Medical Genetics Course

Lecture 5

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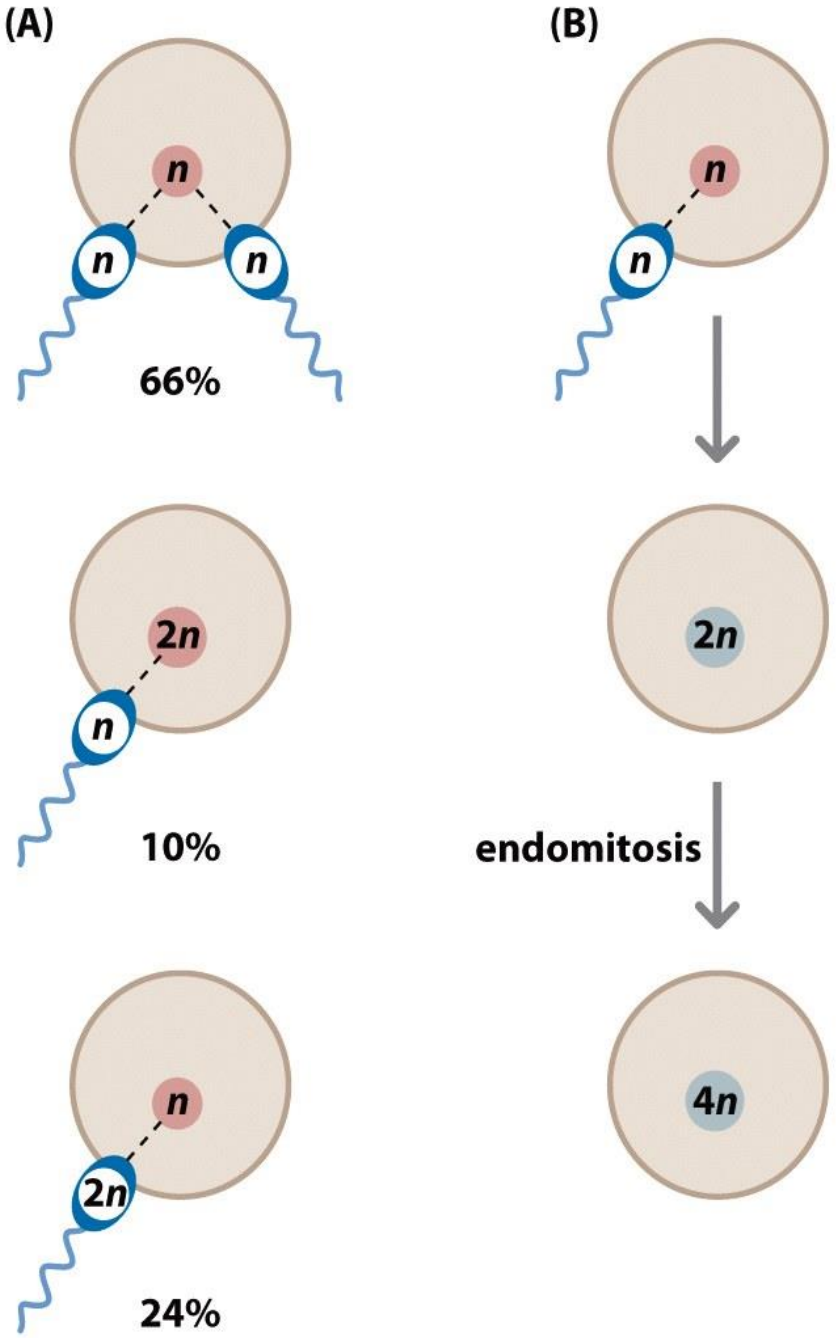


Figure 2.21 Human Molecular Genetics, 4ed. (© Garland Science)

Origins of triploidy and tetraploidy.

(A) Origins of human triploidy. **Dispermy** is the principal cause, accounting for 66% of cases. Triploidy is also caused by **diploid gametes** that arise by occasional faults in meiosis; fertilization of a diploid ovum and fertilization by a diploid sperm account for 10% and 24% of cases, respectively.

- 69,XXX triploidy
- 69,XXY triploidy
- 69,XYY triploidy

(B) **Tetraploidy** involves normal fertilization and fusion of gametes to give a normal zygote. Subsequently, however, tetraploidy arises by endomitosis when DNA replicates without subsequent cell division.

Chromosome Abnormality

Structural Chromosomal Abnormalities

Numerical

- Aneuploidy
  - Monosomy
  - Trisomy
  - Tetrasomy
- Polyploidy
  - Triploidy
  - Tetraploidy

Structural

- Translocations
  - Reciprocal
  - Robertsonian
- Deletions
- Insertions
- Inversions
  - Paracentric
  - Pericentric
- Rings
- Isochromosomes

- **Different Cell Lines (Mixoploidy)**
- Mosaicism
- Chimerism

Chromosome Nomenclature

- **46,XY**
  Normal male
- **46,XX**
  Normal female
- **47,XXY**
  Male with extra X chromosome (Klinefelter syndrome)
- **45,X**
  Female with missing X chromosome (Turner syndrome)
- **46,XY,t(2p;8p)**
  Male with translocation between short arms of chromosomes 2 & 8
- **46,XY, del(5p)**
  Male with deletion in short arm of chromosome 5 (Cri Du Chat syndrome)
- **46,X,r(X)**
  Female with ring chromosomes X (Turner syndrome)

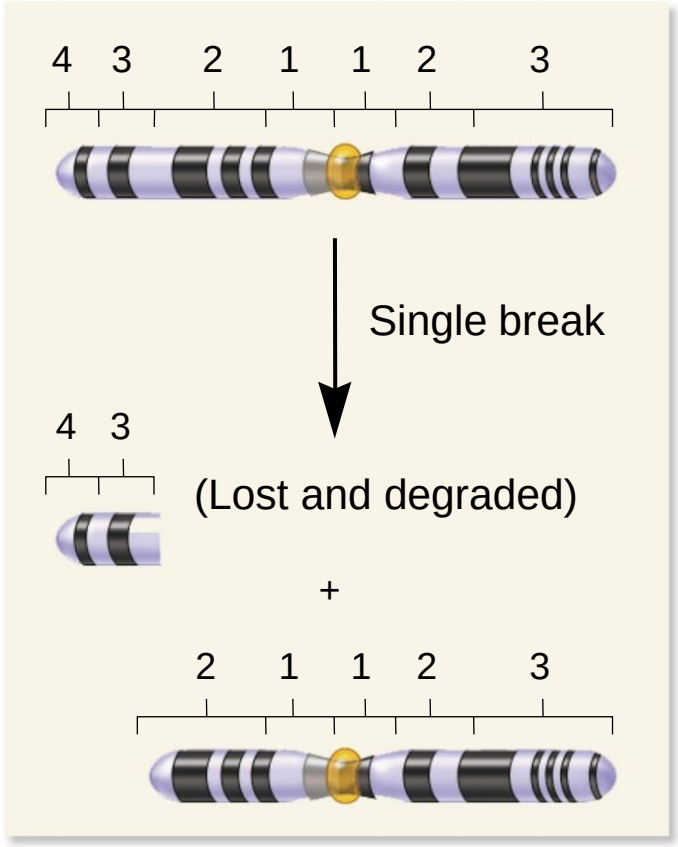
Term	Explanation	Example
p	Short arm	
q	Long arm	
cen	Centromere	
del	Deletion	46,XX,del(1)(q21)
dup	Duplication	46,XY, dup(13)(q14)
fra	Fragile site	
i	Isochromosome	46,X,i(Xq)
inv	Inversion	46XX,inv(9)(p12q12)
ish	In-situ hybridization	
r	Ring	46;XX,r(21)
t	Translocation	46,XY,t(2;4)(q21;q21)
ter	Terminal or end	Tip of arm; e.g., pter or qter
/	Mosaicism	46,XY/47,XXY
+ or –	Sometimes used after a chromosome arm in text to indicate gain or loss of part of that chromosome	46,XX,5p–

