Chromosomal mutations

Contents: Definition; Variations in chromosome structure and number; Discovery of the exact number of human chromosomes; Classification of human chromosomes; Basis of such classification; An outline classification of chromosomal mutations (abnormalities) in man; Structural chromosomal abnormalities with examples; Numerical chromosomal abnormalities with examples; Causes and origin of chromosomal abnormalities; Factors affecting chromosomal abnormalities; Frequencies of chromosomal abnormalities; Conclusions; Suggested reading.

Definition

Any change in the structure or number of chromosomes in organisms is referred to as chromosomal mutations (also known as chromosomal abnormalities or chromosomal aberrations).

Variations in chromosome structure and number

Variations in chromosomes in living organisms may be of two basic types: (1) Structural and (2) Numerical. The structural chromosomal variations may be again of several types and sub-types, the major ones are: Deletions, Duplications, Inversions and Translocations. The numerical chromosomal variations may also be of several types and sub-types, the major ones are: Euploidy (the exact multiple of n numbers like 3n, 4n, 10n etc.) and Aneuploidy (the integral multiple of n numbers like 2n+1, 2n-1, 2n+2, 2n-2 etc.). In this lecture, the chromosomal mutations or abnormalities in man are described in further details.

Discovery of the exact number of human chromosomes

- Chromosomes (L. chromos-colour, soma-body) were discovered by Waldayer in 1888.
- The normal diploid chromosome number (2n = 46) in man was confirmed by Tjio and Levan in 1956.
- Karyotype: Photographs or drawings of the individual chromosomes cut out from the smear of mitotic metaphase or prophase cells, placed and arranged in order according to their size and staining pattern.
- Syndrome: A group of symptoms that occur together and represent a particular disease or disorder.

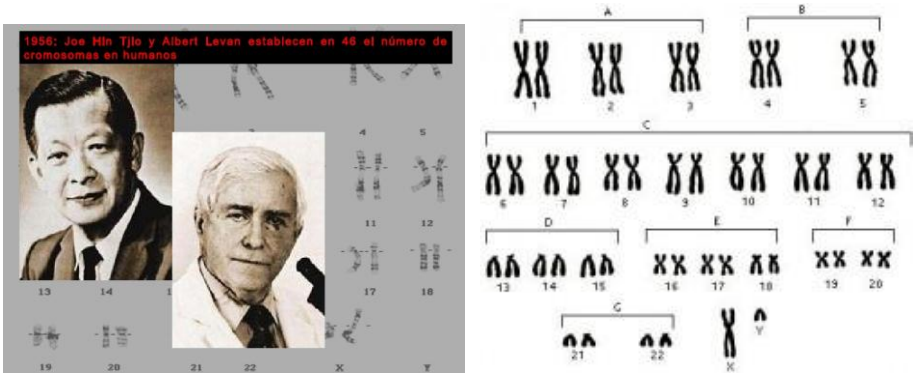

Fig. 10.1 Photographs of J. H. Tjio and A. Levan (left) and human karyotype

Classification of human chromosomes

The classification of human chromosomes was approved at the International Human Genetics Conferences held at Denver (1960), London (1963), Chicago (1966) and Paris (1971). Accordingly, human chromosomes are classified into the following seven groups:

Groups	No. of chromosomes	Types of chromosomes
A	1, 2, 3 = 3	Metacentric
B	4,5 = 2	Metacentric
C	6, 7, 8, 9, 10, 11, 12 = 7+X	Sub-metacentric
D	13, 14, 15 = 3	Acrocentric
E	16, 17, 18 = 3	Acro (16), sub-meta (17-18)
F	19, 20 = 2	Metacentric
G	21, 22 = 2+Y	Acrocentric
7 Groups	22 pairs autosomes + 1 pair sex chromosomes	

Basis of chromosomal classification in man

The chromosomal classification in man is based on:

1. Length of the chromosomes;
2. Position of centromere and relative length of arms;
3. Presence or absence of secondary constrictions or satellites; and
4. Banding or staining pattern.

