

Genetics Review for USMLE (Part 1)

Useful websites with sample questions

1. <http://medgen.genetics.utah.edu/index.htm>
2. <http://www.med.uiuc.edu/m1/genetics/>

Chromosomal abnormalities and Cytogenetics

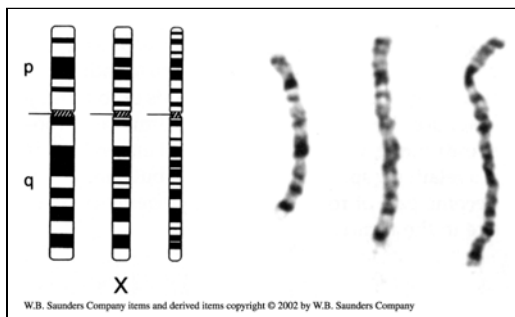
Chromosomal abnormalities are the result of microscopically visible alterations in the number or structure of chromosomes, and when inherited or acquired shortly after fertilization, are responsible for a large proportion of miscarriages, congenital malformations, and mental retardation. In contrast, simple mutations can involve base substitutions or small scale insertions or deletions that are not visible by microscopy.

Acquired chromosomal abnormalities can occur in somatic cells. Acquired chromosomal abnormalities are often observed in cancer cells.

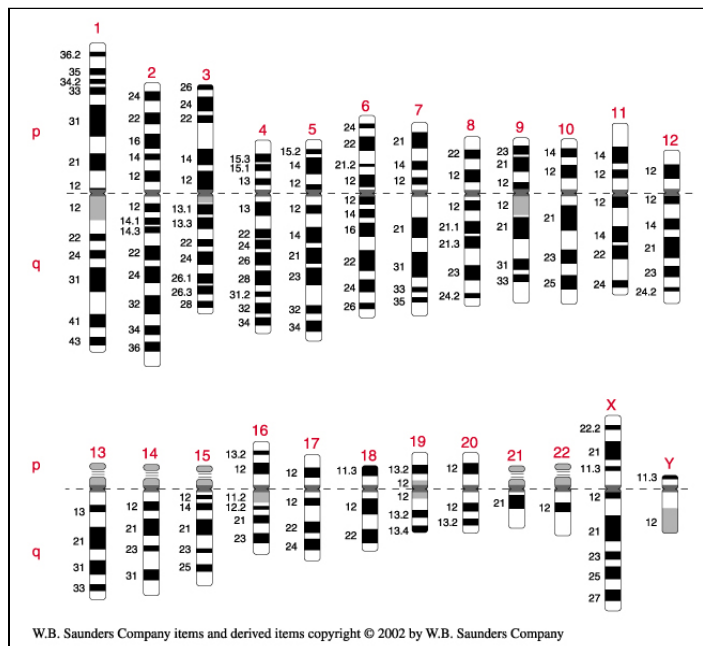
Clinical cytogenetics is the study of microscopically visible changes in chromosome number or structure and their inheritance.

Chromosomes are usually studied in cells that have entered prometaphase or metaphase, when chromosomes are near maximally or maximally condensed. At this stage, each chromosome has replicated, but the resulting **sister chromatids** have not yet separated.

The Giemsa staining method is most commonly used to identify human chromosomes in clinical laboratories. The staining procedure produces a series of dark and light bands. The number of bands observed depends on the degree of condensation of the chromosome. Metaphase chromosomes (most condensed) produce a total of about 450 bands. Prometaphase

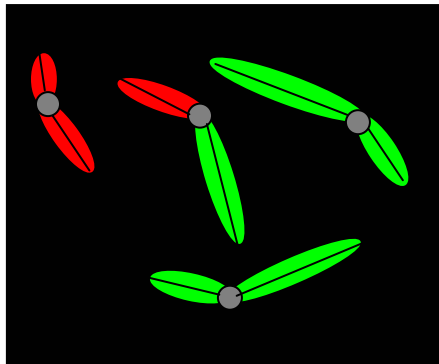


From left to right, X chromosome ideograms and photomicrographs at metaphase, prometaphase and prophase. (From Thompson and Thompson, Genetics in Medicine, Chapt. 9)

