CHAPTER 15
THE CHROMOSOMAL BASIS OF INHERITANCE

Section A: Relating Mendelism to Chromosomes

1. Mendelian inheritance has its physical basis in the behavior of chromosomes during sexual life cycles
2. Morgan traced a gene to a specific chromosome
3. Linked genes tend to be inherited together because they are located on the same chromosome
4. Independent assortment of chromosomes and crossing over produce genetic recombinants
5. Geneticists use recombination data to map a chromosome's genetic loci

Introduction

- It was not until 1900 that biology finally caught up with Gregor Mendel.
- Independently, Karl Correns, Erich von Tschermak, and Hugo de Vries all found that Mendel had explained the same results 35 years before.
- Still, resistance remained about Mendel's laws of segregation and independent assortment until evidence had mounted that they had a physical basis in the behavior of chromosomes.
- Mendel's hereditary factors are the genes located on chromosomes.

1. Mendelian inheritance has its physical basis in the behavior of chromosomes during sexual life cycles

- Around 1900, cytologists and geneticists began to see parallels between the behavior of chromosomes and the behavior of Mendel's factors.
  - Chromosomes and genes are both present in pairs in diploid cells.
  - Homologous chromosomes separate and alleles segregate during meiosis.
  - Fertilization restores the paired condition for both chromosomes and genes.

- Around 1902, Walter Sutton, Theodor Boveri, and others noted these parallels and a **chromosome theory of inheritance** began to take form.
- Thomas Hunt Morgan was the first to associate a specific gene with a specific chromosome in the early 20th century using fruit flies.
- Morgan studies eye color and discovered that the white-eyed trait appeared only in males.
- Morgan concluded that a fly's eye color was linked to its sex.

- Morgan deduced that the gene with the white-eyed mutation is on the X chromosome alone, a sex-linked gene.
  - Females (XX) may have two red-eyed alleles and have red eyes or may be heterozygous and have red eyes.
  - Males (XY) have only a single allele and will be red eyed if they have a red-eyed allele or white-eyed if they have a white-eyed allele.