Chromosome Structural Aberrations

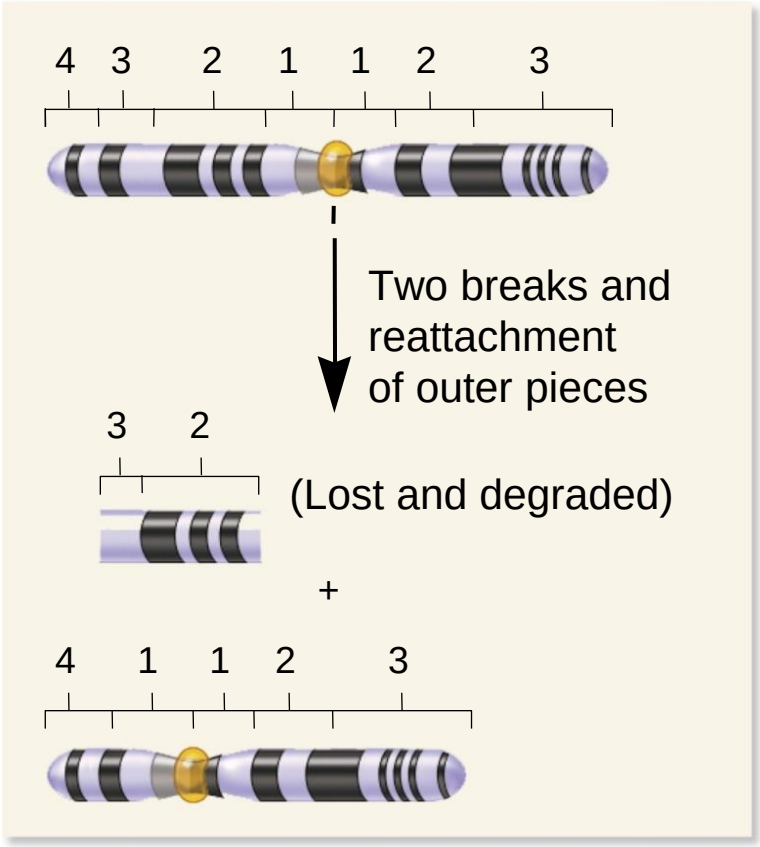
- Structural chromosome abnormalities are relatively frequent in human populations
- Chromosome breaks in the germline can lead to heritable structural abnormalities; those occurring in somatic cells may increase the risk of cancer.
- Chromosomes may break at almost any point, but there are sites of preferred breakage, called hotspots.
- The breaks may be repaired, but because any two broken ends that are sufficiently close together in the nucleus may rejoin , an extremely wide variety of structurally altered chromosomes occur.
- Balanced or unbalanced

Deficiencies (Deletions)

- A chromosomal deficiency occurs when a chromosome breaks and a fragment is lost (Involve loss of chromosomal material)



(a) Terminal deletion



(b) Interstitial deletion

Deletions (del)

Terminal deletions are caused by a single break with loss of the segment distal to the break.

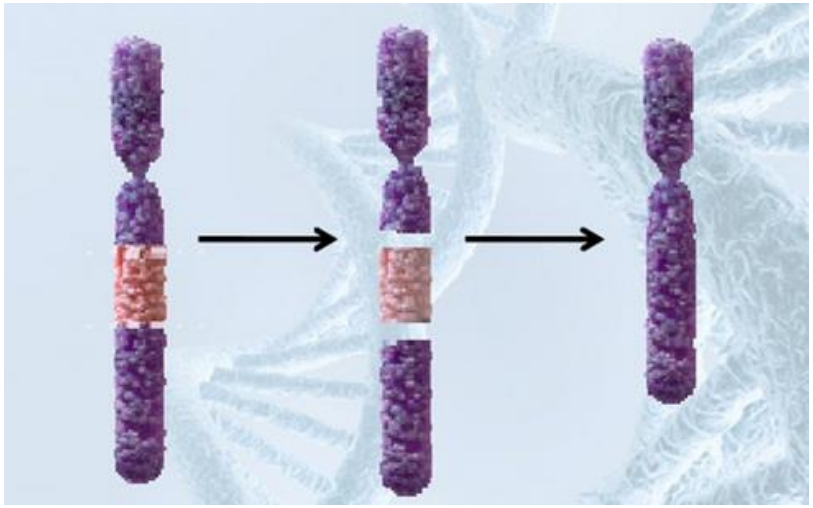
Interstitial deletions result from two breaks in a chromosome, loss of the intervening segment, and reunion of the breakpoints.

del(5)(p15.3)

This describes **a terminal** deletion of the short arm of chromosome 5. All chromosomal material distal to band p15.3 is missing.

del(20)(q11.2q13.3)

This represents an interstitial deletion of the long arm of chromosome 20. The material between bands q11.2 and q13.3 is deleted.



Deletions

- Associated with several genetic disorders

TABLE 6.3 Chromosomal Deletions

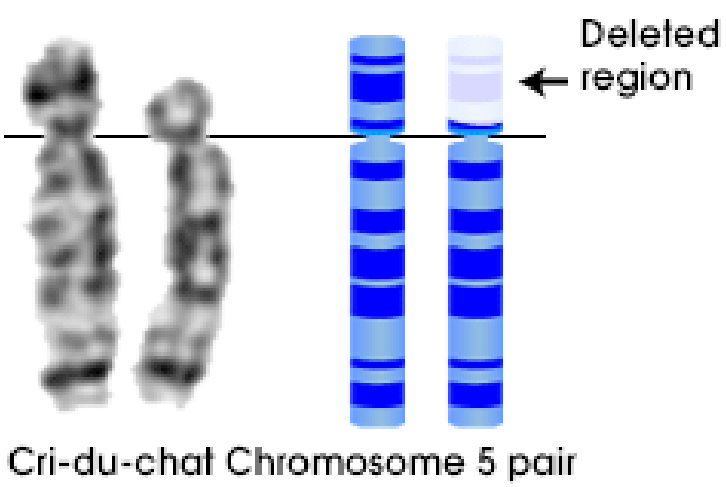
Deletion	Syndrome	Phenotype
5p–	Cri du chat syndrome	Infants have catlike cry, some facial anomalies, severe mental retardation
11q–	Wilms tumor	Kidney tumors, genital and urinary tract abnormalities
13q–	Retinoblastoma	Cancer of eye, increased risk of other cancers
15q–	Prader-Willi syndrome	Infants: weak, slow growth; children and adults: obesity, compulsive eating

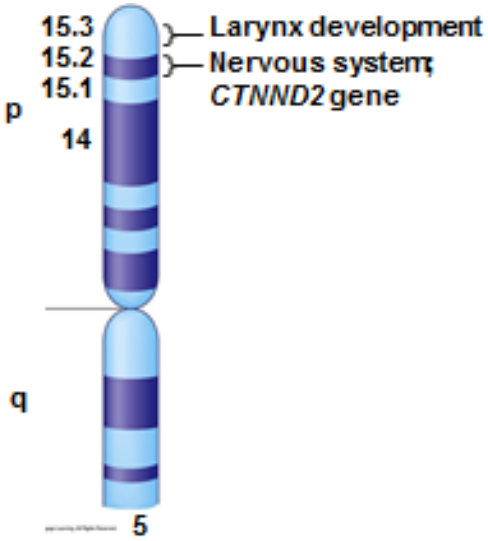
Terminal Deletion

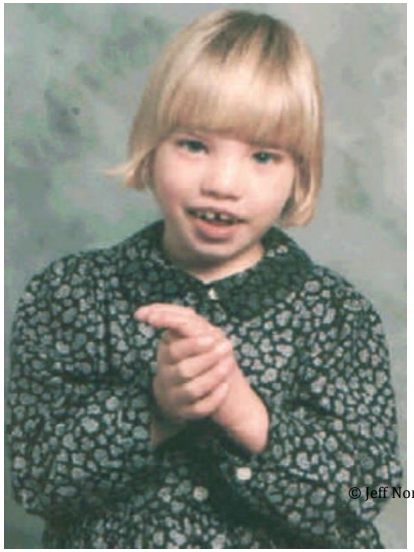
- When deletions have a phenotypic effect, they are usually detrimental
  - Example: **cri-du-chat (cat's cry) syndrome** in humans
    - Associated with an array of malformations
    - The most characteristic of which is an infant cry that resembles a meowing cat due to defects in the larynx

The disorder is characterized by:

- Intellectual disability
- Delayed development
- Small head size (microcephaly),
- Low birth weight,
- Hypotonia in infancy.
- **Distinctive facial features:**
- Widely set eyes (hypertelorism),
- Low-set ears,
- Small jaw, and a rounded face.
- Some children are born with a heart defect.







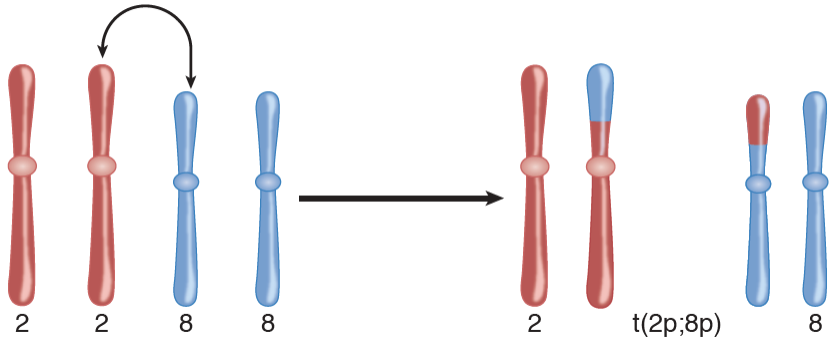
Translocations (t)

- A translocation is an abnormality resulting from an exchange of genetic material between nonhomologous chromosomes.
- Translocations may be **reciprocal and Robertsonian** (the latter resulting in derivative chromosomes and loss or gain or material).