An outline classification of chromosomal mutations in man

1. Structural abnormalities
    i. Deletions (B 4-5)
    ii. Translocation (D14-G21)
    iii. Duplications and inversions are not known in man
2. Numerical abnormalities
    i. Euploidy (3n, 4n)
    ii. Aneuploidy

    (a) Autosomal aneuploidy: D(13) trisomy, E(18) trisomy, G(21) trisomy

    (b) Sex chromosomal aneuploidy:

    i. Females: 45, XO monosomy, 47, XXX trisomy
    ii. Males: 47, XXY trisomy, 47, XYY trisomy
    iii. Intersexes: (a) True hermaphrodites (herms) 48, XXXY
    (b) Pseudofemales (ferms) 46, XX
    (c) Pseudomales (merms) 46, XY

Structural chromosomal abnormalities in man

Deletion (B 4-5)

Characteristics of B(4) deletion: Wolf-Hirschhorn syndrome

a) Bearer has a small deletion of B(4) chromosome;
b) Microcephaly with rounded face;
c) Newborn suffers from severe mental retardation;
d) Cries do not resemble the mewing of a cat.

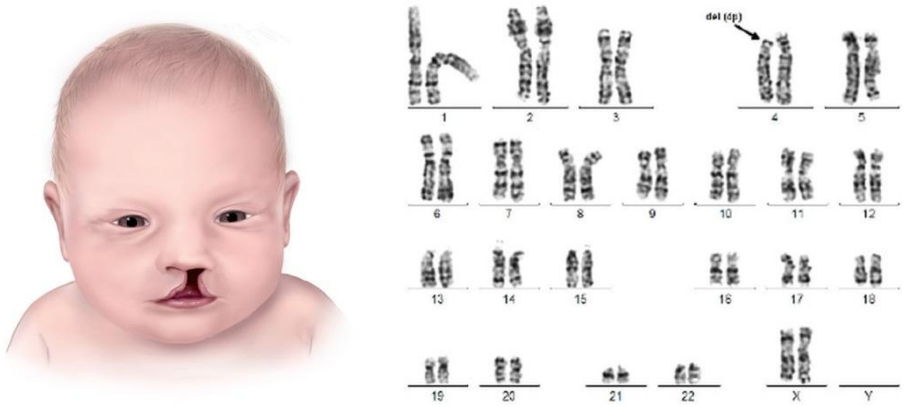

Fig. 10.2 A child suffering from Wolf-Hirschhorn syndrome; karyotype of the syndrome

Characteristics of B(5) deletion: Cri-du-chat syndrome

a) Karyotype has a small deletion of B(5) chromosome;
b) Microcephaly with small chin;
c) Rounded face with widely separated crossed eyes;
d) Cries resemble the mewing of a cat.