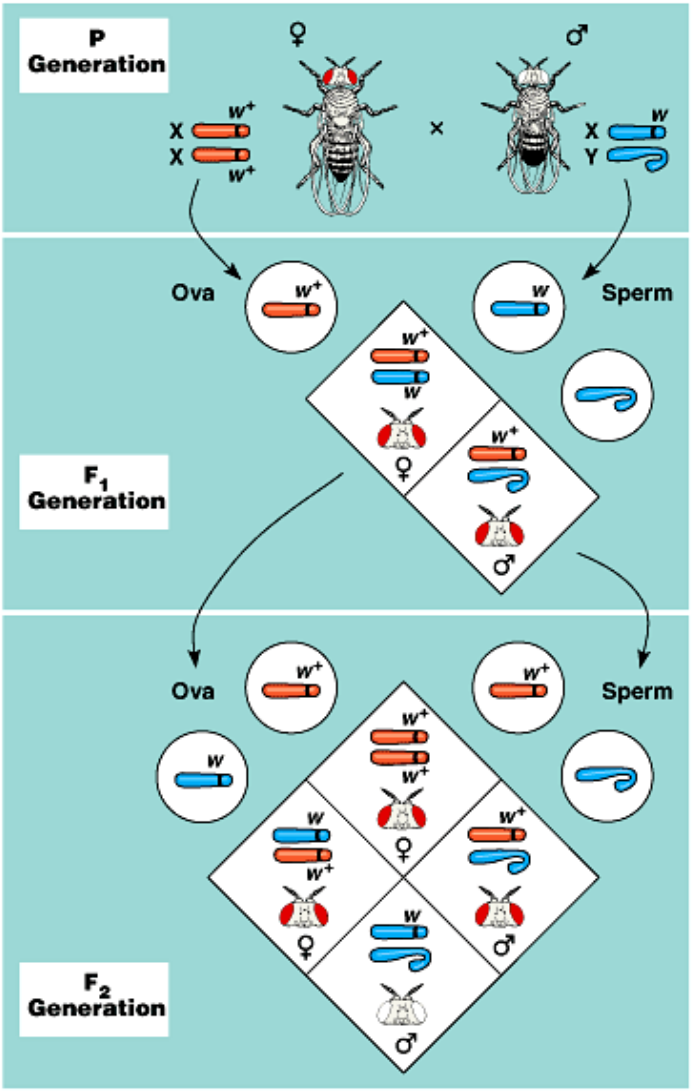

Fig. 15.3

3. Linked genes tend to be inherited together because they are located on the same chromosome

- Each chromosome has hundreds or thousands of genes.
- Genes located on the same chromosome, **linked genes**, tend to be inherited together because the chromosome is passed along as a unit.
- Results of crosses with linked genes deviate from those expected according to independent assortment.

4. Independent assortment of chromosomes and crossing over produce genetic recombinants

- The production of offspring with new combinations of traits inherited from two parents is **genetic recombination**.
- Genetic recombination can result from independent assortment of genes located on nonhomologous chromosomes or from crossing over of genes located on homologous chromosomes.

- In contrast, linked genes, genes located on the same chromosome, tend to move together through meiosis and fertilization.

- Under normal Mendelian genetic rules, we would not expect linked genes to recombine into assortments of alleles not found in the parents.

5. Geneticists can use recombination data to map a chromosome's genetic loci

- One of Morgan's students, Alfred Sturtevant, used crossing over of linked genes to develop a method for constructing a **chromosome map**.

- This map is an ordered list of the genetic loci along a particular chromosome.

- Sturtevant hypothesized that the frequency of recombinant offspring reflected the distances between genes on a chromosome.
- The farther apart two genes are, the higher the probability that a crossover will occur between them and therefore a higher recombination frequency.
  - The greater the distance between two genes, the more points between them where crossing over can occur.
- Sturtevant used recombination frequencies from fruit fly crosses to map the relative position of genes along chromosomes, a **linkage map**.