Reciprocal Autosomal Translocations (include examples

- Reciprocal translocations represent one of the most common structural rearrangements observed in human.
- A reciprocal translocation forms when two different chromosomes exchange segments.
- The resulting chromosomes are called **derivative chromosomes.**
- Reciprocal translocations are frequently balanced because the entire genetic material is present.
- In the example shown in this figure, a balanced translocation involving chromosomes 2 and 8 has occurred.
- The distal short arm of chromosome 2 has replaced the distal short arm material on chromosome 8, and vice versa

The karyotype would be:
46,XY,t(2p;8p) or
46,XX,t(2p;8p).



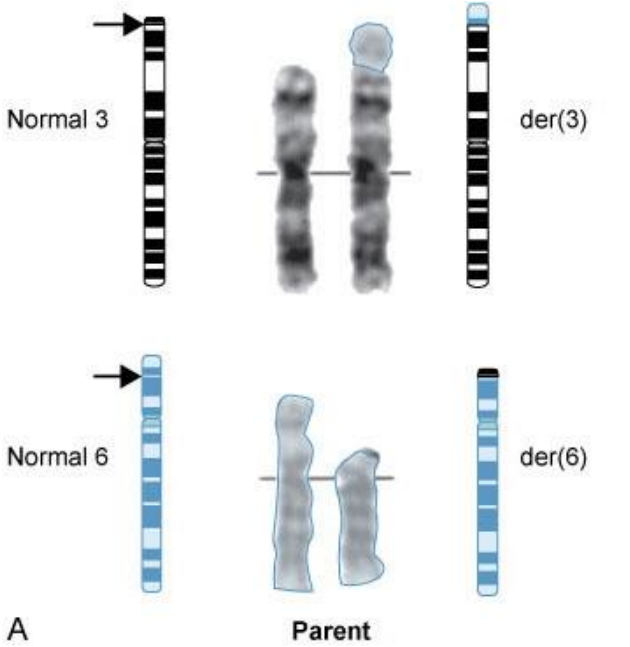
Reciprocal translocation

- Although individuals who carry truly balanced reciprocal translocations are themselves clinically normal, they do have an increased risk for having children with unbalanced karyotypes secondary to meiotic malsegregation of their translocation.

46,XY,t(5p13;10q25)

A male with translocation between 5p13 (band 3 of region 1 of short arm of chromosome 5) and 10q25 (band 5 of region 2 of long arm of chromosome 10)

46,XY,t(5;10)(p13;q25)



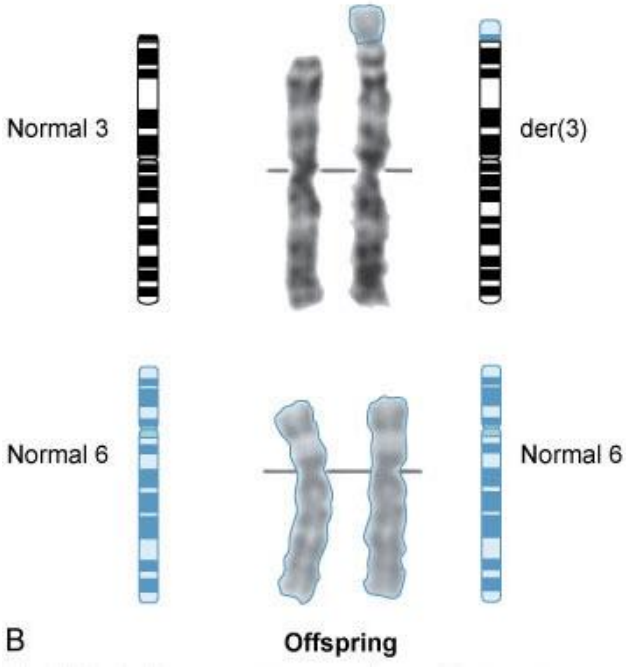


FIG 6-15 A, The parent has a reciprocal balanced translocation involving the short arms of chromosomes 6 and 3.
The distal short arm of the 6 has been translocated to the very distal tip of the 3. A small piece of chromosome 3 is attached to the derivative 6. This person had a child whose chromosomes are depicted in B

This karyotype is 46,XX,t(3p;6p).

The **offspring of this woman received the derivative chromosome3, termed der(3), and the normal 6; thus, the child had a partial trisomy** of the distal portion of chromosome 6 (i.e., 6p trisomy). This is a well-established but rather uncommon chromosomal syndrome.

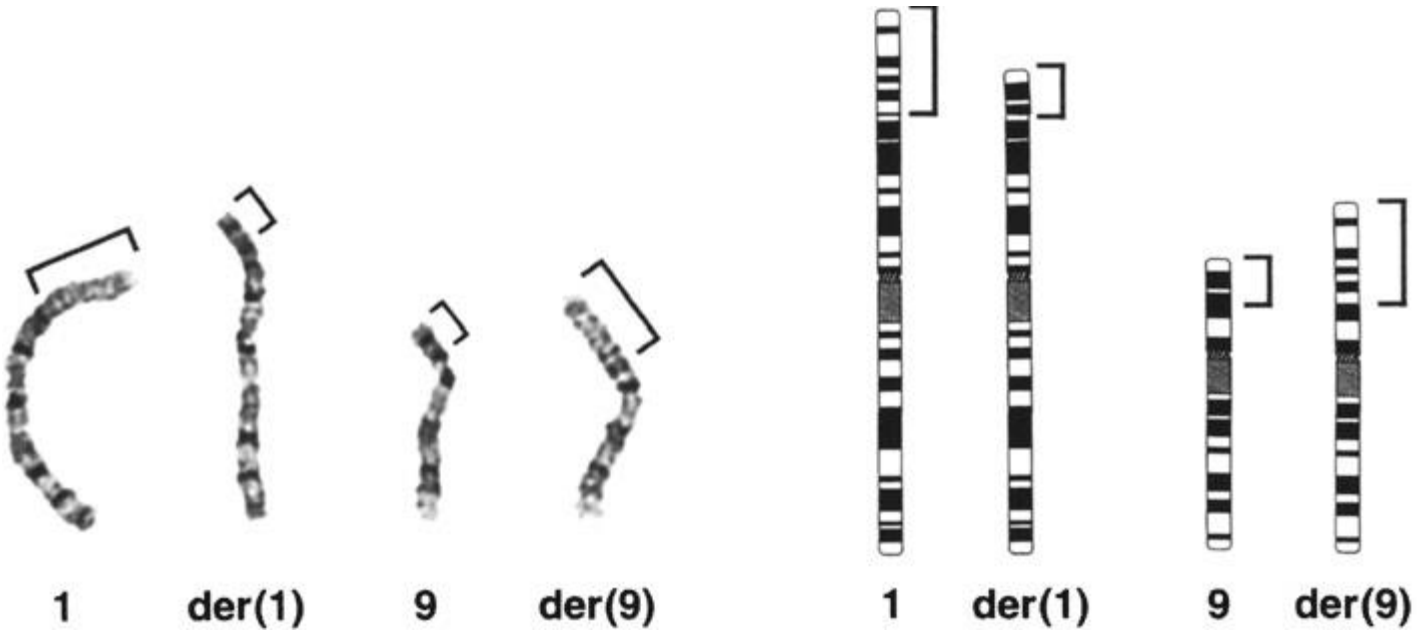


Fig. 9.16 A balanced reciprocal translocation involving the short arm of chromosomes 1 and 9 [t(1;9)(p32.3;p21)]. The translocated segments of each chromosome have been bracketed.

der Derivative or structurally rearranged chromosome: A chromosome that has been altered as a result of a translocation

46,XY,t(5;17)(p13.3;p13) denotes a translocation between the short arms of chromosomes 5 and 17 and region 13, band 3, and region 13, respectively.

Robertsonian translocations

- Much more common than reciprocal translocations
- They occur only in the acrocentric chromosomes (**13, 14, 15, 21 and 22)**.
- They are also called **whole-arm translocations** or **centric-fusion translocations**.
- Involved two homologous (paired) or non-homologous chromosomes
- Involve the loss of the short arms of two of the chromosomes and subsequent fusion of the long arms (the participating chromosomes break at their centromeres and the long arms fuse to form a single, large chromosome with a single centromere).

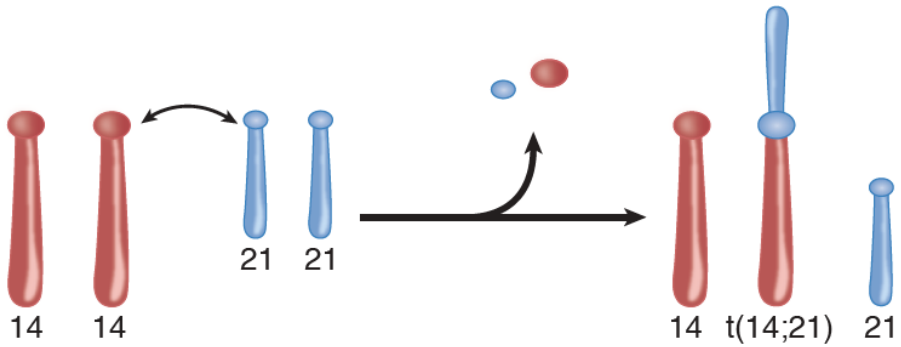


Figure II-3-5. A Robertsonian Translocation

A common Robertsonian translocation involves fusion of the **long arms of chromosomes 14 and 21**. The karyotype of a male carrier of this translocation would be:
45,XY ,der(14;21)(q10;q10).
This individual lacks one normal 14 and one normal 21 and instead has a chromosome derived from a translocation of the entire long arms of chromosomes 14 and 21.