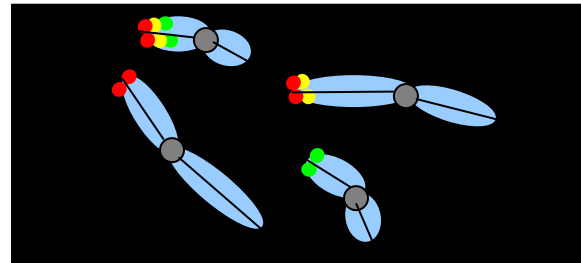


Idiogram (right) showing G-banding patterns for human chromosomes at metaphase, with about 400 bands per haploid karyotype. Human chromosomes are characterized as **metacentric** (central centromere), **submetacentric** (off-centered centromere, or **acrocentric** (centromere at the end of one arm). The short arms of the acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22) have a short mass of chromatin connected to the centromeric region by a narrow stalk. Each stalk contains many repeated copies of ribosomal RNA genes. (From Thompson and Thompson, Genetics in Medicine, 6th ed.

Fluorescence *in situ* hybridization involves hybridizing fluorescent labeled DNA probes to denatured chromosomal DNA and viewing the results by fluorescence microscopy. A mixture of probes directed against an entire chromosome is termed **chromosome painting**,



Whole chromosome X paint (red) and whole chromosome 4 paint (green) is used to detect a translocation between the two. Chromosome painting shows a partial trisomy in 4 and a partial monosomy in X.



Chronic myeloid leukemia results from a t(9:22) reciprocal translocation generating a gene fusion between the ABL oncogene at 9q34 and the BCR gene at 22q11. Hybridization with labeled probes for ABL (red) and BCR (green) is shown to metaphase chromosomes from a patient. The overlapping signals in the translocation der(9) and der(22) chromosomes appear yellow. The blue background is produced by the DAPI stain for chromosomes.

Abnormalities of Chromosome Number (occurs in about 1/25 to 1/30 pregnancies and about 1/160 live births)

Aneuploidy, the presence of a greater or lesser number of chromosomes than 46, is the most common and clinically significant type of human chromosome disorder. Most common cause is meiotic nondisjunction, usually during meiosis I.

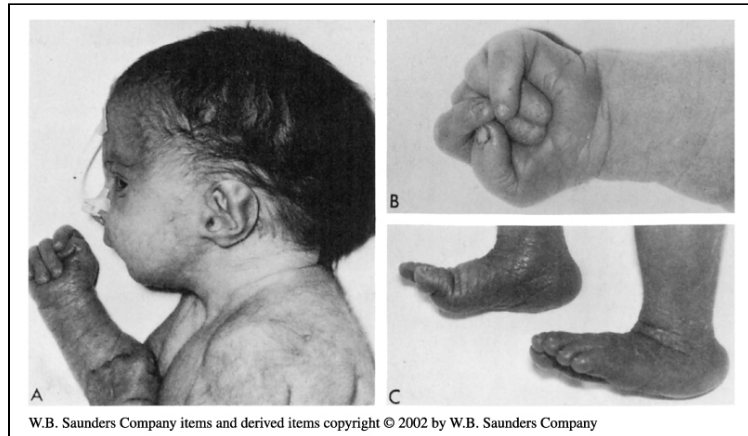
Aneuploidy involving autosomes (From Thompson and Thompson, Genetics in Medicine, Chapt. 10).

Trisomy 21 (Down Syndrome) – Affects 1 in 800 children. Incidence rate increases with maternal age above age 35. 95% of cases due to meiotic nondisjunction, 4% due to robertsonian translocation between chromosomes 14 and 21 (see next section on abnormal chromosome structure) and 1% due to mosaicism. Tissue specific mosaicism can complicate diagnosis. Mosaicism affecting predominantly germ cells can lead to multiple recurrences involving an otherwise normal carrier. Clinical features include:

- Mental retardation
- Flat facial profile
- Prominent epicanthal folds (redundant skin of the inner eyelid)
- Palm of hand shows a single deep flexion crease (simian crease) – 50%
- Structural defects of the heart (40%)
- Gastrointestinal obstructions (3%)
- Early onset Alzheimer's disease
- Increased risk of ALL (acute lymphoblastic leukemia)