- *Pristionchus pacificus* (roundworm) Map

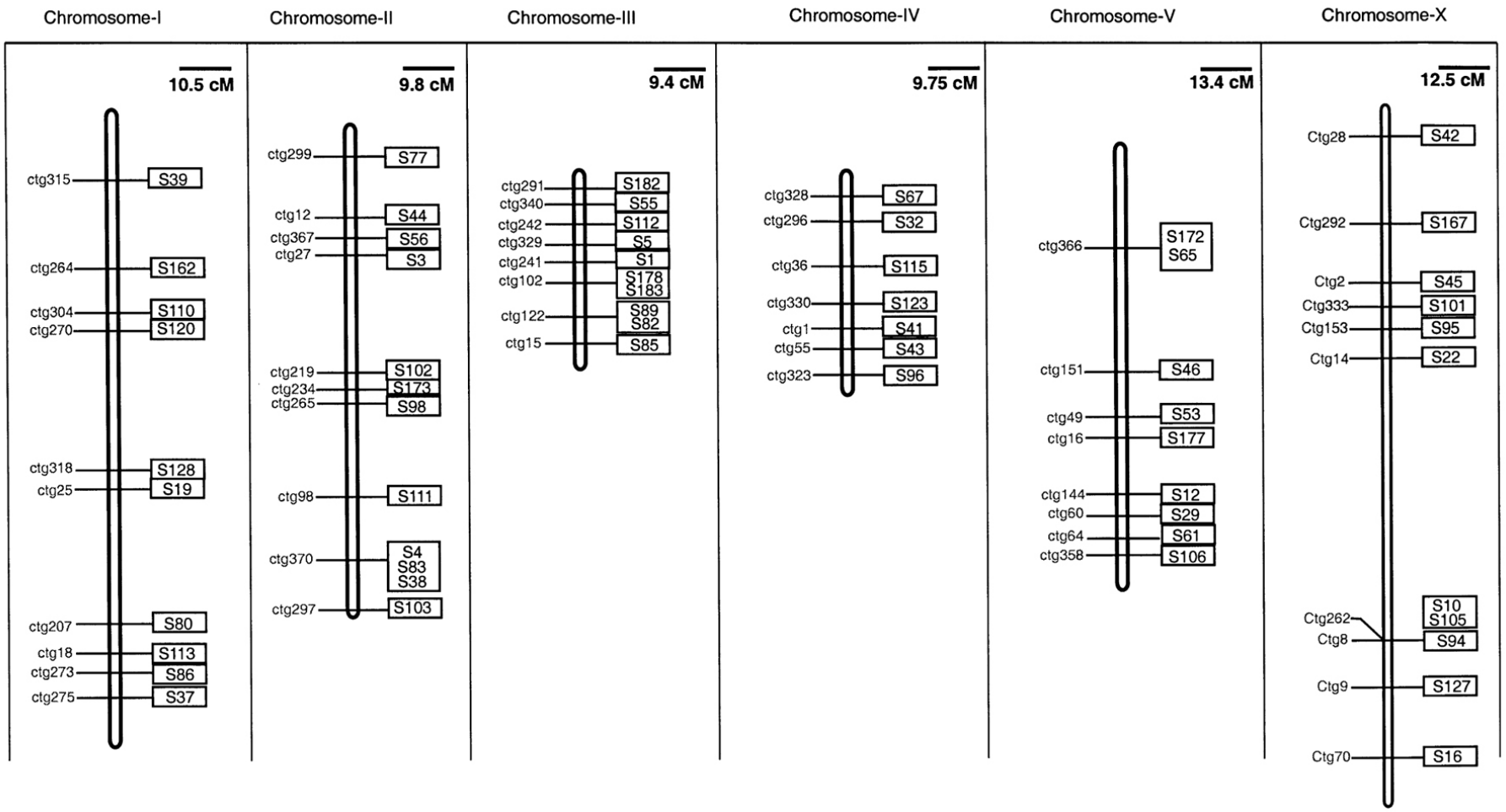

Fig. 15.6

- Some genes on a chromosome are so far apart that a crossover between them is virtually certain.
- In this case, the frequency of recombination reaches is its maximum value of 50% and the genes act as if found on separate chromosomes and are inherited independently.
  - In fact, several genes studies by Mendel are located on the same chromosome.
    - For example, seed color and flower color are far enough apart that linkage is not observed.
    - Plant height and pod shape should show linkage, but Mendel never reported results of this cross.

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Section B: Sex Chromosomes

1. The chromosomal basis of sex varies with the organism
2. Sex-linked genes have unique patterns of inheritance

1. The chromosomal basis of sex varies with the organism

- Although the anatomical and physiological differences between women and men are numerous, the chromosomal basis of sex is rather simple.
- In human and other mammals, there are two varieties of sex chromosomes, X and Y.
  - An individual who inherits two X chromosomes usually develops as a female.
  - An individual who inherits an X and a Y chromosome usually develops as a male.

- This X-Y system of mammals is not the only chromosomal mechanism of determining sex.
- Other options include the X-0 system, the Z-W system, and the haplo-diploid system, and the Temperature-dependent sex determination (TSD)
- TSD only occurs in reptiles and some fish.

