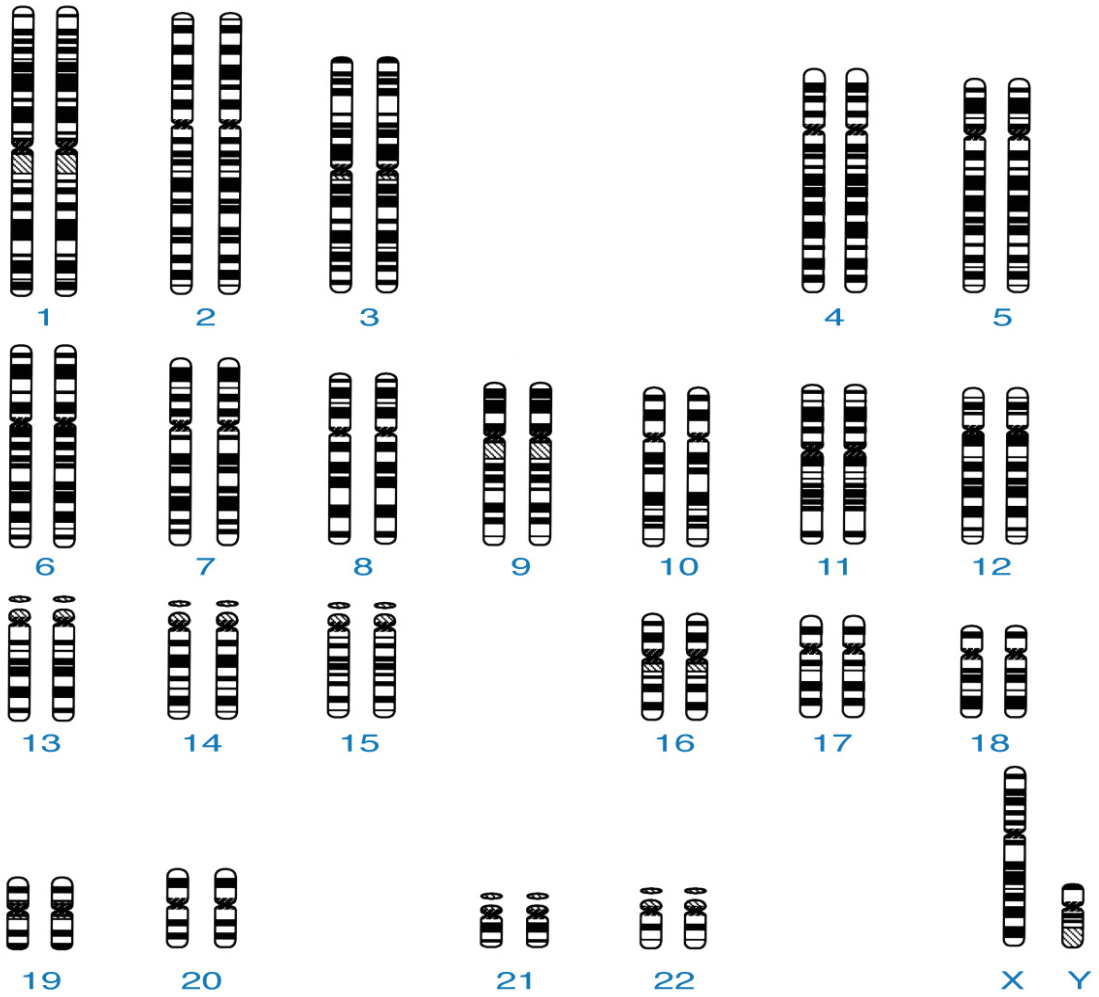