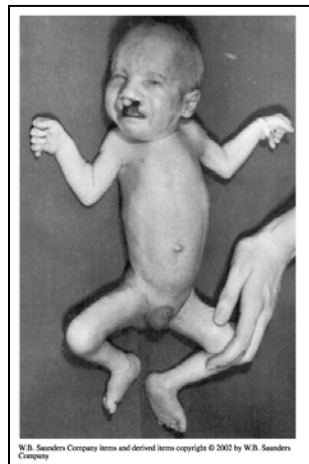
Trisomy 18 (Edwards syndrome) – Observed in 1/6,000 to 1/7,500 births. Clinical features include:

- Mental retardation
- Severe malformation of the Heart (e.g ventricular septal defects)
- Prominent occiput (back part of head)
- Receding jaw
- Low-set, malformed ears
- “Rocker-bottom” feet or left-sided clubfoot
- Characteristic clenched fists
- Death usually within the first year. Survivors have significant developmental disabilities



Trisomy 13 (Patau syndrome) – Observed in about 1/10,000 births. Clinical features include:

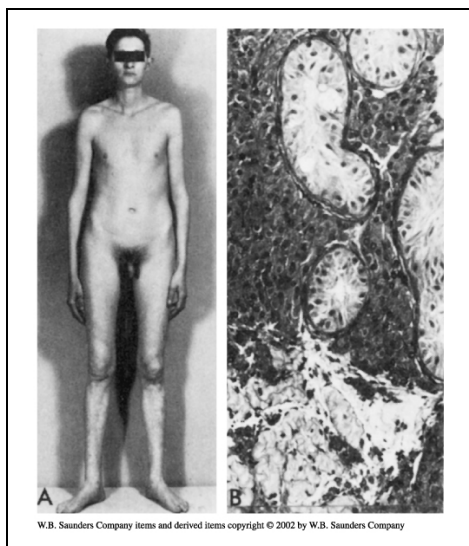
- Oral-facial clefts
- Extra digits on hands and/or feet
- Characteristic clenched fist as in trisomy 18
- “Rocker bottom” feet as in trisomy 18
- Severe central nervous system malformations Such as in holoprocencephaly
- Ocular abnormalities
- Congenital heart and urogenital defects



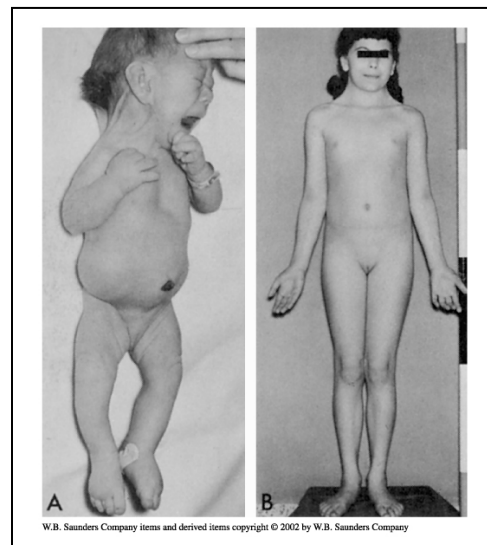
Aneuploidy involving sex chromosomes (Taken from Tables 10-3 and 10-4 and text from Thompson & Tompson, Genetics in Medicine)

Sex	Disorder	Karyotype	Incidence	Phenotype and Clinical Signs
Male	Klinefelter syndrome	47,XXY 48,XXXYY others	1/1,000 1/25,000 1/10,000	Tall stature (after puberty), hypogonadism (infertility), breast development (30%), learning disabilities, diminished intelligence (10-15 points below average), psychosocial problems. XXXYY males are more severely affected
Male	47, XYY syndrome	47,XYY other	1/1,000 1/1,500	Caused by paternal nondisjunction. No obvious abnormal phenotype. However, males tend to be taller, and some have learning disabilities associated with reduced IQ scores (about 10-15 points below average).