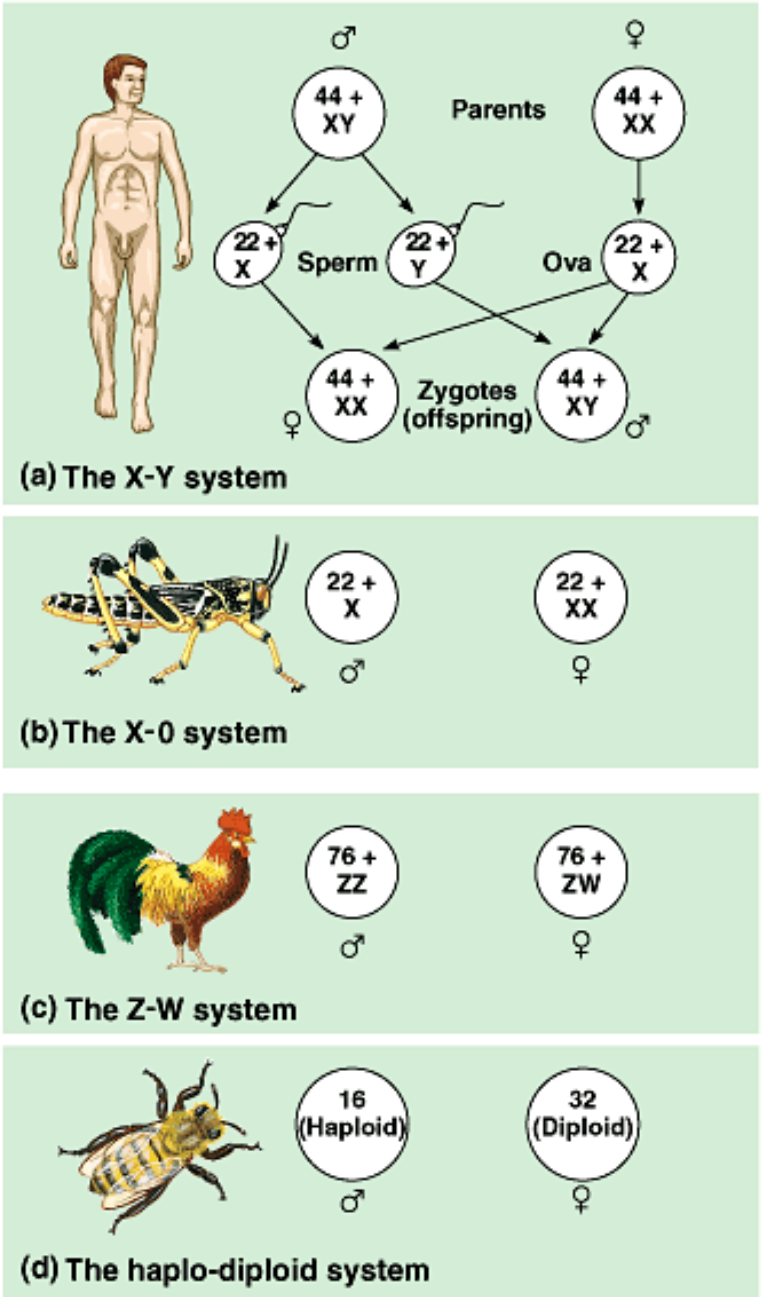


Fig. 15.8

- In the X-Y system, Y and X chromosomes behave as homologous chromosomes during meiosis.
  - In reality, they are only partially homologous and rarely undergo crossing over.
- In both testes (XY) and ovaries (XX), the two sex chromosomes segregate during meiosis and each gamete receives one.
  - Each egg receives an X chromosome.
  - Half the sperm receive an X chromosome and half receive a Y chromosome.
- Because of this, each conception has about a fifty-fifty chance of producing a particular sex.

- In humans, the anatomical signs of sex first appear when the embryo is about two months old.
- In individuals with the *SRY* gene (sex determining region of the Y chromosome), the generic embryonic gonads are modified into testes.
  - Activity of the SRY gene triggers a cascade of biochemical, physiological, and anatomical features because it regulates many other genes.
  - In addition, other genes on the Y chromosome are necessary for the production of functional sperm.
- In individuals lacking the SRY gene, the generic embryonic gonads develop into ovaries.

2. Sex-linked genes have unique patterns of inheritance

- In addition to their role in determining sex, the sex chromosomes, especially the X chromosome, have genes for many characters unrelated to sex.