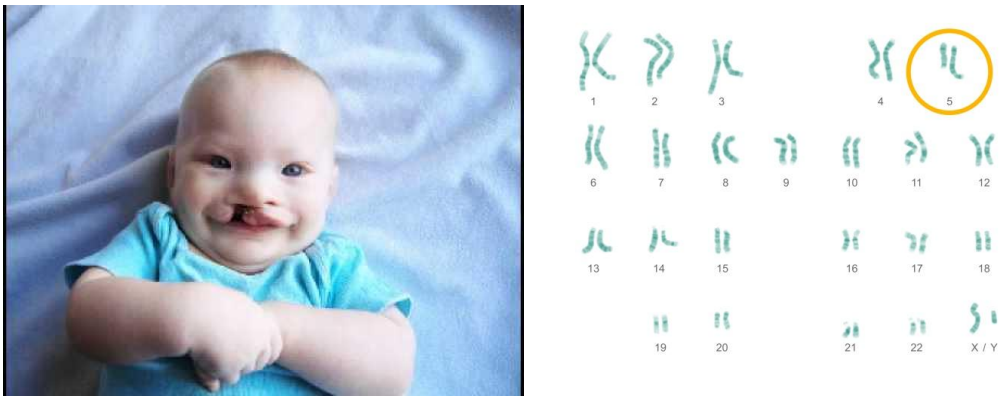

Fig. 10.3 A child suffering from cri-du-chat syndrome; karyotype of the syndrome

Structural chromosomal abnormalities in man: **Translocations**

- Robertsonian translocations between D14-G21 chromosomes;
- Give rise to Down's syndrome [see G(21) trisomy].

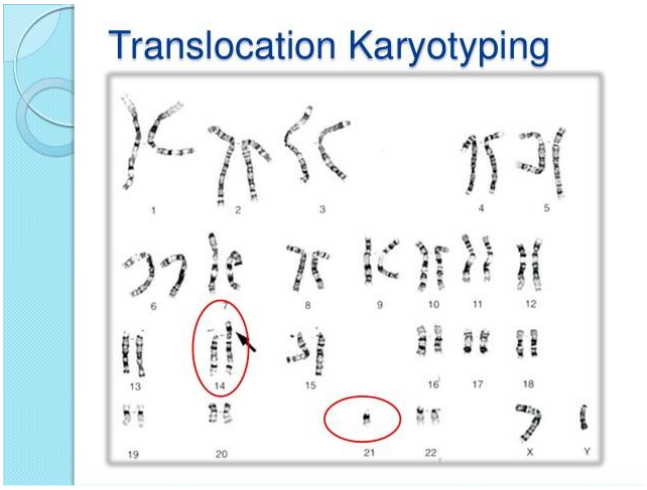

Fig. 10.4 Karyotype of a Down's syndrome, resulted from Robertsonian translocation between D14-G21 chromosomes

Numerical chromosomal abnormalities in man: Euploidy

- 3n and 4n euploidy;
- Spontaneous abortions, stillbirths or neonatal deaths.

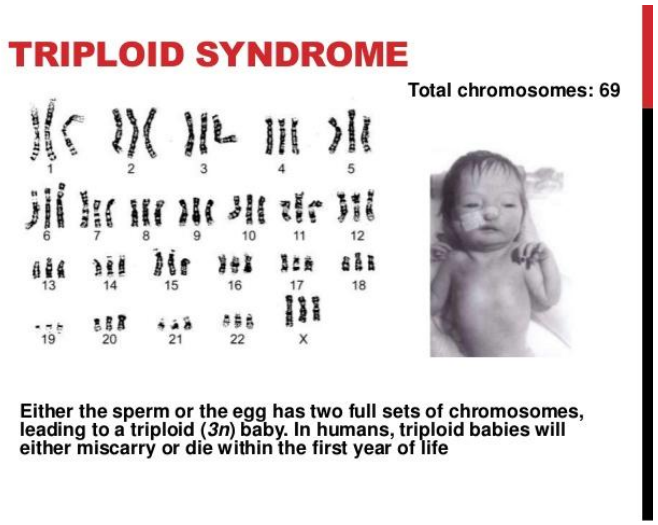

Fig. 10.5 Karyotype of a triploid (3n) baby having 69 chromosomes

Numerical chromosomal abnormalities in man: Autosomal aneuploidy

Three major ones:

(a) D(13) trisomy: Patau's syndrome;
(b) E(18) trisomy: Edwards' syndrome; and
(c) G(21) trisomy: Down's syndrome.