Female	Turner syndrome	45,X	1/5,000	Short stature, webbed neck, broad chest with widely spaced nipples, increased incidence of renal and cardiovascular anomalies, and gonadal dysgenesis. Evidence of fetal and lymphodemia often present at birth.
Female	Trisomy X	47,XXX others	1/1,000 1/3,000	XXX females are phenotypically normal, reduced IQ scores and learning problems (70%), and transition from adolescence to early adulthood may be accompanied by behavioral problems. Increasing number of X chromosomes as in 48,XXXX and 49,XXXXX result in serious retardation in physical and mental development



(A) Phenotype of an adult male with 47,XXY Klinefelter syndrome. Relatively small genitalia, and the body proportions (elongated limbs and somewhat feminine body shape). Gynecomastia (enlarged breasts), not present in this patient, is a feature seen in some patients. (B) Section of a testicular biopsy showing seminiferous tubules without germ cells. (From Thompson & Thompson, Genetics in Medicine, Chapt. 10)

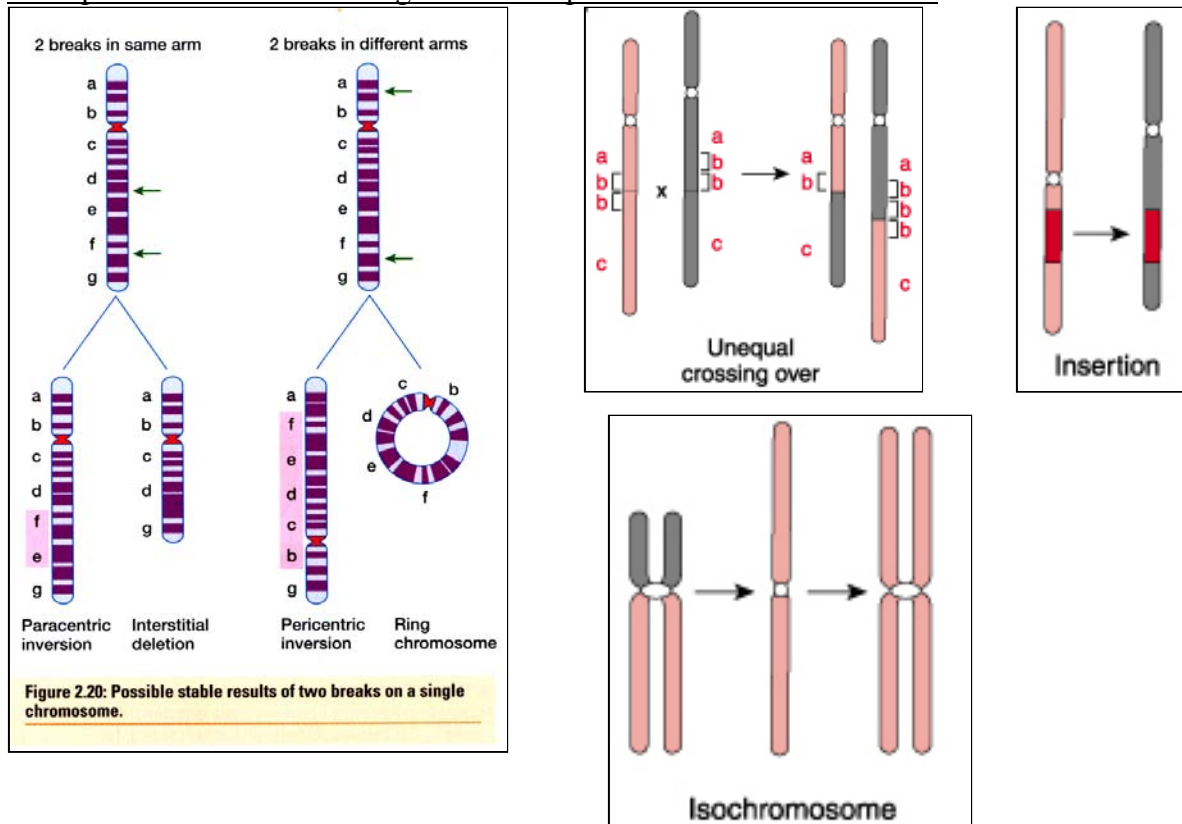


Phenotype of females with 45,X Turner syndrome. (A) Newborn infant with webbed neck and lymphedema of the hands and feet. (B) A 13-year-old girl showing classic Turner features, short stature, webbed neck, delayed sexual maturation, broad, shield-like chest with widely spaced nipples. (From Thompson & Thompson, Genetics in Medicine, Chapt. 10)