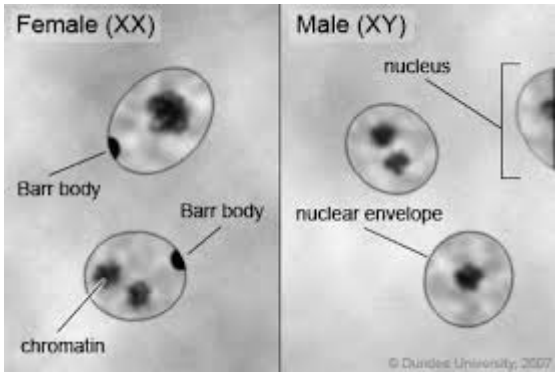
Fig. 15.9

- If a sex-linked trait is due to a recessive allele, a female will have this phenotype only if homozygous.
  - Heterozygous females will be carriers.
- Because males have only one X chromosome (*hemizygous*), any male receiving the recessive allele from his mother will express the trait.
- The chance of a female inheriting a double dose of the mutant allele is much less than the chance of a male inheriting a single dose.
- Therefore, males are far more likely to inherit sex-linked recessive disorders than are females.

- Several serious human disorders are sex-linked.
- **Duchenne muscular dystrophy** affects one in 3,500 males born in the United States.
  - Affected individuals rarely live past their early 20s.
  - This disorder is due to the absence of an X-linked gene for a key muscle protein, called dystrophin.
  - The disease is characterized by a progressive weakening of the muscles and loss of coordination.

- **Hemophilia** is a sex-linked recessive trait defined by the absence of one or more clotting factors.
  - These proteins normally slow and then stop bleeding.
- Individuals with hemophilia have prolonged bleeding because a firm clot forms slowly.
  - Bleeding in muscles and joints can be painful and lead to serious damage.
- Individuals can be treated with intravenous injections of the missing protein.

- Although female mammals inherit two X chromosomes, only one X chromosome is active.
- Therefore, males and females have the same effective dose (one copy) of genes on the X chromosome.
  - During female development, one X chromosome per cell condenses into a compact object, a **Barr body.**
  - This inactivates most of its genes.



- The condensed Barr body chromosome is reactivated in ovarian cells that produce ova.

- Mary Lyon, a British geneticist, has demonstrated that the selection of which X chromosome to form the Barr body occurs randomly and independently in embryonic cells at the time of X inactivation.
- As a consequence, females consist of a mosaic of cells, some with an active paternal X, others with an active maternal X.
  - After Barr body formation, all descendent cells have the same inactive X.
  - If a female is heterozygous for a sex-linked trait, approximately half her cells will express one allele and the other half will express the other allele.

- In humans, this mosaic pattern is evident in women who are heterozygous for a X-linked mutation that prevents the development of sweat glands.
  - A heterozygous woman will have patches of normal skin and skin patches lacking sweat glands.

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Section C: Errors and Exceptions in Chromosomal Inheritance

1. Alterations of chromosome number or structure cause some genetic disorders
2. The phenotypic effects of some mammalian genes depend on whether they are inherited from the mother or the father (imprinting)
3. Extranuclear genes exhibit a non-Mendelian pattern of inheritance

Introduction

- Sex-linked traits are not the only notable deviation from the inheritance patterns observed by Mendel.
- Also, gene mutations are not the only kind of changes to the genome that can affect phenotype.
- Major chromosomal aberrations and their consequences produce exceptions to standard chromosome theory.
- In addition, two types of normal inheritance also deviate from the standard pattern.

1. 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.