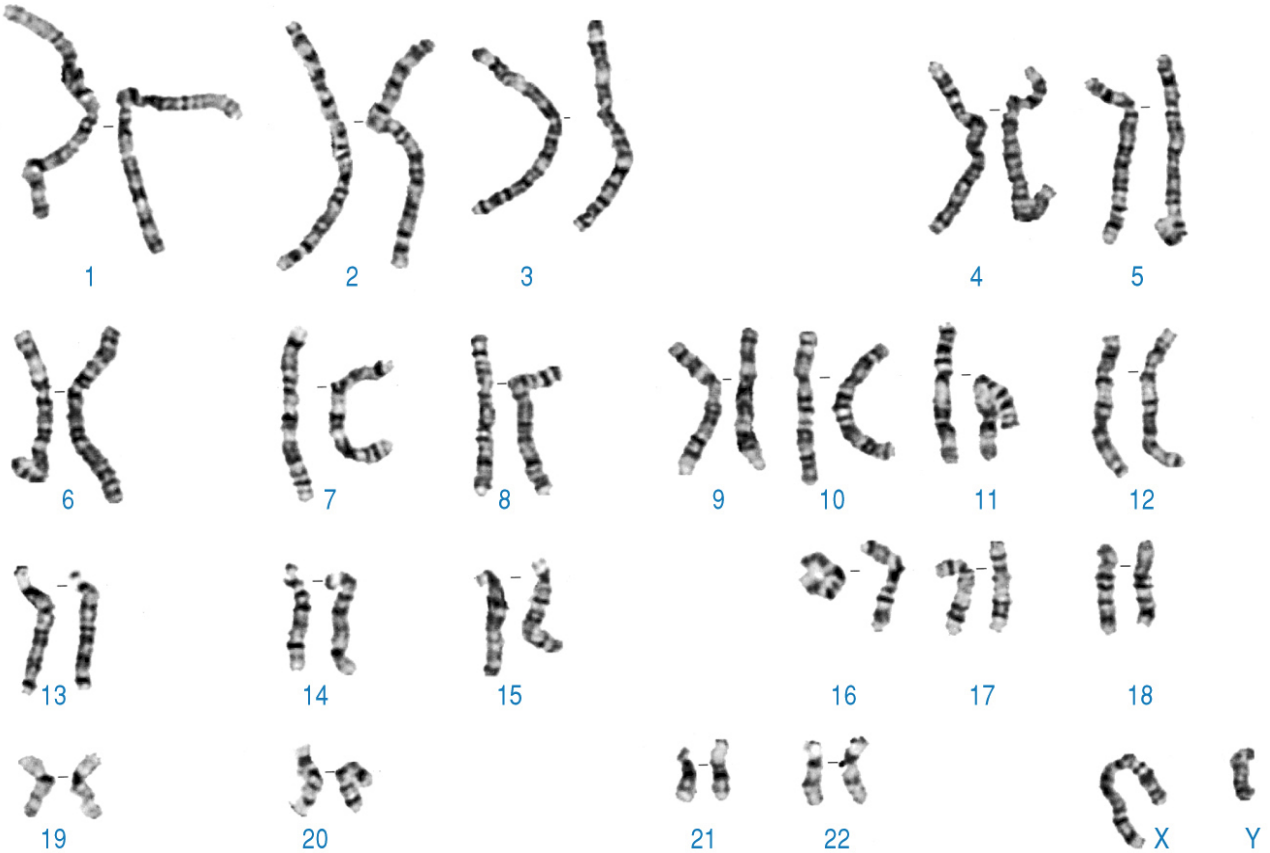