Abnormalities of Chromosome Structure (present in about 1/375 new borns)

*These are microscopically observable changes in chromosome appearance. **Balanced rearrangements** involve a reshuffling of genetic material without any significant loss or gain (see diagram below). **Carriers appear normal.** **Unbalanced rearrangements** result from a loss (deletion) or (less commonly) a gain of genetic material, and generally produce an abnormal phenotype on transmission. Rearranged chromosomes are **stable** (transmitted through meiosis and mitosis) if they retain normal structural features such as single functional centromere.*

Examples of structural rearrangements that produce stable chromosomes



Origins of Translocations

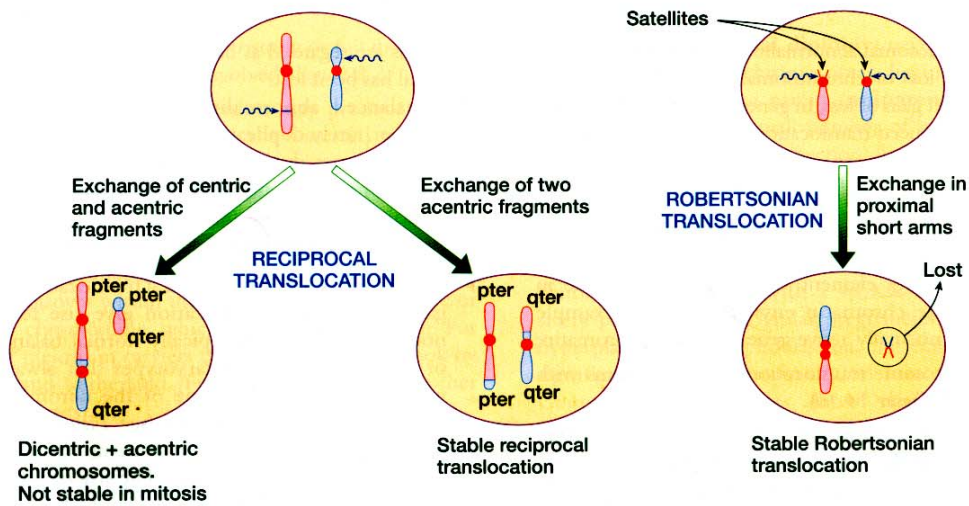


Figure 2.21: Origins of translocations.

Dicentric and acentric chromosomes are not stable through mitosis. Robertsonian translocations are produced by exchanges between the proximal short arms of the acrocentric chromosomes 13, 14, 15, 21 and 22 (arrays of repeated ribosomal DNA genes on the short arms of the acrocentric chromosomes 13, 14, 15, 21 and 22 often appear as thin stalks carrying knobs of chromatin – *satellites*). In a Robertsonian translocation both centromeres are present, but they function as one and the chromosome is stable. The small acentric fragment is lost, but this has no pathological consequences because it contains only repeated rDNA sequences, which are also present on the other acrocentric chromosomes.

Meiosis in carriers of balanced translocations can produce unbalanced offspring

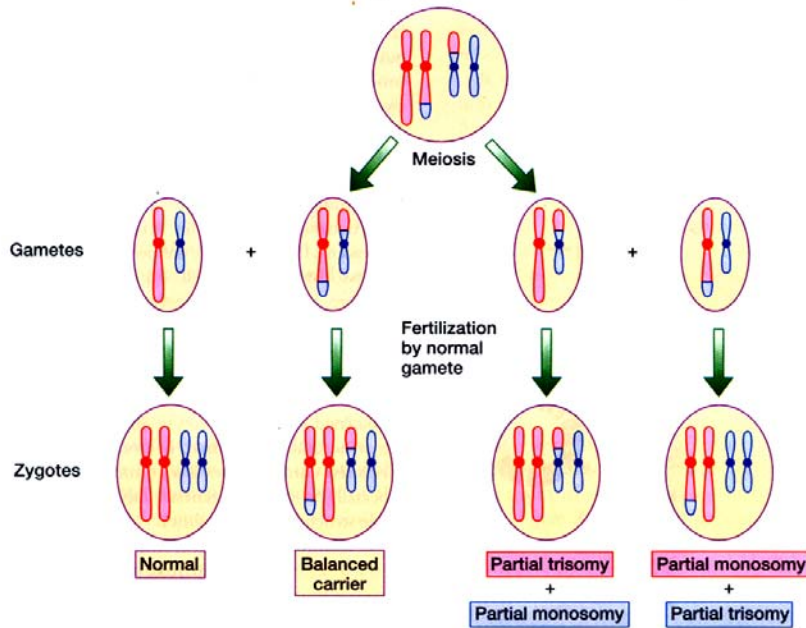


Figure 2.22: Results of meiosis in a carrier of a balanced reciprocal translocation.