Approximately 5% of Down syndrome cases are the result of a Robertsonian translocation affecting chromosome 14 and chromosome 21.

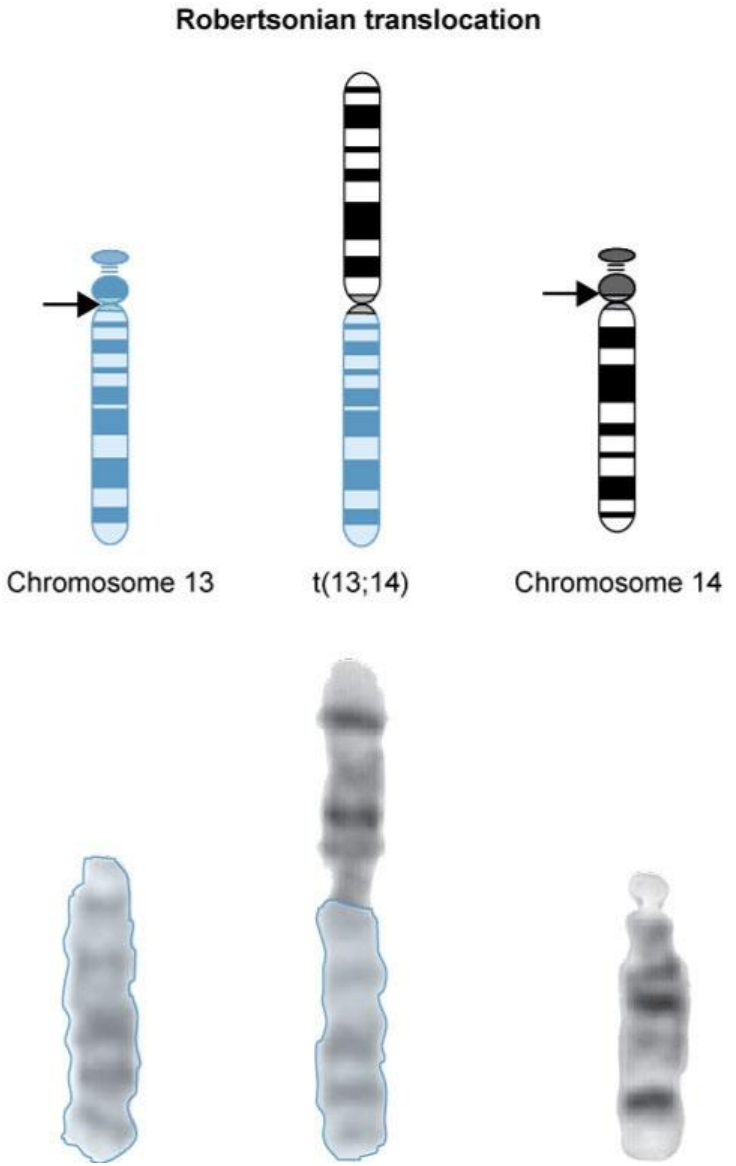


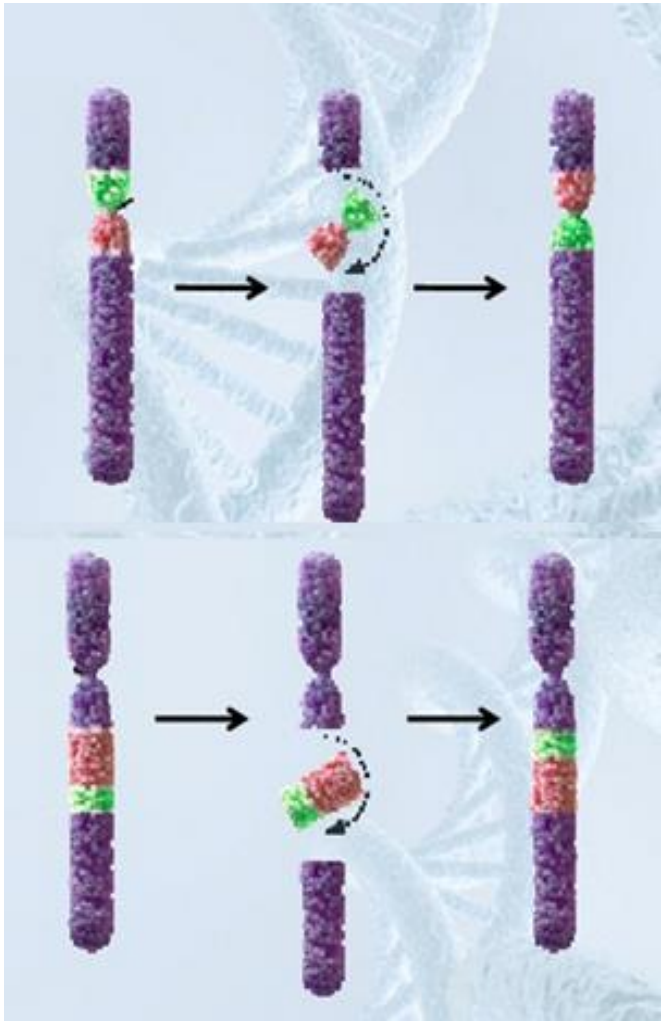
FIG 6-16 In a Robertsonian translocation, shown here, the long arms of two acrocentric chromosomes (13 and 14) fuse, forming a single chromosome.

Robertsonian Translocations

- The carrier of a Robertsonian translocation can produce conceptions with monosomy or trisomy of the long arms of acrocentric chromosomes.
- Carriers of Robertsonian translocations have an increased risk for infertility, spontaneous abortions and chromosomally unbalanced offspring, but are otherwise healthy.
- Balanced carriers of Robertsonian translocations therefore typically have 45 chromosomes rather than the usual 46.
- The only notable genetic material within the short arm region of each of these chromosomes is a nucleolar organizer region composed of multiple copies of the ribosomal RNA genes.
- Because this is redundant information, loss of this material from the two chromosomes involved in the translocation is therefore not clinically significant.

Inversions (inv)

- In an inversion, a chromosomal segment breaks, reorients 180°, and reinserts itself.
- If an inversion involves **the centromere**, with one break in each chromosome arm, it is said to be pericentric (**precentric** which involve both arms of a chromosome).



ABCDEFG might become **ABEDCFG** after an inversion

- A **paracentric** inversion is isolated to one chromosome arm and does not involve the centromere. (involve only one arm of a chromosome)

Inversions (inv)

- 46,XX,inv(16)(p13.1q22)
- This is a pericentric (**both arms**) inversion of chromosome 16. A break has occurred in the short arm at band 16p13.1 and the long arm at band 16q22.
- The chromosome segment between these bands is present but inverted.
- **This aberration is commonly observed in acute myelomonocytic leukemia with eosinophilia**

- Parents with inversions are usually normal in phenotype but can produce offspring with deletions or duplications.

Types of duplications (*Dp*)