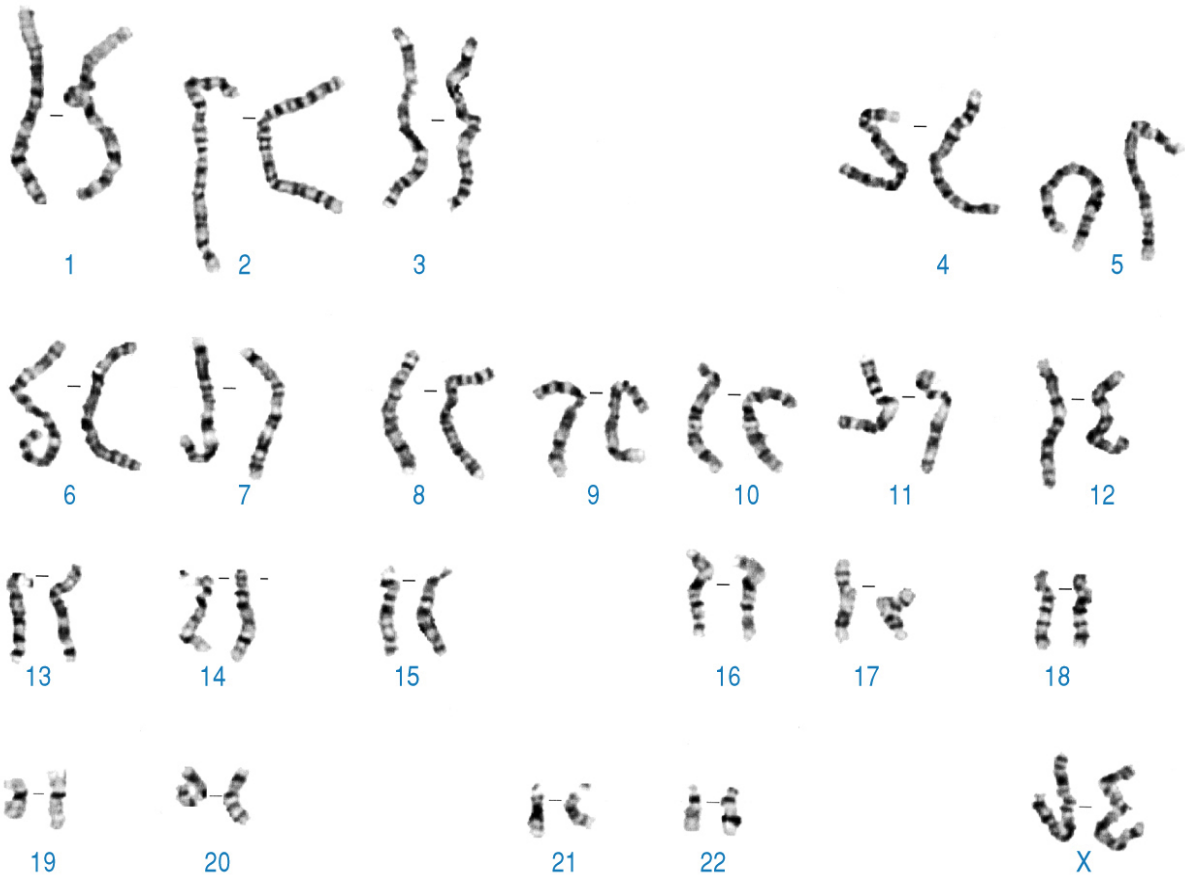