Other modes of segregation are also possible, for example 3 : 1 segregation. The relative frequency of each possible gamete is not readily predicted. The risk of a carrier having a child with each of the possible outcomes depends on its frequency in the gametes and also on the likelihood of a conceptus with that abnormality developing to term. See the book by Gardner and Sutherland (Further reading) for discussion.

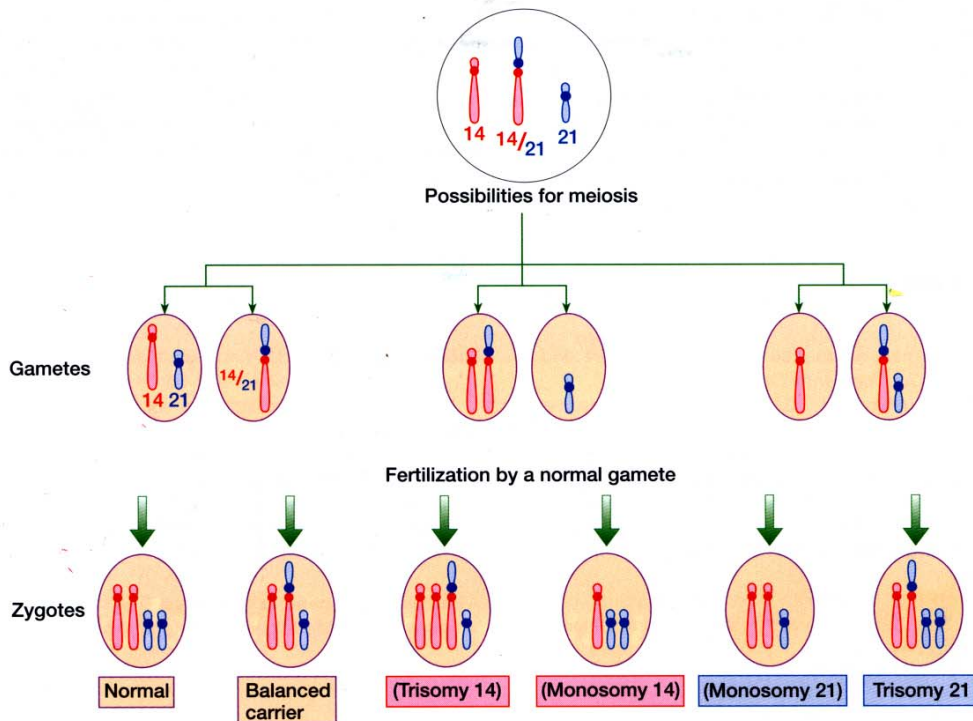
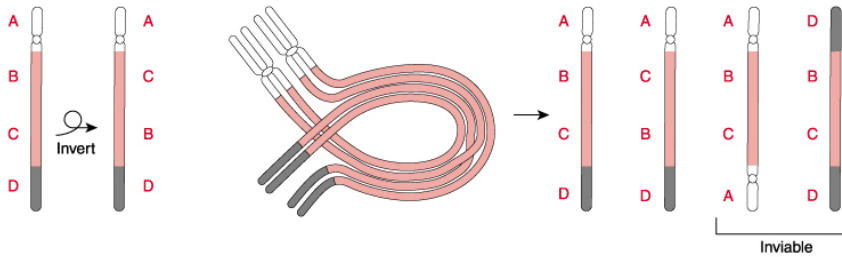


Figure 2.23: Results of meiosis in a carrier of a Robertsonian translocation.