Characteristics of D(13) trisomy: Patau's syndrome

a) Karyotype shows an autosomal trisomy of D(13) chromosome
b) Mouth with cleft-lip and the face is severely deformed
c) Slopping forehead, small and abnormal eyes, low set and deformed ears
d) Mental retardation with apparent deafness
e) Polydactyly are almost always present
f) Abnormal genitalia, congenital cardiac defects and defective kidneys, colon and small intestine

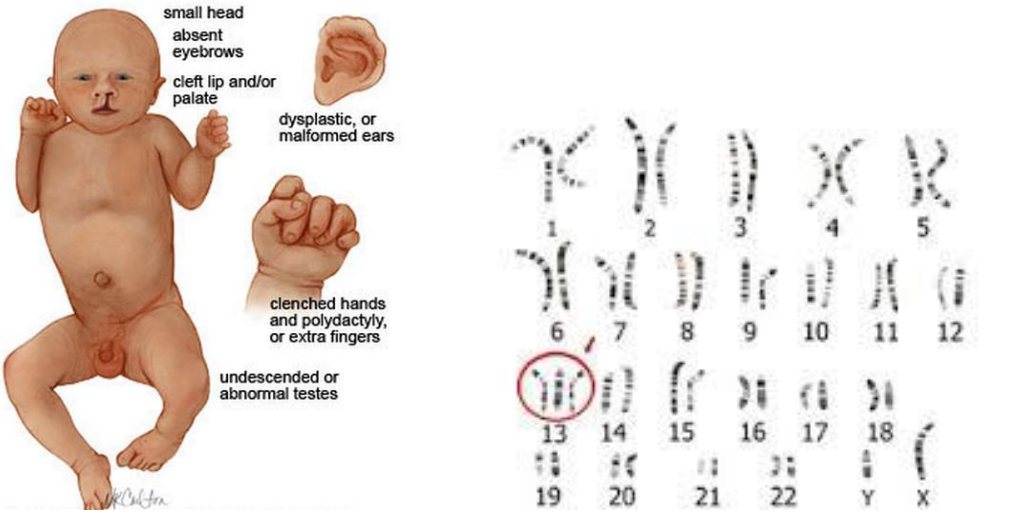

Fig. 10.6 A child suffering from Patau's syndrome; karyotype of the syndrome

Characteristics of E(18) trisomy: Edwards' syndrome

a) Karyotype shows an autosomal trisomy of E(18) chromosome;
b) Mental retardation with various deformities of skull, skeleton, sternum and pelvis;
c) Face with small chin and 'rocker bottom' feet with flexion fingers;
d) Congenital cardiac defects, hernias, various defective organs and abnormal genitalia.

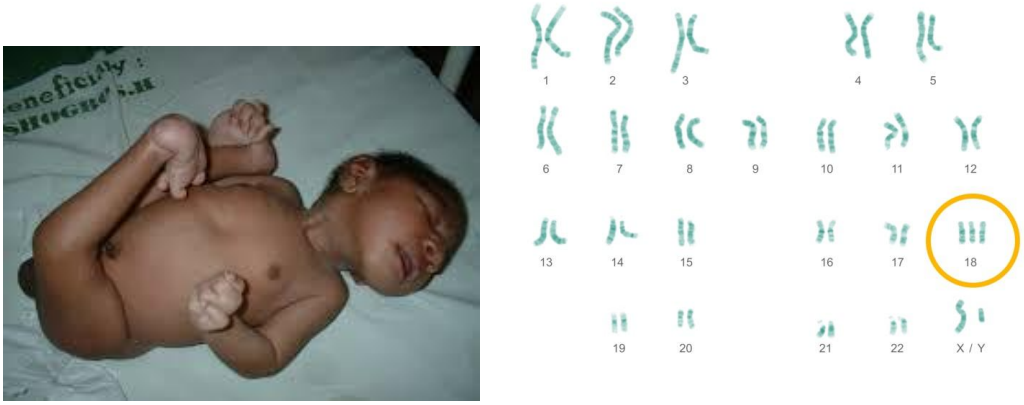

Fig. 10.7 A child suffering from Edwards' syndrome; karyotype of the syndrome

Characteristics of G(21) trisomy: Down's syndrome

a) Karyotype exhibits trisomy of G(21) chromosome;
b) Head small and round with slopping forehead, short stature with mental retardation;
c) Upper eyelids have epicanthal folds, characteristics to the mongoloid race;
d) Mouth large, usually open with protruding tongue, dental deformities, low or flattened nose bridge and underdeveloped genitalia.