*Image courtesy of Vysis, Inc., Downers Grove, Illinois

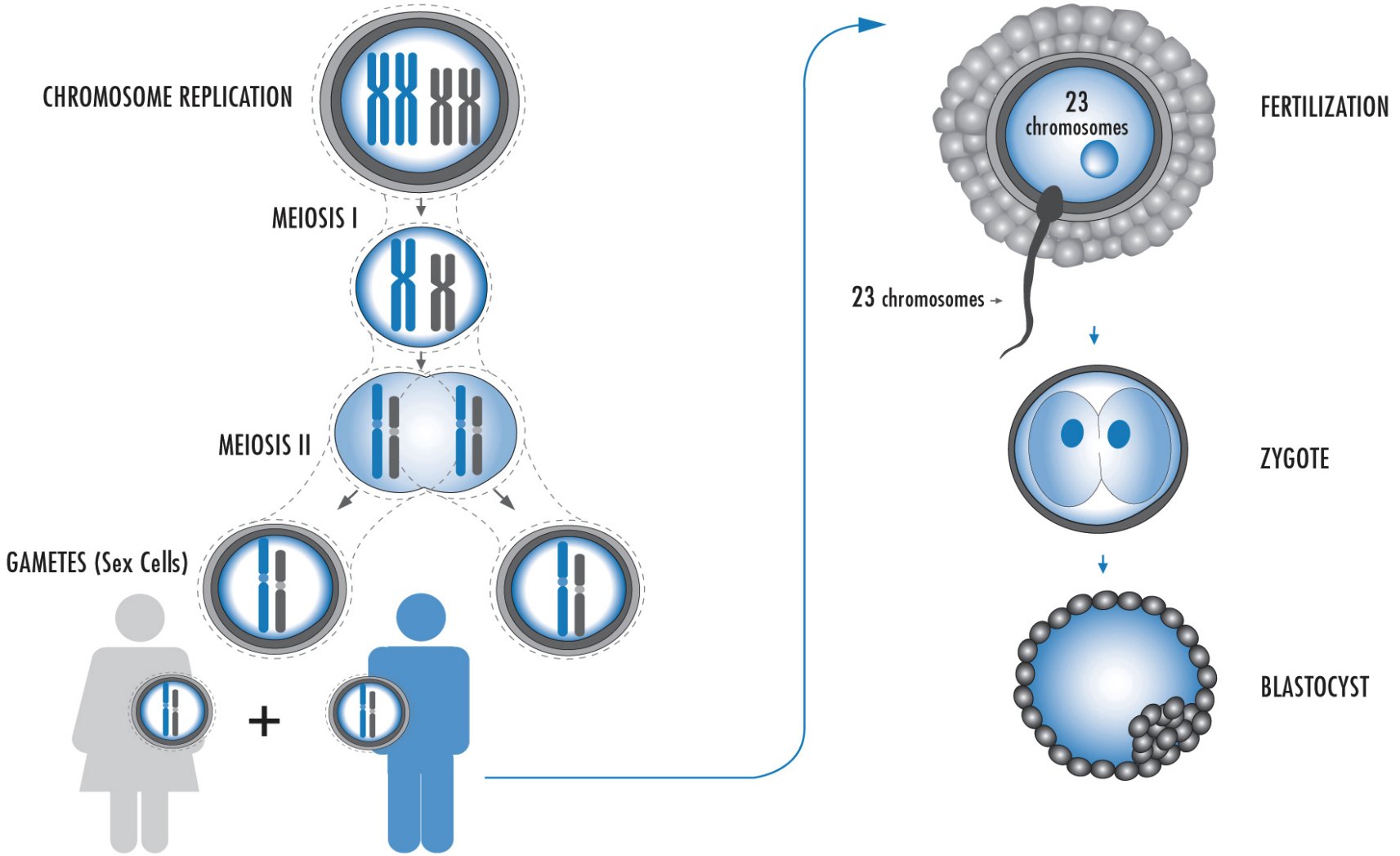
Normal Male - 46,XY



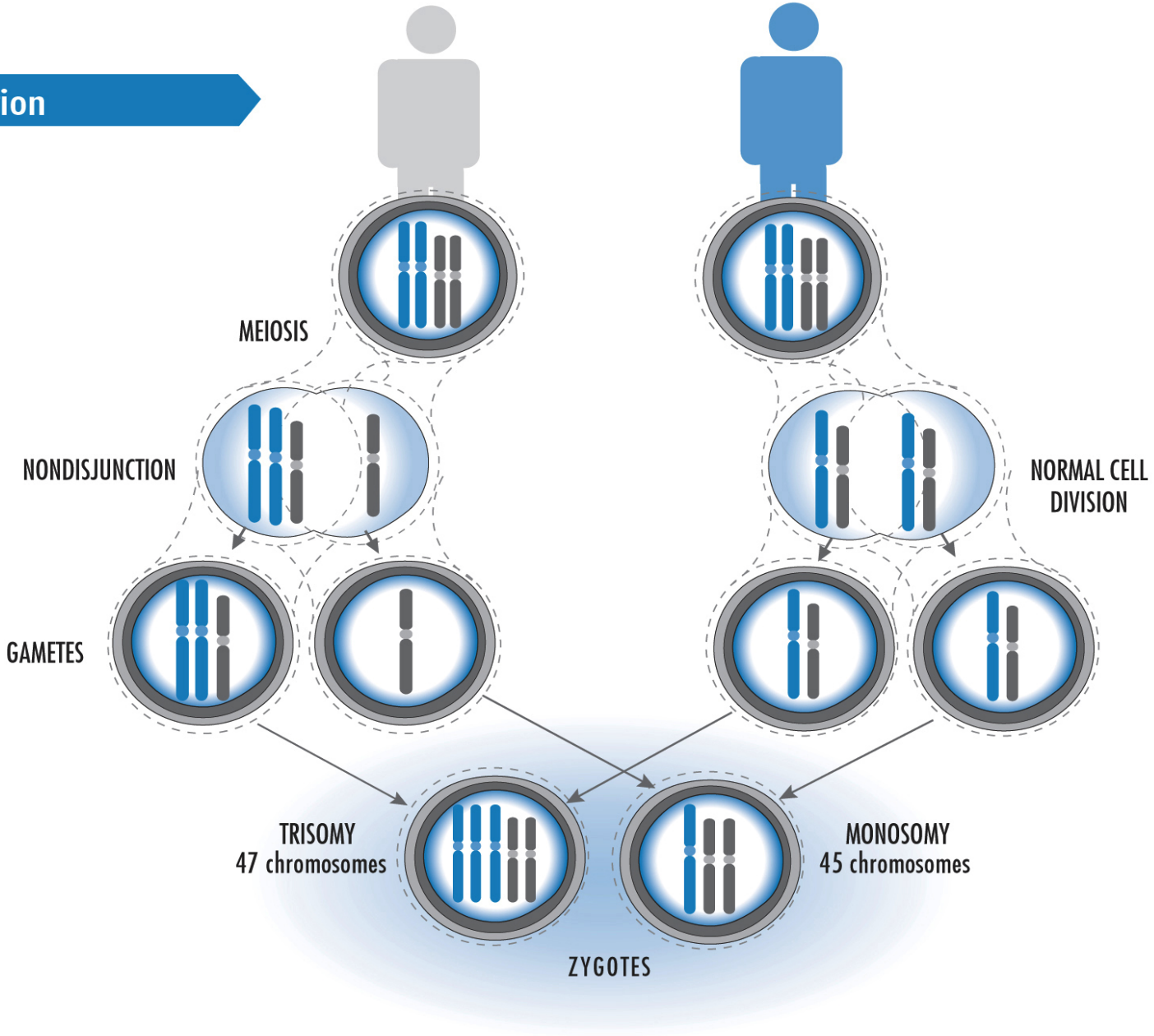
Normal Female - 46,XX



Meiosis and Fertilization

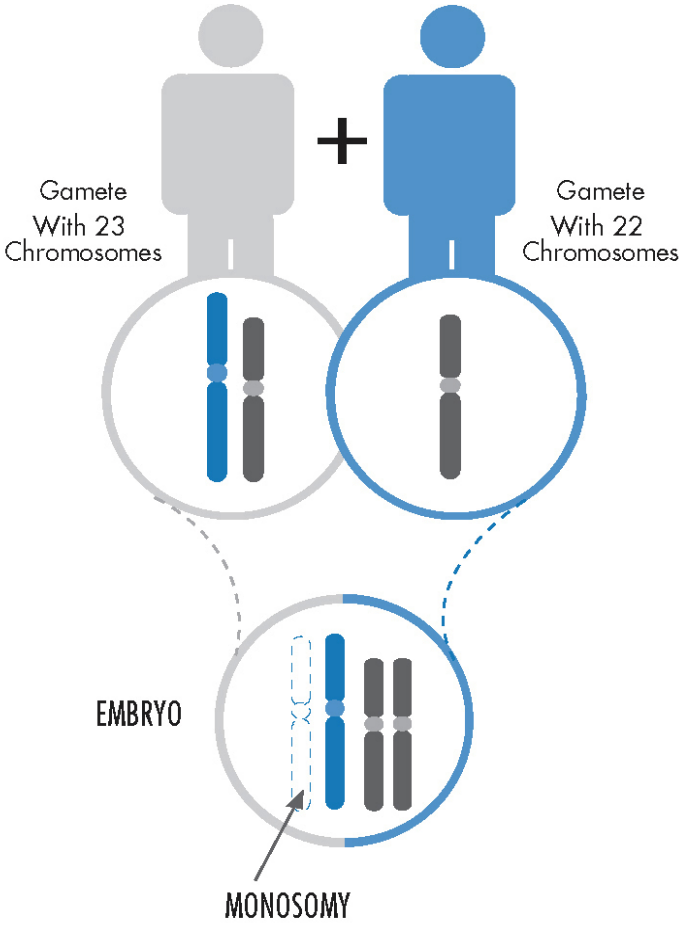


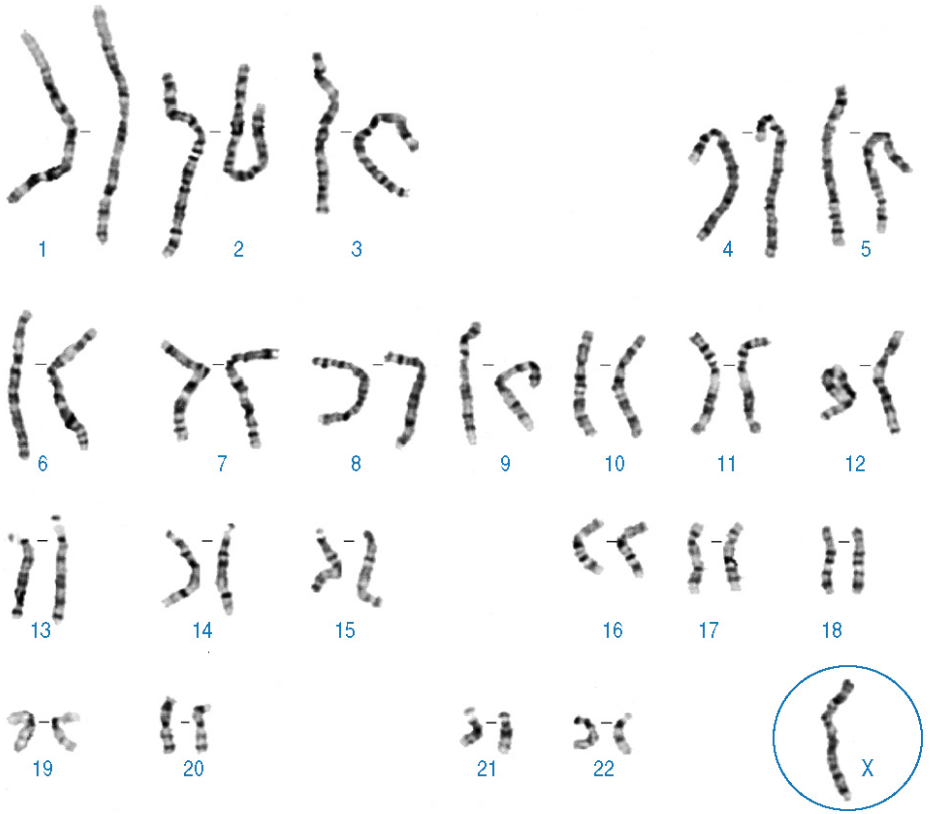
Nondisjunction



Turner Syndrome Karyotype
45,X

Monosomy X - Turner Syndrome 45,X





When Turner's Syndrome may be diagnosed

- Before birth
  - baby with excess fluid (hydrops)
  - Incidentally
- At Birth
  - Excess fluid (lymphoedema)
  - congenital heart disease (aortic problems)
  - incidentally
- As child
  - Short stature
  - Delayed Puberty

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Medical Follow Up

- Cardiac Disease – not just as newborn
- Kidney scan – if normal at birth may be no need to repeat
- Check for underactive thyroid as teenager/ adult
- Endocrinology follow up