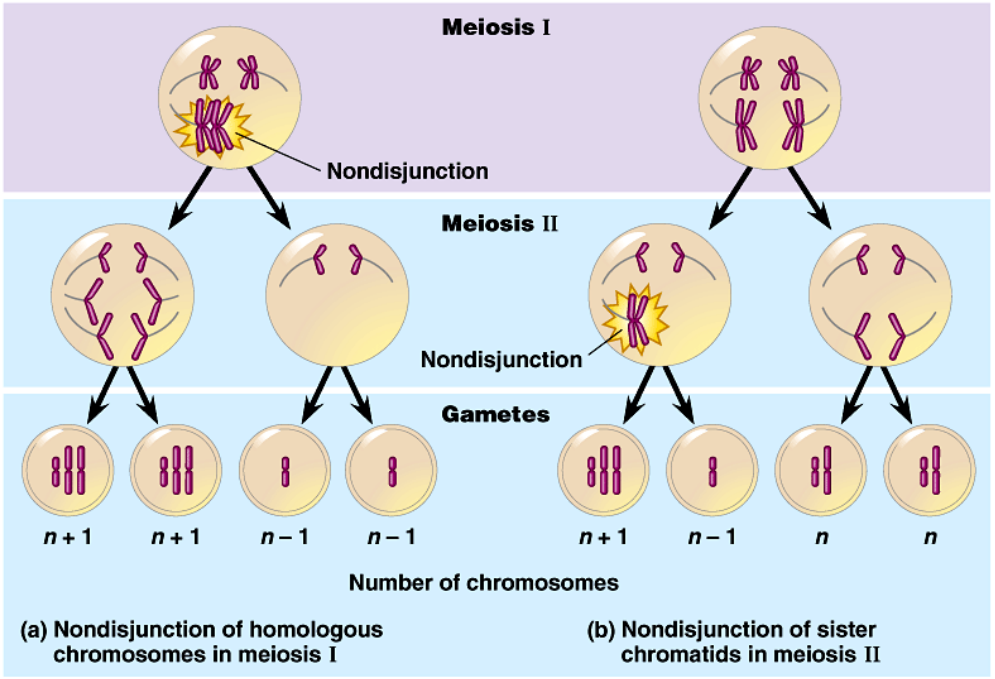

Fig. 15.11

- 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 **polypoidy**.
- 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.
  - Recently, researchers in Chile have identified a new rodent species which may be the product of polyploidy.

Fig. 15.12

- 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

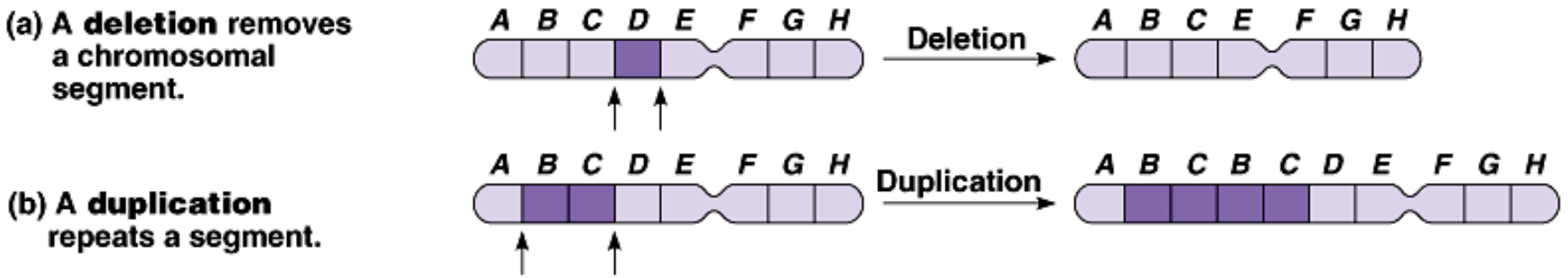

Fig. 15.13a & b

- 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. (XX-males!)
  - Some translocations are reciprocal, others are not.