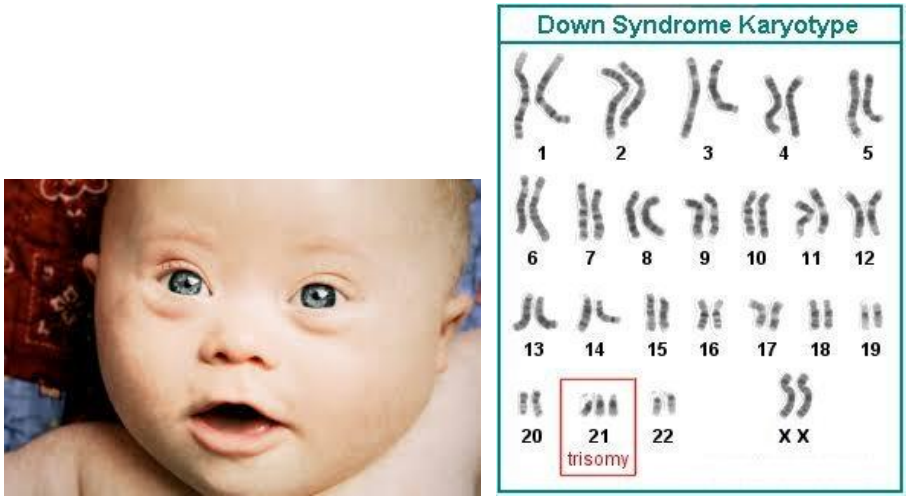

Fig. 10.8 A child suffering from Down's syndrome; karyotype of the syndrome

Numerical chromosomal abnormalities in man: Sex chromosomal aneuploidy

In females, two major types:

(a) 45, XO monosomy: Turner's syndrome
(b) 47, XXX trisomy: Triplo-X female or superfemale

In males: two major types:

(a) 47, XXY trisomy: Klinefelter's syndrome
(b) 47, XYY trisomy: Supermale

Intersexes: three major types:

(a) True hermaphrodites (herms): 48, XXXY tetrasomy
(b) Pseudofemales (ferms): 46, XX with male genitalia
(c) Pseudomales (merms): 46, XY with female genitalia

Characteristics of 45, XO monosomy: **Turner's syndrome**

a) Karyotype shows a sex chromosomal monosomy (45, XO);
b) Phenotypically female, but sterile, has an underdeveloped breasts (shield chest) with abnormal jaw bones;
c) Short stature, curved forearms (cubitus valgus) and webbed neck;
d) Congenital abnormalities, cardiac disease and small uterus.

