

Alterations of chromosome number or structure cause some genetic disorders

- **Nondisjunction** occurs when problems with the meiotic spindle cause errors in daughter cells.
 - This may occur if tetrad chromosomes do not separate properly during meiosis I.
 - Alternatively, sister chromatids may fail to separate during meiosis II.
- As a consequence of nondisjunction, some gametes receive two of the same type of chromosome and another gamete receives no copy.
- Offspring results from fertilization of a normal gamete with one after nondisjunction will have an abnormal chromosome number or **aneuploidy**.
 - **Trisomic** cells have three copies of a particular chromosome type and have $2n + 1$ total chromosomes.
 - **Monosomic** cells have only one copy of a particular chromosome type and have $2n - 1$ chromosomes.
- If the organism survives, aneuploidy typically leads to a distinct phenotype.
- Aneuploidy can also occur during failures of the mitotic spindle.
- If aneuploidy happens early in development, this condition will be passed along by mitosis to a large number of cells.
- This is likely to have a substantial effect on the organism.
- Organisms with more than two complete sets of chromosomes, have undergone **polyploidy**.
- This may occur when a normal gamete fertilizes another gamete in which there has been nondisjunction of all its chromosomes.
 - The resulting zygote would be *triploid* ($3n$).
- Alternatively, if a $2n$ zygote failed to divide after replicating its chromosomes, a *tetraploid* ($4n$) embryo would result from subsequent successful cycles of mitosis.
- Polyploidy is relatively common among plants and much less common among animals.
 - The spontaneous origin of polyploid individuals plays an important role in the evolution of plants.
 - Both fishes and amphibians have polyploid species.
- Polyploids are more nearly normal in phenotype than aneuploids.
- One extra or missing chromosome apparently upsets the genetic balance during development more than does an entire extra set of chromosomes.
- Breakage of a chromosome can lead to four types of changes in chromosome structure.
- A **deletion** occurs when a chromosome fragment lacking a centromere is lost during cell division.
 - This chromosome will be missing certain genes.
- A **duplication** occurs when a fragment becomes attached as an extra segment to a sister chromatid.

- An **inversion** occurs when a chromosomal fragment reattaches to the original chromosome but in the reverse orientation.
- In **translocation**, a chromosomal fragment joins a nonhomologous chromosome.
 - Some translocations are reciprocal, others are not.
- Deletions and duplications are common in meiosis.
 - Homologous chromatids may break and rejoin at incorrect places, such that one chromatid will lose more genes than it receives.
- A diploid embryo that is homozygous for a large deletion or male with a large deletion to its single X chromosome is usually missing many essential genes and this leads to a lethal outcome.
 - Duplications and translocations are typically harmful.
- Reciprocal translocation or inversion can alter phenotype because a gene's expression is influenced by its location.
- Several serious human disorders are due to alterations of chromosome number and structure.
- Although the frequency of aneuploid zygotes may be quite high in humans, most of these alterations are so disastrous that the embryos are spontaneously aborted long before birth.
 - These developmental problems result from an imbalance among gene products.
- Certain aneuploid conditions upset the balance less, leading to survival to birth and beyond.
 - These individuals have a set of symptoms - a syndrome - characteristic of the type of aneuploidy.
- One aneuploid condition, **Down syndrome**, is due to three copies of chromosome 21.
 - It affects one in 700 children born in the United States.
- Although chromosome 21 is the smallest human chromosome, it severely alters an individual's phenotype in specific ways.
- Most cases of Down syndrome result from nondisjunction during gamete production in one parent.
- The frequency of Down syndrome correlates with the age of the mother.
 - This may be linked to some age-dependent abnormality in the spindle checkpoint during meiosis I, leading to nondisjunction.
- Trisomies of other chromosomes also increase in incidence with maternal age, but it is rare for infants with these autosomal trisomies to survive for long.
- Nondisjunction of sex chromosomes produces a variety of aneuploid conditions in humans.
- Unlike autosomes, this aneuploidy upsets the genetic balance less severely.
 - This may be because the Y chromosome contains relatively few genes.
 - Also, extra copies of the X chromosome become inactivated as Barr bodies in somatic cells.