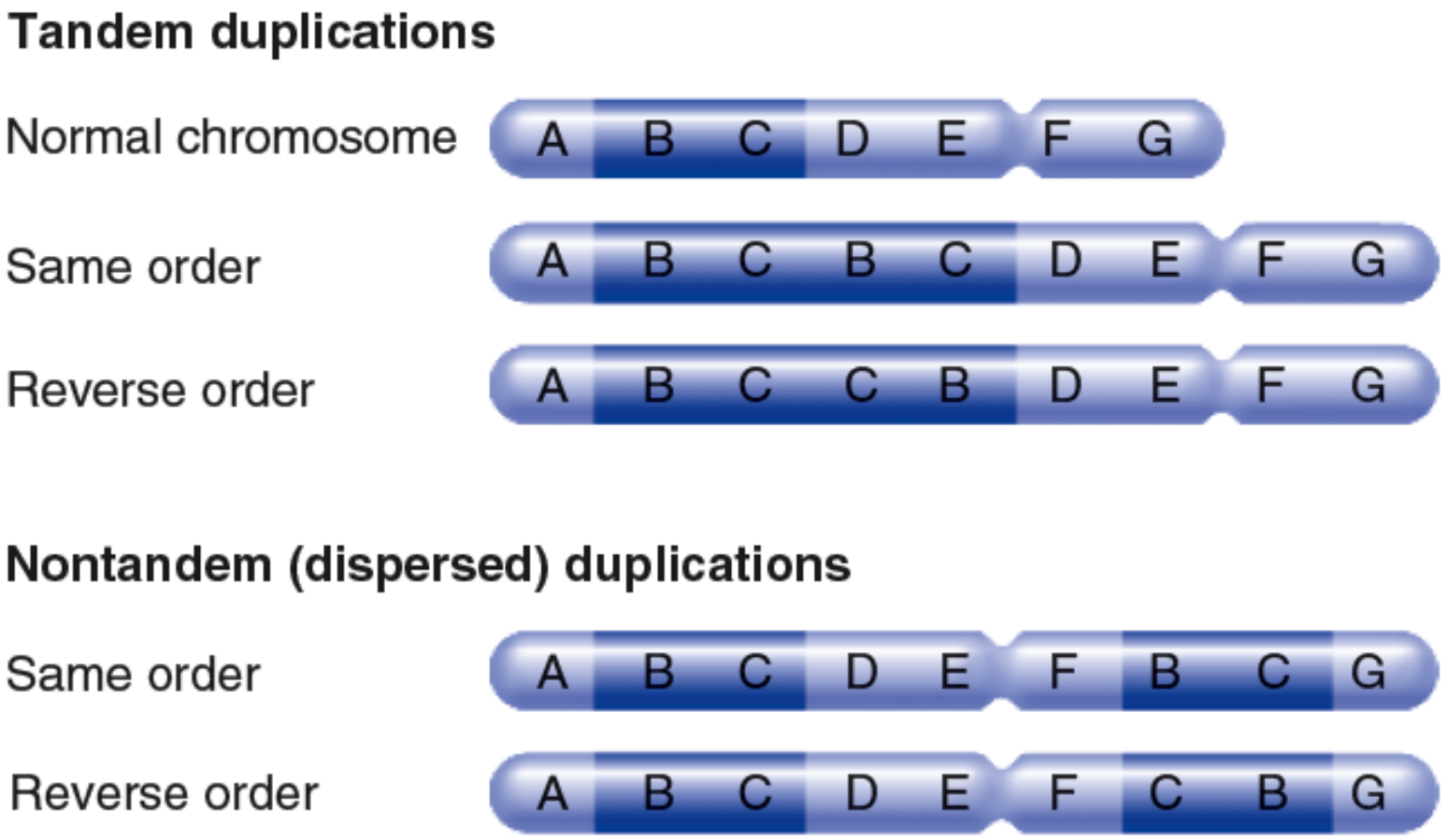


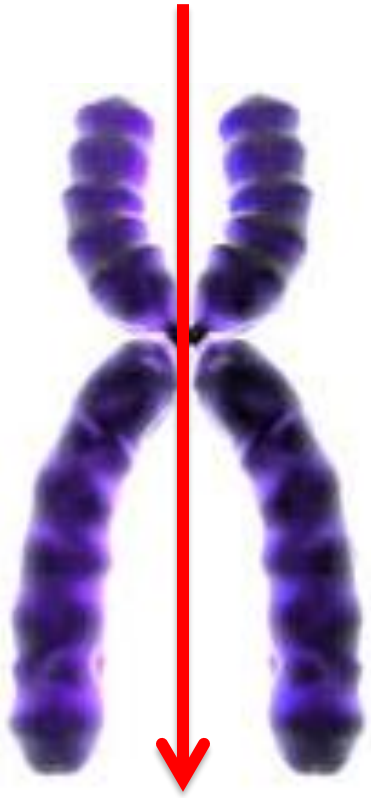
Fig. 13.11a

Duplications (dup)

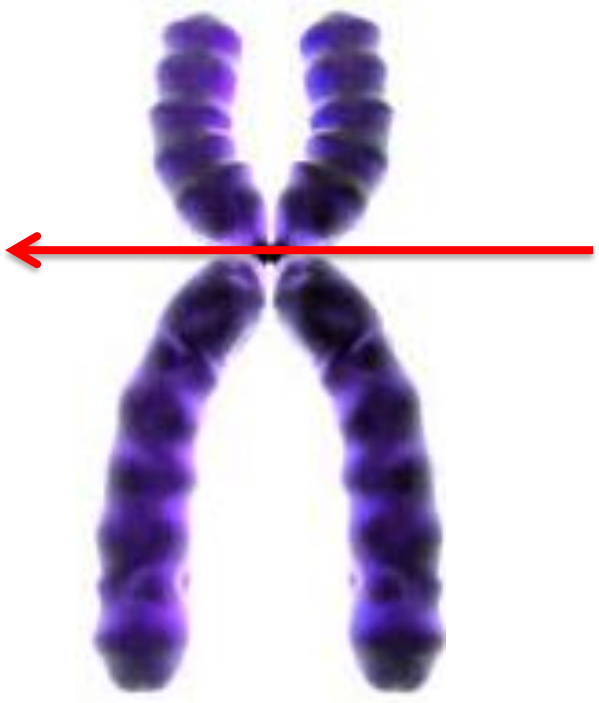
- The **orientation of duplications is either *direct* or *inverted*** and is indicated by the order of the bands with respect to the centromere in the karyotype designation.
- **46,XY,dup(1)(q21q42)**
- This is a direct duplication of the segment between bands 1q21 and 1q42 in the long arm of chromosome 1.

- **46,XX,dup(13)(q34q21)**
- This is an inverted duplication of the segment between bands 13q21 and 13q21 in the long arm of chromosome 13.

Normal process

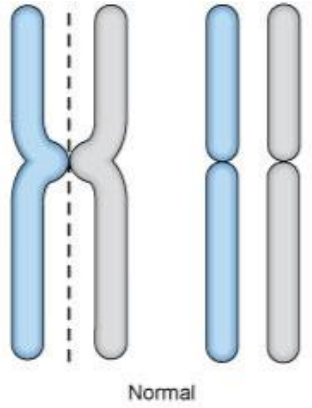


Isochromosomes (i)



Isochromosomes (i)

- Is an abnormal chromosome with two identical arms due to duplication of one arm and loss of the other arm
- An isochromosome consists of two copies of the same chromosome arm joined through a single centromere in such a way that the arms form mirror images of one another.
- 46,XY,i(6)(p10): An isochromosome for the short arm of chromosome 6 has replaced one copy of chromosome 6.



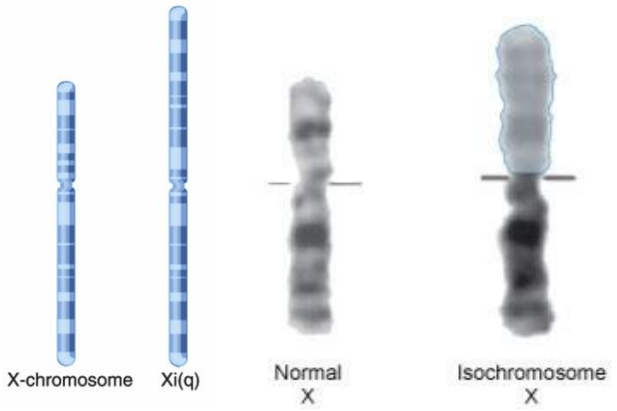


Figure II-3-10. The karyotype of an isochromosome for the long arm of the X chromosome would be 46,X,i(Xq); this karyotype results in an individual with Turner syndrome, indicating that most of the critical genes responsible for the Turner phenotype are on Xp.

Isochromosomes (i)

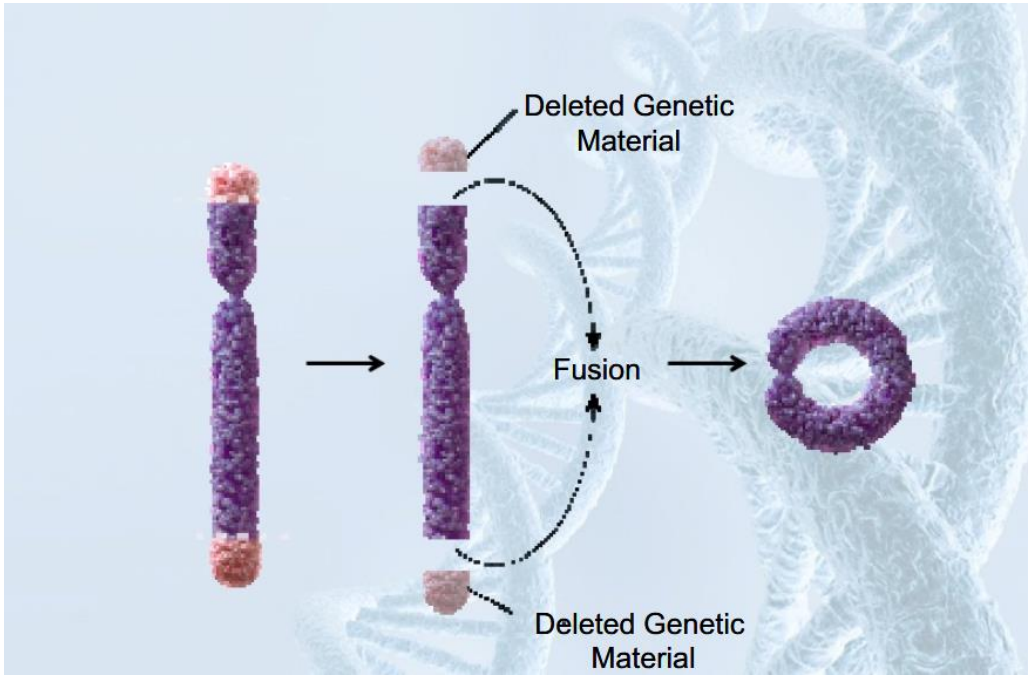
- Individuals with 46 chromosomes, one of which is an isochromosome, are monosomic for the genes within the lost arm and trisomic for all genes present on the isochromosome.
- The **neoplasia** created from i(17q) is caused by a decrease and increase in gene dosage from the monosomy of the p arm and trisomy of the q arm, respectively.
- In general, the smaller the isochromosome, the smaller the imbalance and the more likely the survival of the fetus or child that carries the isochromosome.
- It is therefore not surprising that, with few exceptions, the most frequently reported autosomal isochromosomes tend to involve chromosomes with small arms.
- Some of the more common chromosome arms involved in isochromosome formation include 5p, 8p, 9p, 12p, 18p, and 18q.
- isochromosomes of most autosomes are lethal

Ring Chromosomes (r)

- Ring chromosomes, or rings, are donut shaped structures that may involve one or more chromosomes
- Autosomal ring chromosomes are rare and usually arise *de novo*.
- Rings have been reported for all chromosome pairs, although those involving chromosomes 13 and 18 are among the most common.
- Rings are traditionally thought to form as a result of breakage in both arms of a chromosome, with subsequent fusion of the ends and loss of the distal segments.