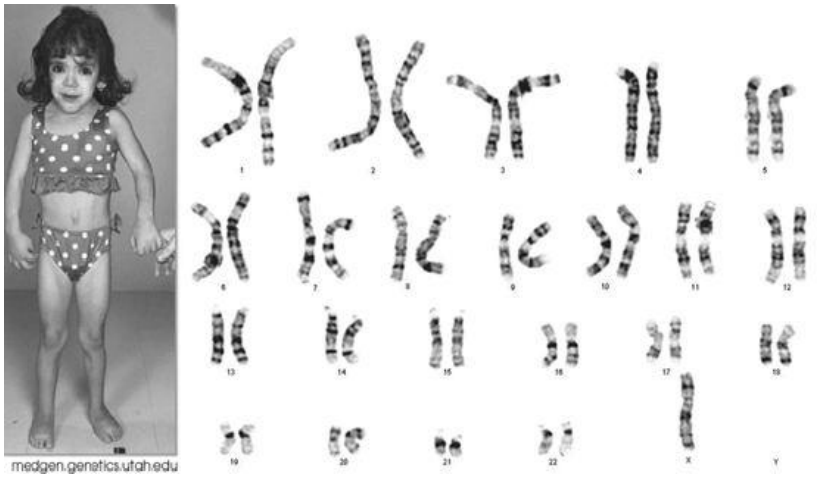

Fig. 10.9 A baby suffering from Turner's syndrome; karyotype of the syndrome

Characteristics of 47, XXX trisomy: **Triplo-X female or superfemale**

a) Phenotypically female but with infantile genitalia at maturity, marked underdeveloped breasts and internal genitalia
b) Mental retardation, abnormal primary and secondary sexual characteristics and sterile
c) About 1% of all mentally retarded females in psychological or mental hospitals are these females

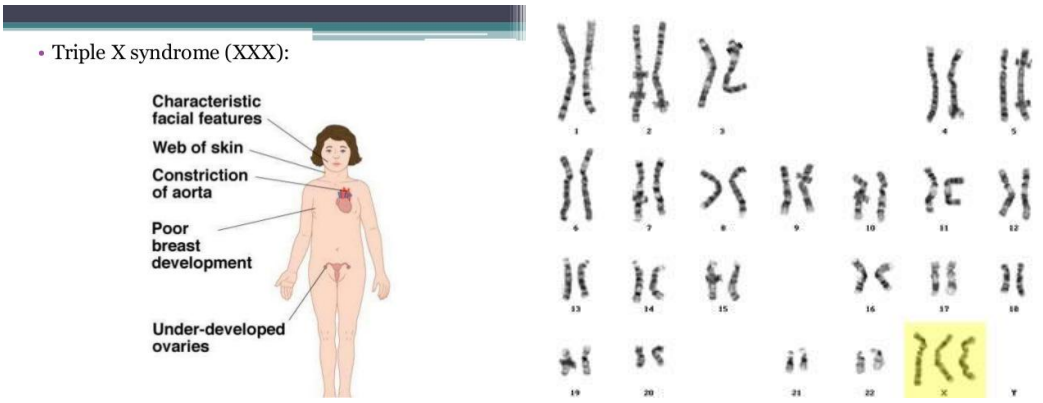

Fig. 10.10 A triplo-X female; karyotype of such female

Characteristics of 47, XXY trisomy: **Klinefelter's syndrome**

a) Karyotype has a sex chromosomal trisomy (47, XXY);
b) Phenotypically male but has enlarged breasts and broad pelvis;
c) It is sterile, accompanied by small testes and atrophied prostate glands;
d) Usually tall, arms are longer than average, voice is of higher pitch than normal males;
e) Mentally retarded, aggressive and criminally insane.