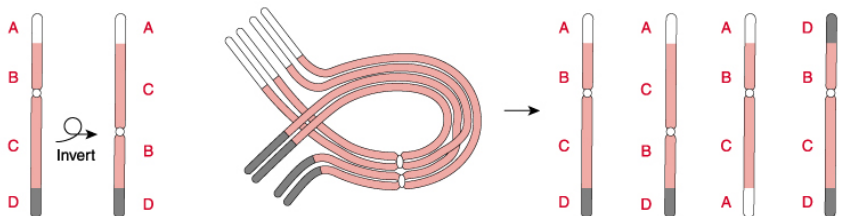
Carriers are asymptomatic but often produce unbalanced gametes that can result in a monosomic or trisomic zygote. The bracketed monosomic and trisomic zygotes in this example would not develop to term.

Carriers of paracentric inversions produce balanced offspring, whereas carriers of pericentric inversions can produce unbalanced offspring

A Paracentric



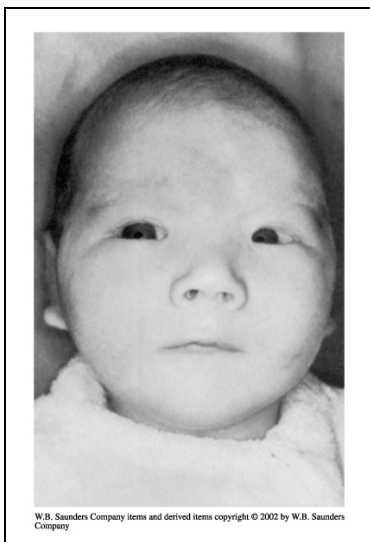
B Pericentric



Crossing over within inversion loops formed during meiosis I in carriers with paracentric and pericentric inversions. In paracentric inversion (A), gametes at the end of meiosis II usually contain a normal copy of the chromosome or are carriers of the parental, balanced paracentric inversion, because the dicentric and acentric products are inviable. In pericentric inversion (B), gametes produced after the second meiosis may be normal, balanced, or may carry an unbalanced duplication and deletion.

Autosomal Deletion Syndromes

Cytogenetically detectable deletions result in dysmorphic patients. Although the overall incidence is about 1/7,000 live births, any given deletion is usually very rare. One well described deletion syndrome is **Cri Du Chat Syndrome**, which involves deletion of much of the short arm of chromosome 5. Crying infants with this disorder sound like mewling cats. Other features include severe mental retardation (accounts for 1% of all institutionalized mental retardation patients), microcephaly, epicanthal folds, low-set ears, small jaws (micrognathia), and widely spaced eyes.

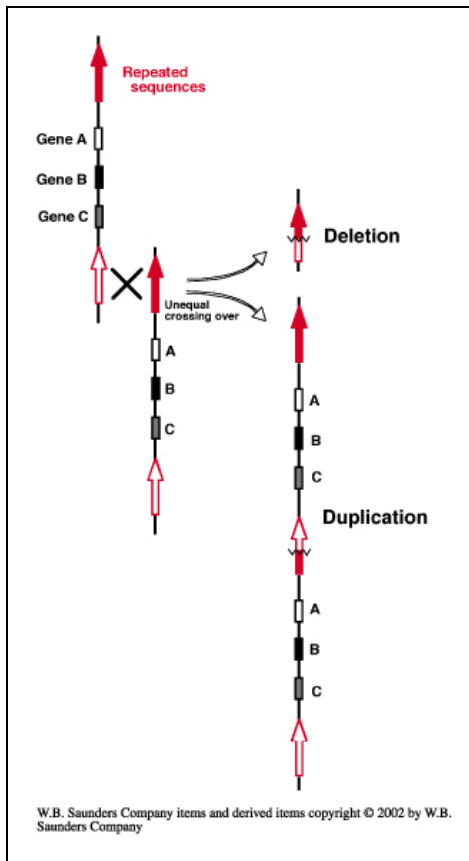


Infant with cri du chat syndrome, which results from deletion of part of the short arm of chromosome 5 (5p). From Thompson and Thompson, Genetics in Medicine, Chapt. 10.

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Microdeletion and Duplication Syndromes

These often result from unequal crossing over between misaligned sister chromatids or homologous chromosomes containing highly homologous copies of a repeat DNA sequence.