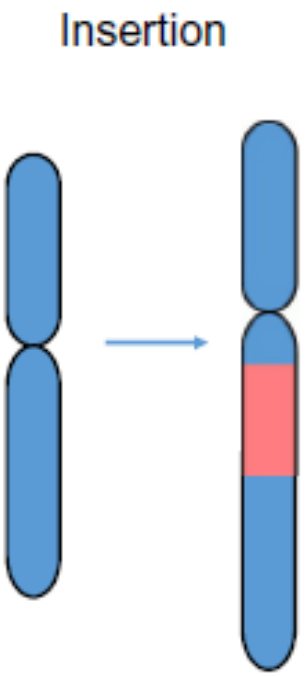
Ring chromosomes are often **lost**, resulting in a monosomy, example:
loss of a ring X chromosome would produce Turner syndrome (45,X)

The karyotype of a female
with a ring X chromosome is 46,X,r(X).



Insertions (ins)

- As the name implies, an insertion involves the movement of a segment of intrachromosomal material from one chromosomal location into another.
- **The recipient can be another chromosome or a different part of the chromosome of origin.**
- The orientation of the inserted segment **may be direct, retained in its original orientation, or inverted**.
- Eg. 46,XX,ins(2)(p13q21q31)



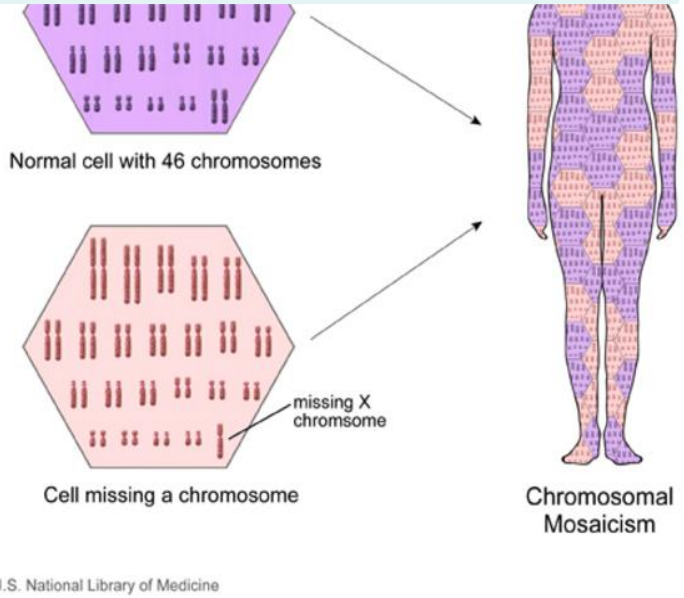
Mosaicism

chromosome abnormalities can be classified into two types

- Constitutional abnormality: presents in all nucleated cells of the body
- Somatic (or acquired): presents in only certain cells or tissues of a person, who is therefore a genetic mosaic

Mosaicism : describe a situation in which different cells in the same individual have different numbers or arrangements of chromosomes .

- It is called “mosaicism” because the cells of the body are similar to the tiles of a mosaic.
- A mosaic individual is made of 2 or more cells populations coming from one zygote .
- Is denoted by a slash between the various clones observed, e.g. 46,XY / 47,XY,21+) .
- Usually due to a mitotic non-disjunction .
- Can affect any type of cells, including :
  - * Somatic cells .
  - * Germ cells.



Mosaicism vs chimerism

- **Mosaicism**: the presence of at least two genetically distinct, but related cell lines (clones) arising in the same individual
  - e.g. Turner syndrome: 45,X[15]/46,XX[5]
  - e.g. CML: 46,XX,t(9;22)(q34;q11.2)[9]/46,XX[11]
  - **Mosaicism can be found in 1% of** Down Syndrome patients

- **Chimerism**: the presence of at least two genetically distinct cell lines that are derived from different conceptions
  - e.g. tissue/organ transplants
  - e.g. Bone marrow transplant patient: 46,XX[3]//46,XY[17]

Mosaicism vs chimerism

Clinical presentation may be similar, variable, milder, or normal; may see skin pigmentation anomalies; may be identified by a recurrent cytogenetic abnormality in the children of parents who have normal karyotypes (i.e. gonadal mosaicism)

- Mosaic loss of chromosome Y in blood cells increases morbidity and mortality in old age.
- Mosaic Klinefelter syndrome (46, XY/47, XXY) causes the small size of testes and reduced production of testosterone by the gonads.
- Frequency of low-level and high-level mosaicism has a role in sporadic retinoblastoma severity and the onset of the retinoblastoma.

Conventional Karyotype

ALL chromosomes and sex chromosome constitution

- Total number of chromosomes (aneuploidy)
- Size and structure of each chromosome
  - Detects large chromosomal imbalances (e.g. subchromosomal deletion)
  - Detects balanced translocations: where there is no loss of total amount of genetic material
  - Detects unbalanced translocations: where there is a change in the total amount of genetic material
- Deletions, duplications or rearrangements must be large enough (approximately >5 Mb) to be visualised under the microscope to be detected by conventional karyotype
- Small changes will not be detected.

Chromosomal Microarray (CMA)

- Chromosomal Microarray (CMA) is a microchip-based testing platform that allows automated analysis of many pieces of DNA at once
- ALL chromosomes and sex chromosome constitution
  - CMA chips use probes that hybridize with specific chromosomal regions to detect copy number variations (CNVs)
- There are two types of Chromosomal microarray:
  - Comparative Genomic Hybridization array (aCGH)
  - Single Nucleotide Polymorphism (SNP) Array
- aCGH and SNP arrays are used to detect copy number gains and losses.
- They are the first-tier test* for individuals with:
  - Developmental disabilities
  - Autism spectrum disorders
  - Multiple congenital anomalies
  - Mental retardation
  - Prenatal: Microarray is useful when you have a fetus with:
    - 1 or more congenital abnormalities detected on ultrasound
    - Nuchal Translucency greater than 3.5mm

Microarray CGH

- Array CGH is a significant advance in technology that allows detection of chromosome imbalances that are too small to be detected by looking down the microscope.
- Array-CGH is the equivalent of conducting thousands of FISH experiments at once, and it provides better quantification of copy number
- It is faster and has a better resolution than available molecular cytogenetic tools.

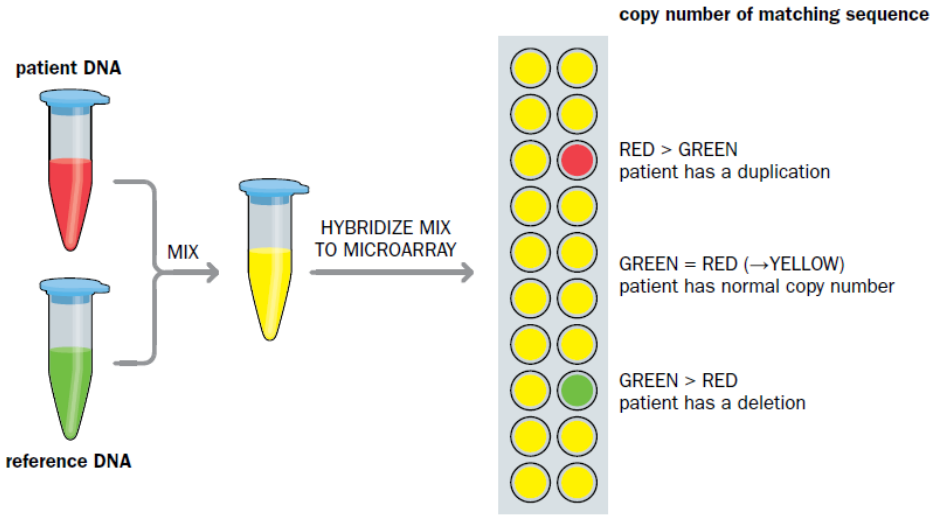
Microarray CGH

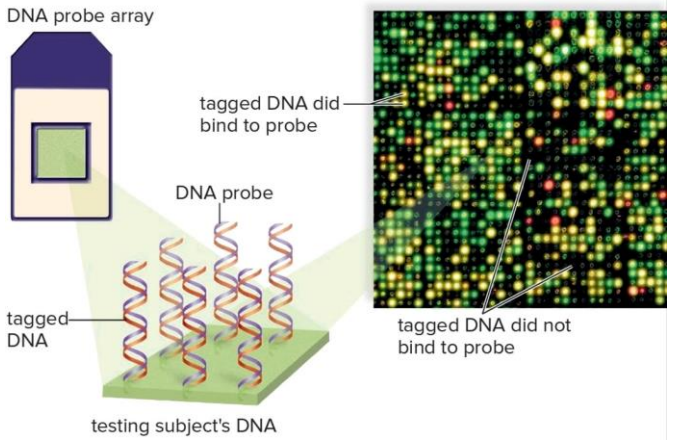
Cytogenetic microarray testing does detect:

- Micro-duplications or micro-deletions of chromosomal segments are minuscule to see under a microscope, but they contain various multiple genes.
- Abnormalities in a chromosome number (Down, trisomy, monosomy, etc.).
- Major unbalanced rearrangements of chromosome structure
- Mosaicism

Cytogenetic microarray testing does not detect:

- Point mutations: Micro changes in the sequence of single genes
- Tiny deletions or duplications of DNA segments.
- Balanced chromosomal rearrangements, also known as balanced translocations and inversions.
- Low level mosaicism: Most cytogenetic microarray testing cannot detect mosaicism below 20-25%.





- Genomic DNA from the patients is labeled with one fluorescent dye, while a control sample is labeled with a different dye, and these samples are then co-hybridized to an array containing genomic DNA targets.
- Chromosomal imbalance across the genome can be quantified and positionally defined by analyzing the ratio of fluorescence of the two dyes with the aid of computer software
- The first-generation array had a coverage of about **1 MB**. This resolution has been recently increased to cover the genome at a density of **10-100 kb.**

Single Nucleotide Polymorphism-Based Microarrays (SNP-array)

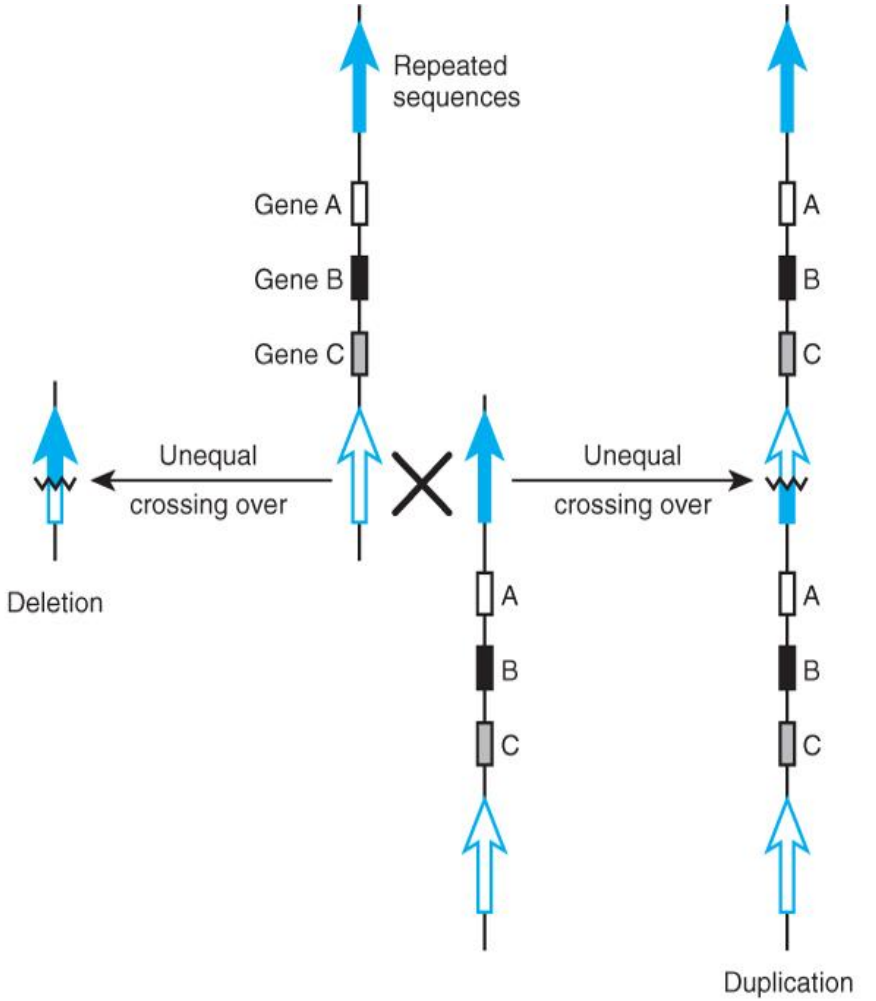
- In contrast to aCGH, SNP-based arrays do not directly compare a patient and a control specimen.
- SNP arrays compare the dosage of the patient at any given locus to a database of control individuals. As with aCGH, gains and losses of the genome are readily detectable using this method
- SNP arrays have the added advantage of being able to detect DNA base alterations, or genotyping, for any given SNP.

Microdeletions and microduplications Syndromes:

- Many dysmorphic syndromes associated with small deletions that lead to genetic imbalance.
- These deletions produce clinically recognizable syndromes.
- Can be detected by high-resolution banding, FISH, a-CGH
- The term contiguous gene syndrome has been applied to many of them. i.e., haploinsufficiency for multiple contiguous genes within deleted region
- For other disorders, phenotype is apparently due to deletion of a single gene, despite association of a chr. deletion with the condition.

Model of rearrangements underlying genomic disorders.

Unequal crossing over between misaligned sister chromatids or homologous chromosomes containing highly homologous copies of a long-repeated DNA sequence can lead to deletion or duplication products, which differ in the number of copies of the sequence. The copy number of any gene or genes (such as A, B, and C) that lie between the copies of the repeat will change as a result of these genome rearrangements



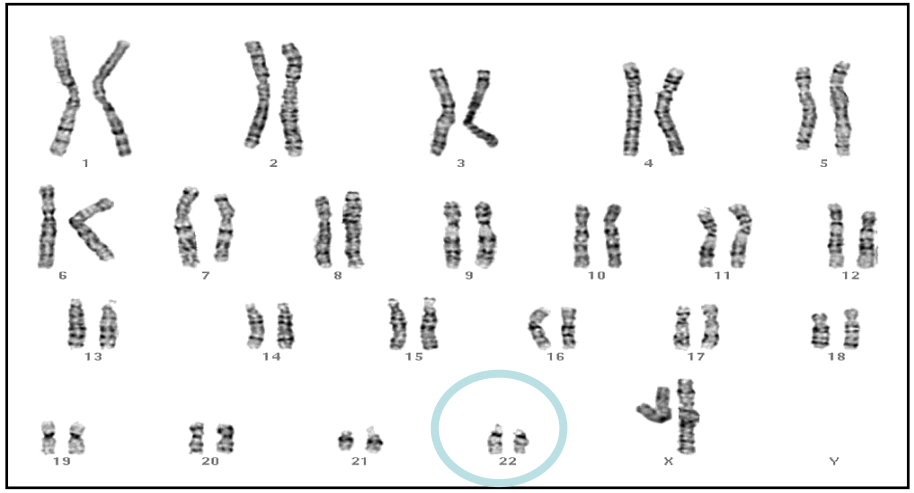
DiGeorge Syndrome

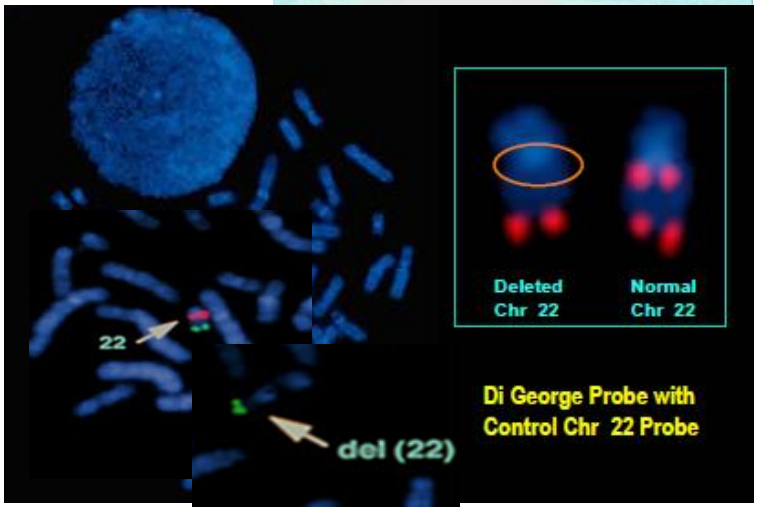
Velocardiofacial Syndrome

Disease characteristics: 3-megabase (Mb) deletion

- Congenital heart disease (74%)
- Palatal abnormalities (69%)
- Characteristic facial features
- Learning difficulties (70 - 90%)
- Many affected individuals are able to reproduce