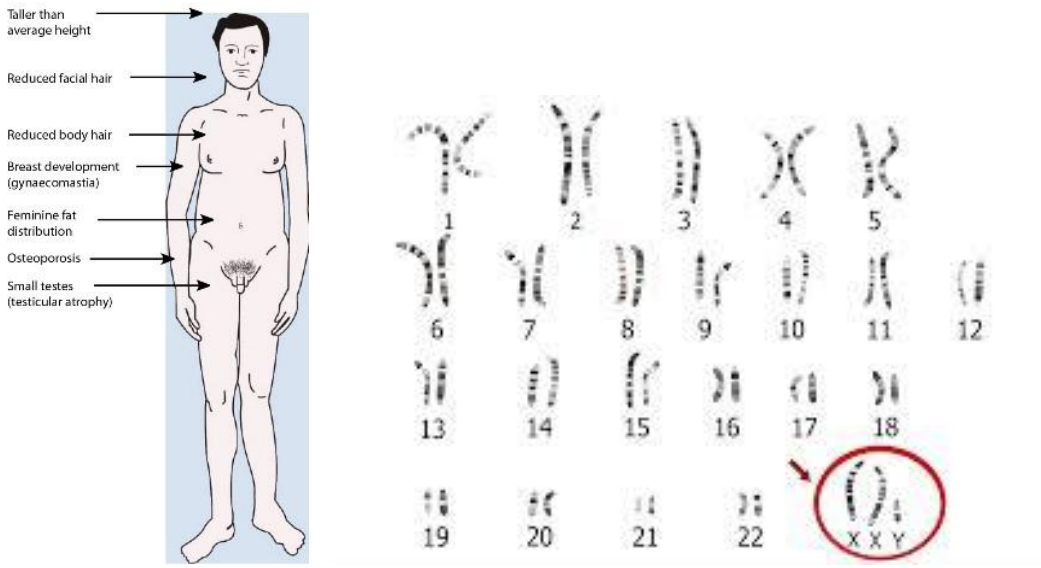

Fig. 10.11 A person suffering from Klinefelter's syndrome; karyotype of the syndrome

Characteristics of 47, XYY trisomy or supermale

a) Karyotype shows 47, XYY trisomy;
b) Phenotypically male, usually over 6 ft tall, low IQ with aggressive antisocial behaviour and mentally subnormal;
c) Abnormalities of external and internal genitalia but without major defects;
d) More likely to commit crime and violence than normal males.

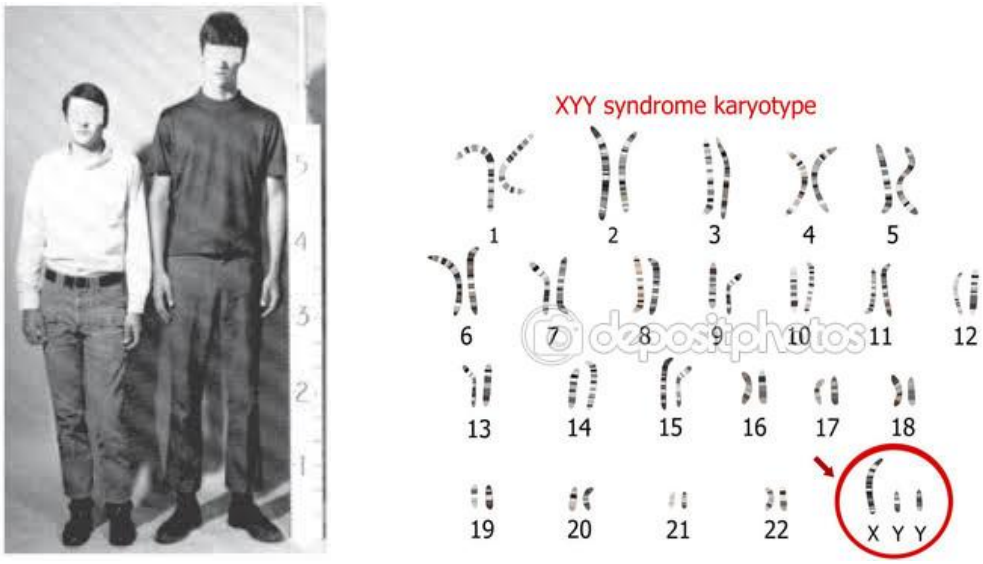

Fig. 10.12 The person on the right is a supermale; karyotype of such person

Characteristics of 48, XXXY tetrasomy: True hermaphrodites or 'herms'

a) Karyotypes have sex chromosomal tetrasomy (48, XXXY);
b) Presence of both testicular and ovarian tissues in the body;
c) Ambiguous genitalia, some reared as males, others as females;
d) The bearers of these karyotypes may be sexually active but are always sterile.