- *Klinefelter's syndrome*, an XXY male, occurs once in every 2000 live births.
 - These individuals have male sex organs, but are sterile.
 - There may be feminine characteristics, but their intelligence is normal.
- Males with an extra Y chromosome (XYY) tend to be somewhat taller than average.
- Trisomy X (XXX), which occurs once in every 2000 live births, produces healthy females.
- Monosomy X or *Turner's syndrome* (X0), which occurs once in every 5000 births, produces phenotypic, but immature females.
- Structural alterations of chromosomes can also cause human disorders.
- Deletions, even in a heterozygous state, cause severe physical and mental problems.
- One syndrome, *cri du chat*, results from a specific deletion in chromosome 5.
 - These individuals are mentally retarded, have a small head with unusual facial features, and a cry like the mewling of a distressed cat.
 - This syndrome is fatal in infancy or early childhood.
- Chromosomal translocations between nonhomologous chromosomes are also associated with human disorders.
- Chromosomal translocations have been implicated in certain cancers, including *chronic myelogenous leukemia (CML)*.
 - CML occurs when a fragment of chromosome 22 switches places with a small fragment from the tip of chromosome 9.
- Some individuals with Down syndrome have the normal number of chromosomes but have all or part of a third chromosome 21 attached to another chromosome by translocation.

The phenotypic effects of some mammalian genes depend on whether they were inherited from the mother or the father (imprinting)

- For most genes it is a reasonable assumption that a specific allele will have the same effect regardless of whether it was inherited from the mother or father.
- However, for some traits in mammals, it does depend on which parent passed along the alleles for those traits.
 - The genes involved are not sex linked and may or may not lie on the X chromosome.
- Two disorders, *Prader-Willi syndrome* and *Angelman syndrome*, with different phenotypic effects are due to the same cause, a deletion of a specific segment of chromosome 15.
 - Individuals with Prader-Willi syndrome are characterized by mental retardation, obesity, short stature, and unusually small hands and feet.
 - These individuals inherit the abnormal chromosome from their father.
 - Individuals with Angelman syndrome exhibit spontaneous laughter, jerky movements, and other motor and mental symptoms.
 - This is inherited from the mother.

- The difference between the disorders is due to **genomic imprinting**.
- In this process, a gene on one homologous chromosome is silenced, while its allele on the homologous chromosome is expressed.
- The imprinting status of a given gene depends on whether the gene resides in a female or a male.
 - The same alleles may have different effects on offspring, depending on whether they arrive in the zygote via the ovum or via the sperm.
- In the new generation, both maternal and paternal imprints are apparently “erased” in gamete-producing cells.
- Then, all chromosomes are re imprinted according to the sex of the individual in which they reside.
- In many cases, genomic imprinting occurs when methyl groups are added to cytosine nucleotides on one of the alleles.
 - Heavily methylated genes are usually inactive.
 - The animal uses the allele that is not imprinted.
- In other cases, the absence of methylation in the vicinity of a gene plays a role in silencing it.
 - The active allele has some methylation.
- Several hundred mammalian genes, many critical for development, may be subject to imprinting.
 - Imprinting is critical for normal development.
- **Fragile X syndrome**, which leads to various degrees of mental retardation, also appears to be subject to genomic imprinting.
 - This disorder is named for an abnormal X chromosome in which the tip hangs on by a thin thread of DNA.
 - This disorder affects one in every 1,500 males and one in every 2,500 females.
- Inheritance of fragile X is complex, but the syndrome is more common when the abnormal chromosome is inherited from the mother.
 - This is consistent with the higher frequency in males.
 - Imprinting by the mother somehow causes it.

Extranuclear genes exhibit a non-Mendelian pattern of inheritance

- Not all of a eukaryote cell's genes are located in the nucleus.
- Extranuclear genes are found on small circles of DNA in mitochondria and chloroplasts.
- These organelles reproduce themselves.
- Their cytoplasmic genes do not display Mendelian inheritance.
 - They are not distributed to offspring during meiosis.
- Karl Correns in 1909 first observed cytoplasmic genes in plants.
- He determined that the coloration of the offspring was determined only by the maternal parent.
- These coloration patterns are due to genes in the plastids which are inherited only via the ovum, not the pollen.
- Because a zygote inherits all its mitochondria only from the ovum, all mitochondrial genes in mammals demonstrate maternal inheritance.
- Several rare human disorders are produced by mutations to mitochondrial DNA.
 - These primarily impact ATP supply by producing defects in the electron transport chain or ATP synthase.
 - Tissues that require high energy supplies (for example, the nervous system and muscles) may suffer energy deprivation from these defects.
 - Other mitochondrial mutations may contribute to diabetes, heart disease, and other diseases of aging.