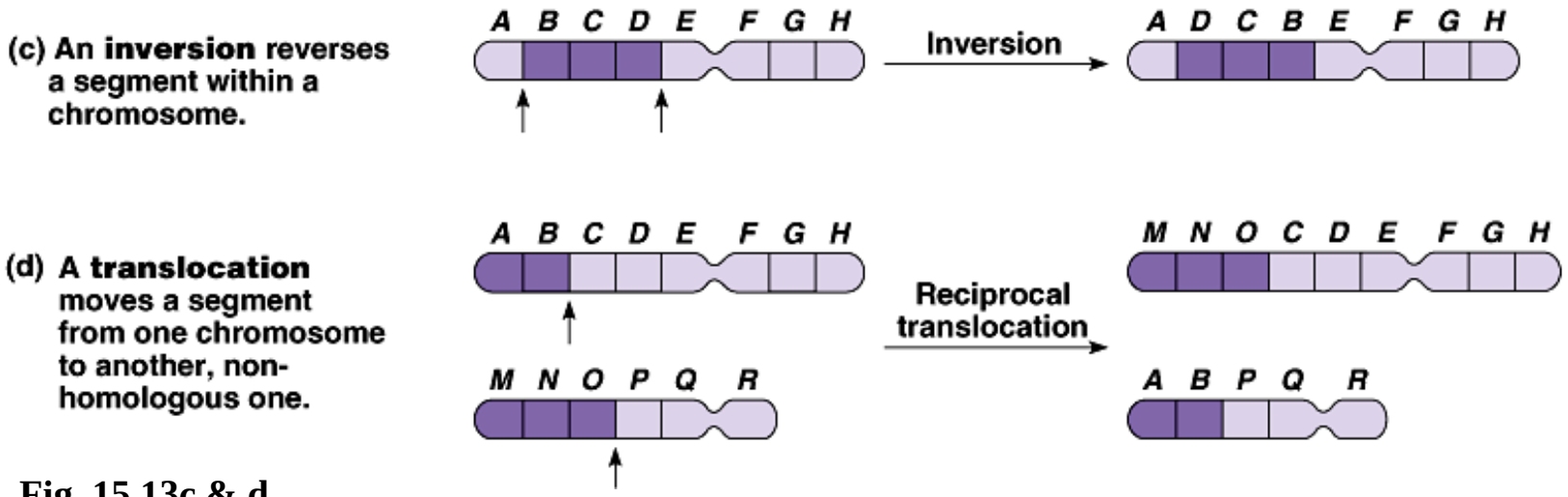

Fig. 15.13c & d

- Deletions and duplications are common in meiosis.
  - Homologous chromatids may break and rejoin at incorrect places, such that one chromatid will loose 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 results 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.

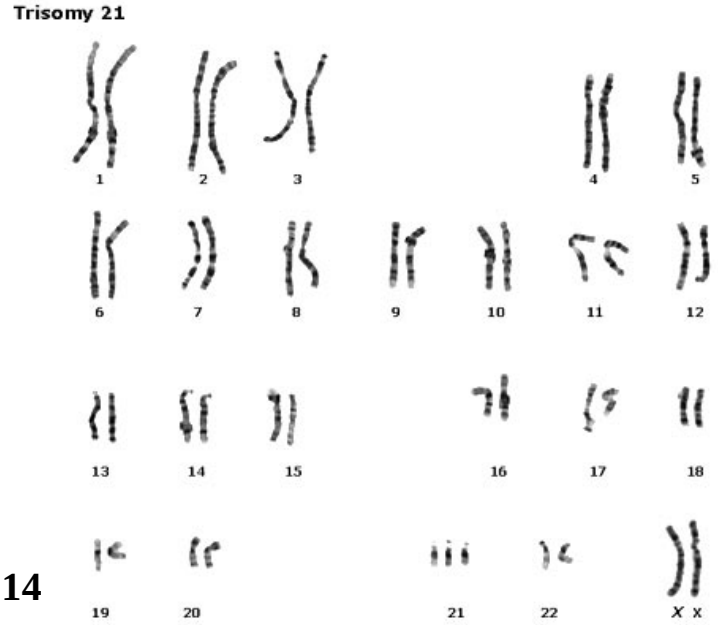

Fig. 15.14

- 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 (enlarged breasts, extra fat), but their intelligence is normal.
- Males with an extra Y chromosome (XYY) tend to be somewhat taller than average and may have developmental disorders (learning disabilities, language disabilities)

- Trisomy X (XXX), which occurs once in every 2000 live births, produces healthy females (1 active X chromosome + 2 Barr bodies) often with developmental disabilities.