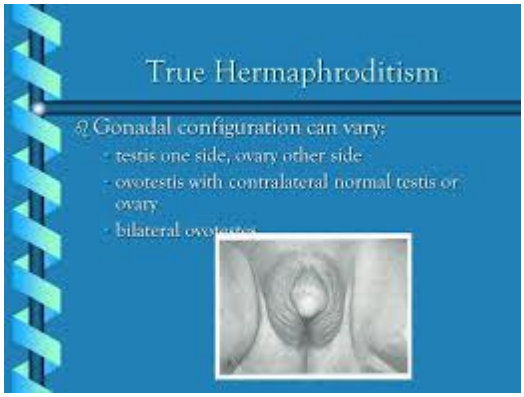

Fig. 10.13 Characteristics of true hermaphrodites (herms)

Characteristics of 46, XX pseudofemales or 'ferms'

a) Karyotypes bear chromosomes characteristic to females *i.e*. 46, XX;
b) Phenotypically females with ambiguous male genitalia;
c) Have ovaries but lack testes.

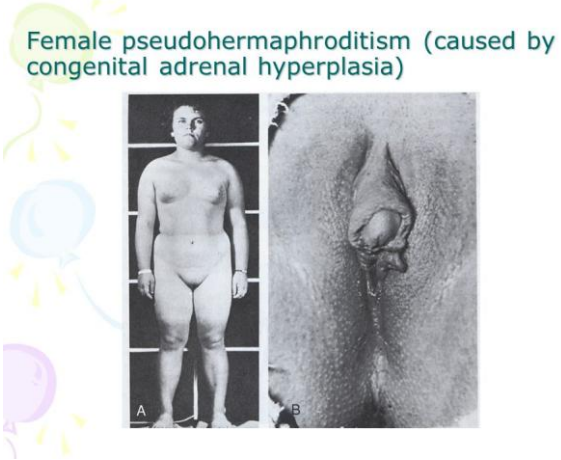

Fig. 10.14 A pseudofemale (ferm) and her ambiguous genitalia

Characteristics of 46, XY pseudomales or 'merms'

a) Karyotypes bear chromosomes characteristic to males *i.e*. 46, XY;
b) Phenotypically males with ambiguous female male genitalia;
c) Have testes, but lack ovaries.
d)

Fig. 10.15 Ambiguous genitalia of a pseudomale (merm)

Principal causes and origin of chromosomal abnormalities in man

1. Primary (at meiosis-I) and secondary (at meiosis-II) non-disjunction during spermatogenesis or oogenesis
2. Microdeletion
3. Robertsonian translocation between D(14) and G(21) chromosomes

Factors affecting chromosomal abnormalities in man

1. Maternal age (>35 years)
2. Exposed to high risk factors like irradiation, drugs, narcotics, mutagens etc
3. Viruses (like SV40) interfering with chromosomal segregation at meiosis
4. Familial tendency for certain disorders like Down's syndrome
5. Delayed fertilization

Frequency or incidence of chromosomal abnormalities in man

Chromosomal abnormalities	Incidence per 1000 births
B(4-5) deletion	0.02
D(13) trisomy	0.20-0.45
E(18) trisomy	0.23-0.30
G(21) trisomy	0.16-0.20
45, XO monosomy	0.20-0.30 ♀ births
47, XXX trisomy	1.00
47, XXY trisomy	1.00 ♂ births
47, XYY trisomy	0.69

Ref: G. W. Burns (1980); E. Novitski (1977)

Conclusions

1. Autosomal and sex chromosomal trisomics are more frequent than the corresponding monosomics perhaps because monosomics have much drastic effects on human beings;
2. Autosomes play no role in sex determination in man;
3. Y chromosome determines maleness; a single Y can outweigh any number of X in producing males; *e.g.* 47, XXY or 47, XYY are males;
4. In absence of Y, X chromosomes determine femaleness; *e.g.* 45, XO or 47, XXX are females.

Suggested reading:

Burns, GW. (1980)
Gardner *et al*. (1991)
Islam, MS. (2018)
Novitski, E. (1977)
Stern, C. (1960)
Winchester, AM. (1966)
Wikipedia: www.wikipedia.com
ইসলাম, ম.সা. ও অন্যান্য ২০১৭।