  - Growth hormone use
  - Oestrogen replacement from puberty

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Clinical Features

- Consistent Features
  - short stature
  - Ovarian dysgenesis (failure to develop)
    - Primary amenorrhoea (absent periods)
    - infertility
- Variable Features
  - Webbed Neck
  - Peripheral lymphoedema (swollen feet and hands)
  - Coarctation (narrowing) of descending aorta
- IQ normal

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Clinical Genetics

New genetic event in the girl with Turner's

Likelihood of another affected child for parents is under 1%

No implication for unaffected sisters' children

Very few women with Turner's ovulate

- Pregnancy in women with Turner's can be achieved using donor eggs
- Women with Turners' may also adopt children

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Other genetic forms of Turner's syndrome

- >50% of Turner's 45,X in all cells
- <30% have 46 chromosomes, with one normal X, but a second X which is missing a significant amount of genes

  e.g. 46,XX,del(X)(q21-q27)
- <20% have mosaic Turner's 46,XX/45,X

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Mosaic Turner's

- Some cells in the body have 46,XX (usual female pattern)
- Some cells in the body have 45,X (Turner's pattern)

- Can be a milder form, with greater final height, and sometimes ovarian function

- Mosaic pattern in blood does not reflect pattern in other tissues

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Other genetic forms of Turner's syndrome

- Ring X chromosome
- 46,X, r(X)
- Turner's syndrome with usual clinical features
- Learning disability frequent in ring X Turner's but not in usual form of Turner's

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Why don't men get Turner Syndrome ?