- Monosomy X or *Turner's syndrome* (X0), which occurs once in every 5000 births, produces phenotypic, but immature females (symptoms vary).

- 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 developmentally disabled, may have a small head with unusual facial features, and a cry like the mewing of a distressed cat when very young (≤ 2yrs).
  - This syndrome is fatal in ~10% of affected individuals.

- Chromosomal translocations between nonhomologous chromosome 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.

2. 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 reimprinted according to the sex of the individual in which they reside.

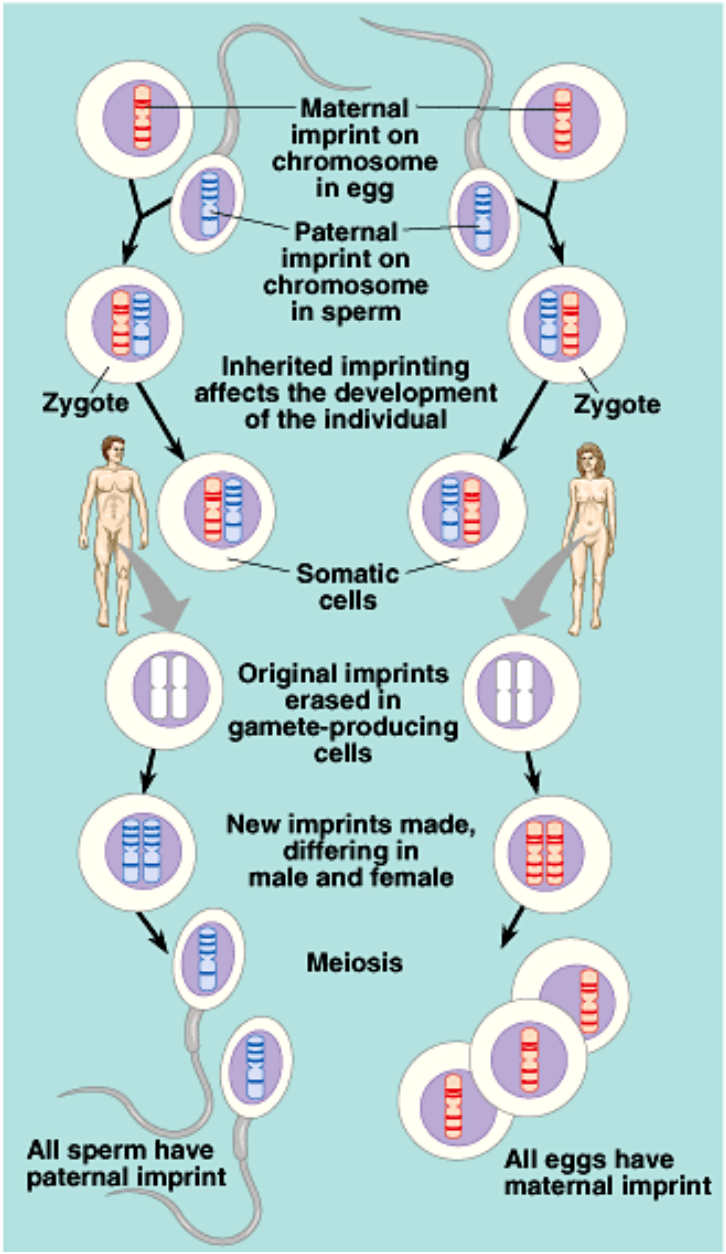

Fig. 15.15

- In many cases, genomic imprinting occurs when methyl groups are added to cytosine nucleotides on one of the alleles.(epigenetic)
  - 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.

3. 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.

- 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.