Microdeletion or Contiguous Gene Syndromes Involving Recombination between Repeated Sequences

Disorder	Site	Rearrangement		Repeat Length (kb)
		Type	Size (kb)	
Prader-Willi/ Angelman syndromes	17p11.2	Deletion	5000	200
Neurofibromatosis type I	17q11.2	Deletion	1500	~50 - 400
Charcot-Marie-Tooth disease	17p12	Deletion	1500	24
HNLPP		Duplication		
DiGeorge syndrome/ velocardiofacial syndrome	22q11	Deletion	3000	200
Cat-eye syndrome		Duplication		

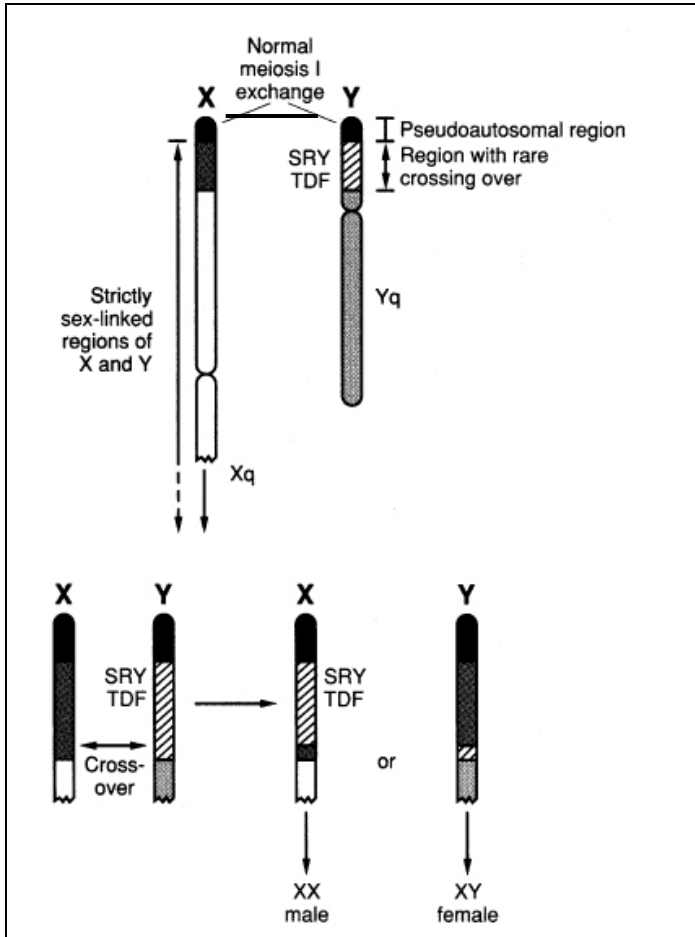
Prader-Willi/Angelman syndromes are likely subjects of exam questions and will be discussed in a later section.

Neurofibromatosis type I is a relatively common autosomal dominant disorder, which often involves a deletion of part of a single large gene (*NF1*, 2,000 kb located at 17q11.2). The disorder is characterized by numerous benign tumors (neurofibromas) affecting the peripheral nervous system, but a minority of patients also show increased incidence of malignancy, such as neurofibrosarcoma, astrocytoma, Schwann cell cancers and childhood CML (chronic myelogenous leukemia)

DiGeorge syndrome/velocardiofacial syndrome is among the most common cytogenetic deletions (frequency of 1/2,000 to 1/4,000 births). It is associated with craniofacial anomalies, mental retardation, and heart defects. This specific deletion is thought to be associated with 5% of all congenital heart defects.

Sex Reversal caused by aberrant crossing over between X and Y chromosomes in the region adjacent to the pseudoautosomal boundary.

In an otherwise normal genetic background, the region containing *Sry* gene acts in a dominant manner to direct male specific differentiation.



Male	XX males	46, XX	1/20,000 males	Caused by abnormal meiotic recombination leading to the gain of the <i>Sry</i> (sex-determining region of the Y chromosome) by the X chromosome during spermatogenesis.
Female	XY females	46,XY	1/20,000 females	Caused by abnormal meiotic recombination between X and Y chromosomes resulting in the loss of the <i>Sry</i> region of the Y chromosome during spermatogenesis.

See pages 176 and 177 in Thompson and Thompson, Genetics in Medicine, 6th ed., for other causes of female and male pseudohermaphroditism.