Men
One X chromosome in every cell

Women
one X chromosome active in any cell
One X chromosome is inactivated early in embryogenesis randomly in each cell

X-inactivation aka Lyonisation

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Effect of Diagnosis

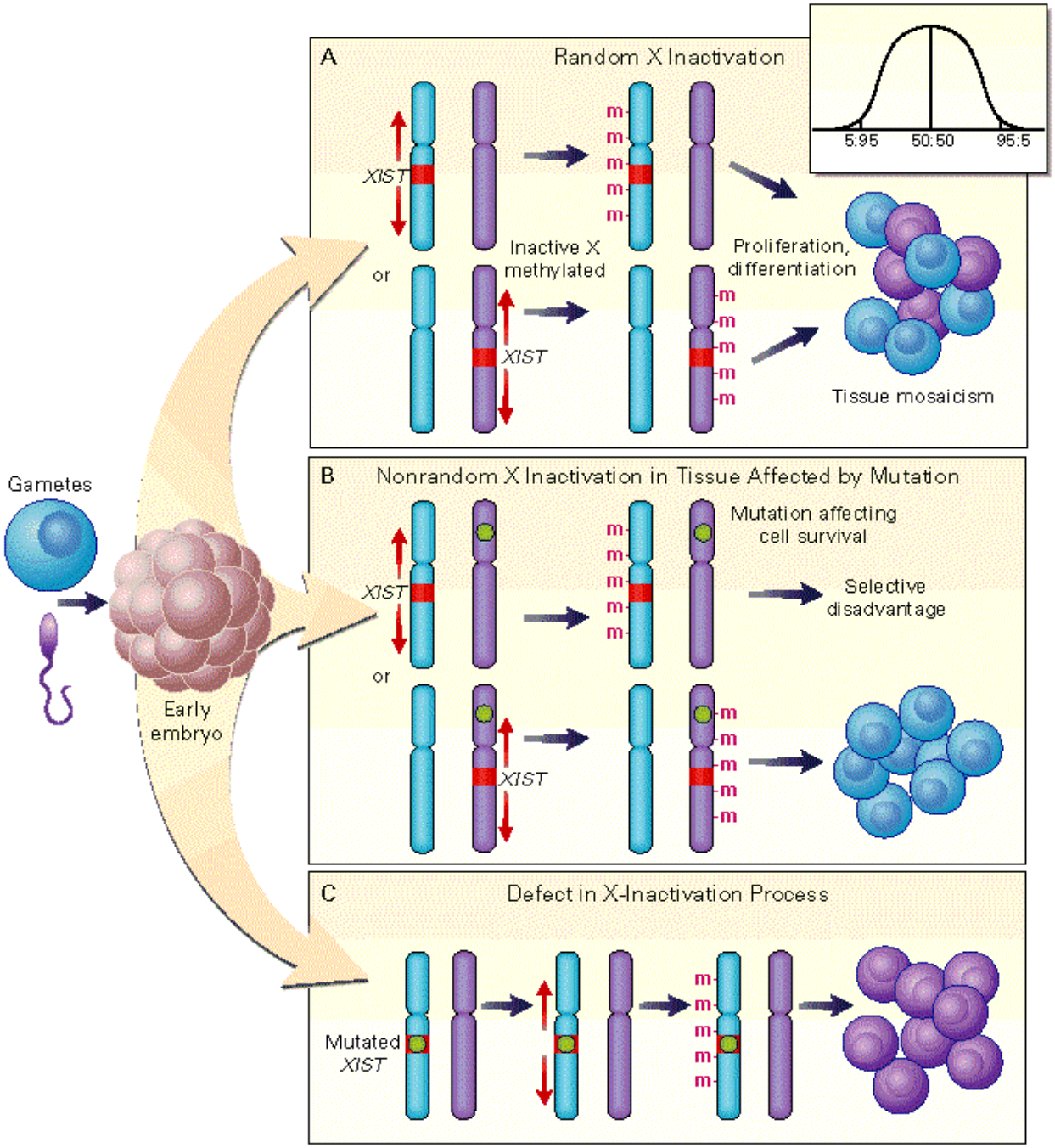
- Internet and conflicting information
- When to tell and who?
- How to tell?