Diagnosis: 22q11 submicroscopic deletion

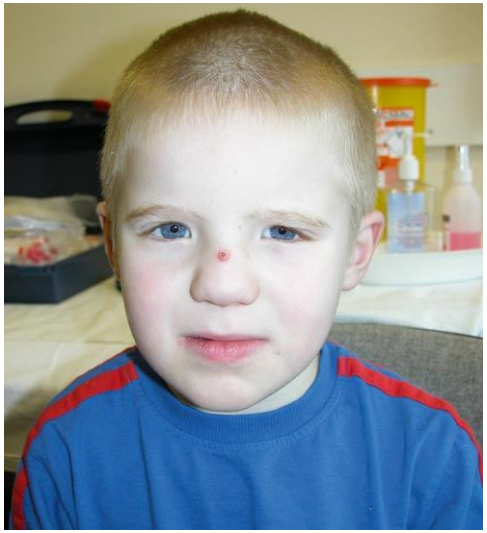




Microdeletions and microduplications Syndromes:

Duplication 22q11.2: The problems range from isolated mild ID to multiple abnormalities with nonspecific dysmorphic features:

- Congenital heart disease
- Cleft palate
- Hearing loss
- Postnatal growth deficiency
- Intellectual disability
- Delayed speech and language skills
- Behavioral issues
- Distinctive facial features.

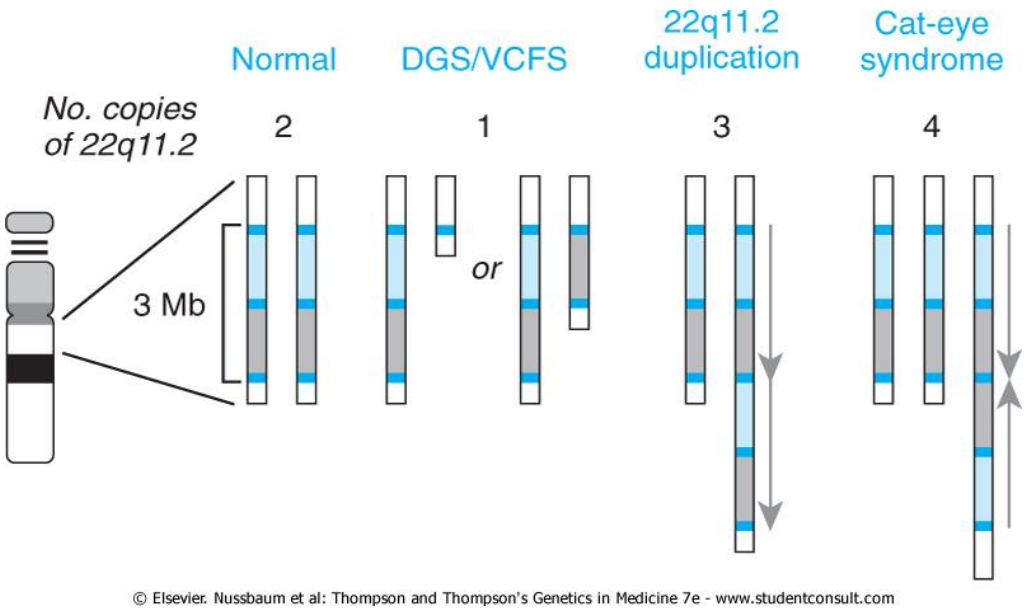


Duplication 22q11.2

Microdeletions and microduplications Syndromes:

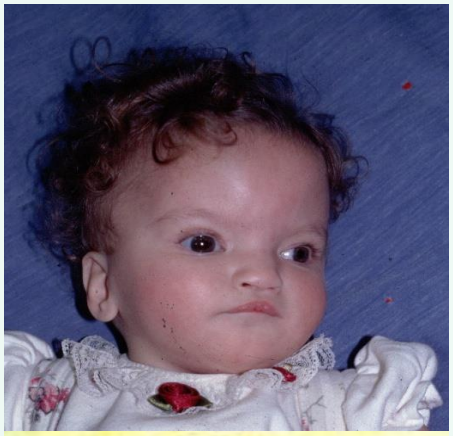
Cat Eye Syndrome (Schmid-Fraccaro Syndrome) Inverted Duplication 22q11.2:

- Typical eye appearance
- Congenital heart disease (occasional)
- Intellectual disability
- Developmental delays
- Distinctive facial features
- Abnormalities in various organ systems.



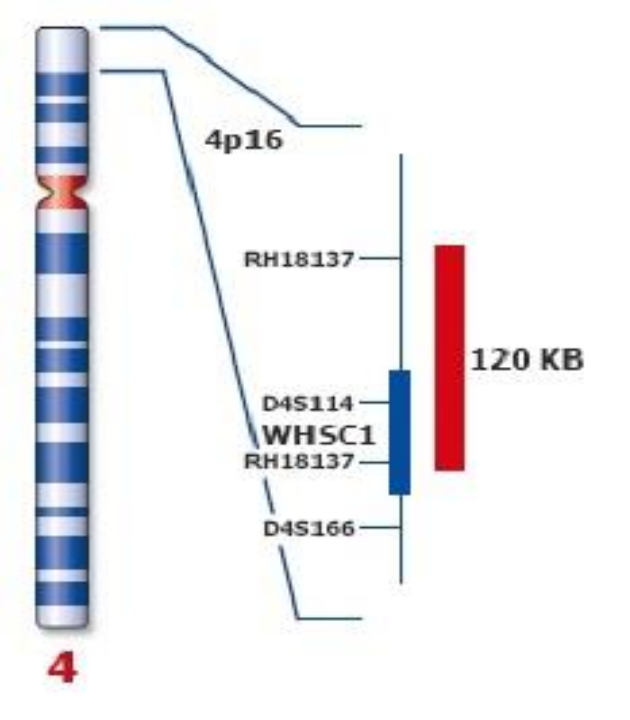
Wolf-Hirschorn Syndrome (- 4p)

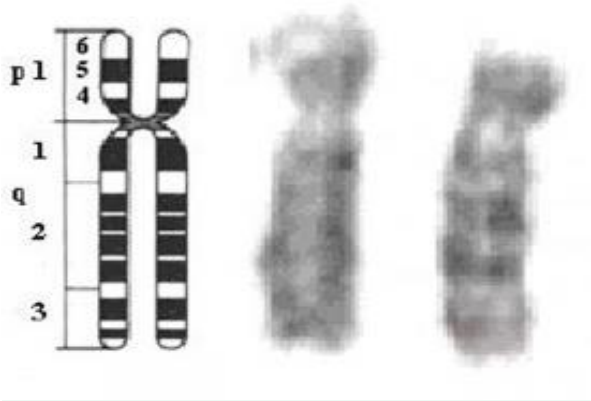
- ✓Partial monosomy of the short arm of chromosome 4
- ✓9 putative genes identified in this region
- ✓Critical region at 4p16.3 – 165 kb segment
- ✓**Clinical features:**
  - Distinctive “greek helmet” facies
  - Cardiac defects in 50%
  - Mental retardation, Microcephaly
  - Most are stillborn or die in infancy
  - Frequent seizures
  - 85-90% de novo deletions
  - abnormal facies. Cardiac, renal, and genital abnormalities.



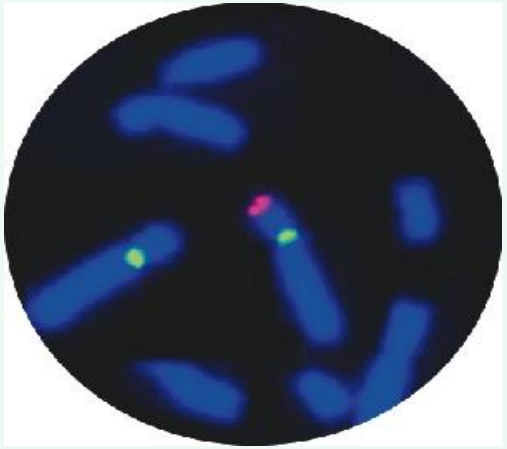
46,XY,del(4p)

Wolf-Hirschhorn Syndrome





wide-spaced eyes and repaired cleft lip



de novo deletion *(WHSC1, WHSC2)* ----- *87%*
WHSC1=Wolf-Hirschhorn syndrome candidate 1
Translocation of 4p ------ 13%

Examples of Genomic Disorders Involving Recombination Between Low-Copy Repeat Sequences

REARRANGEMENT				
Disorder	Location	Type	Size (kb)	Repeat Length (kb)
Smith-Magenis syndrome	17p11.2	Deletion	4000	175-250
dup(17)(p11.2p11.2)		Duplication		
Charcot-Marie-Tooth (*CMT1A*)/HNLPP	17p12	Duplication	1400	24
		Deletion		
Williams syndrome	7q11.23	Deletion	1600	300-400
Neurofibromatosis	17q11.2	Deletion	1400	85
Sotos syndrome	5q35	Deletion	2000	400
Azoospermia (AZFc)	Yq11.2	Deletion	3500	230