The impact of words

- Some words have an inherent negative connotation; e.g.,
- Risk
- Faulty genes
- Abnormal genes

Use of more neutral words are favoured; e.g.,

- Chance/ likelihood
- Altered genes


A
Random X Inactivation
5:95
50:50
95:5
XIST
m
Inactive X
methylated
or
XIST
Proliferation,
differentiation
Tissue mosaicism
Gametes
Early
embryo
B
Nonrandom X Inactivation in Tissue Affected by Mutation
Mutation affecting
cell survival
Selective
disadvantage
XIST
or
XIST
C
Defect in X-Inactivation Process
Mutated
XIST

Incomplete X inactivation

X inactivation is incomplete

On every X chromosome – several regions which "escape " X inactivation

Xp22.3 & Xq21– pseudoautosomal regions

Girl get Turners, partly because they lack two copies of pseudoautosomal region of the X chromosome

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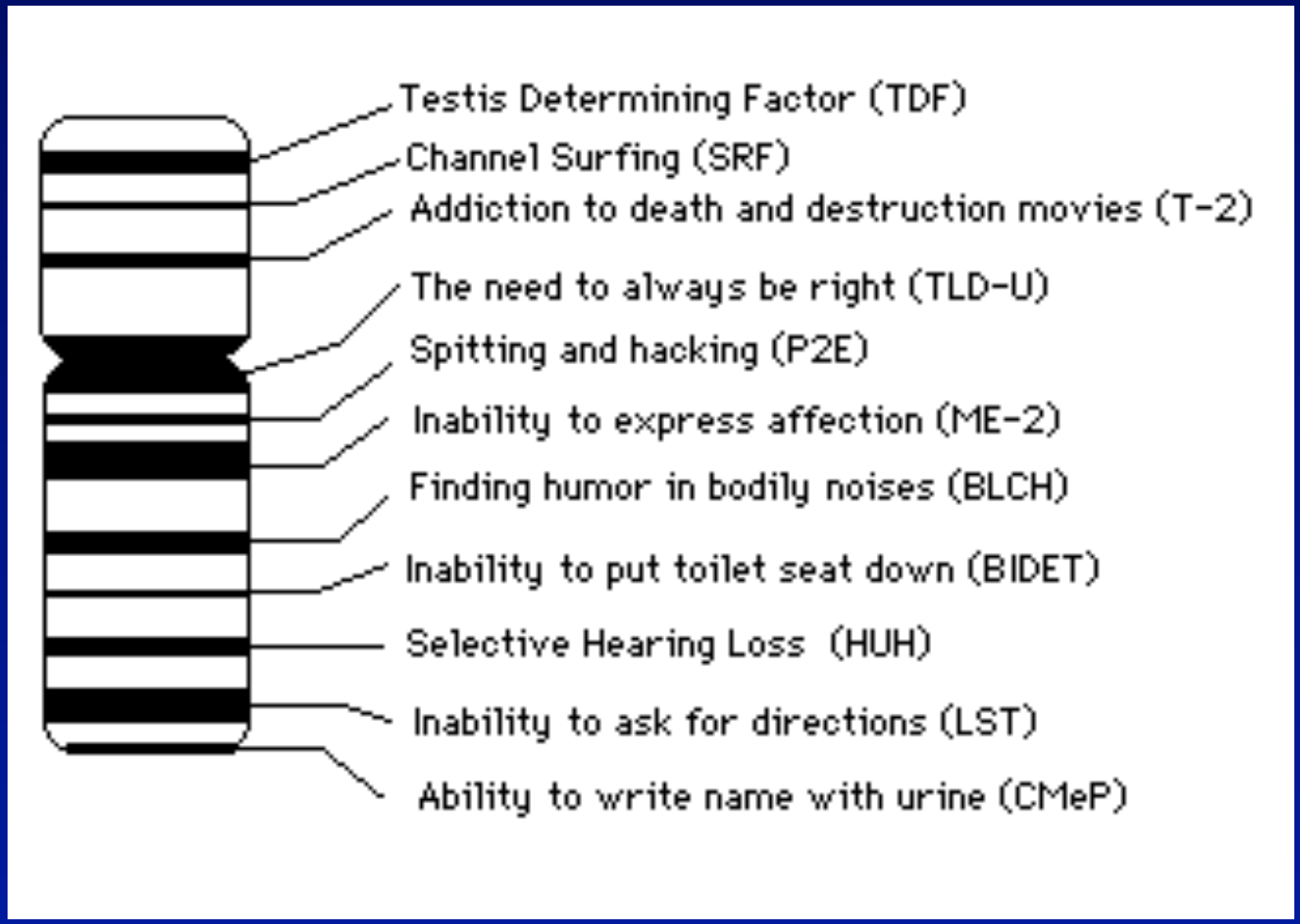
Y chromosome - After the Human genome



How do genes actually work?