CHAPTER 14
MENDEL AND THE GENE IDEA

OUTLINE

I. Gregor Mendel's Discoveries
   A. Mendel brought an experimental and quantitative approach to genetics: *science as a process*
   B. By the law of segregation, the two alleles for a character are packaged into separate gametes
   C. By the law of independent assortment, each pair of alleles segregates into gametes independently
   D. Mendelian inheritance reflects rules of probability
   E. Mendel discovered the particulate behavior of genes: *a review*

II. Extending Mendelian Genetics
   A. The relationship between genotype and phenotype is rarely simple

III. Mendelian Inheritance in Humans
   A. Pedigree analysis reveals Mendelian patterns in human inheritance
   B. Many human disorders follow Mendelian patterns of inheritance
   C. Technology is providing new tools for genetic testing and counseling

OBJECTIVES

After reading this chapter and attending lecture, the student should be able to:

1. Describe the favored model of heredity in the 19th century prior to Mendel, and explain how this model was inconsistent with observations.
2. Explain how Mendel's hypothesis of inheritance differed from the blending theory of inheritance.
3. List several features of Mendel's methods that contributed to his success.
4. List four components of Mendel's hypothesis that led him to deduce the law of segregation.
5. State, in their own words, Mendel's law of segregation.
6. Use a Punnett square to predict the results of a monohybrid cross and state the phenotypic and genotypic ratios of the F_2 generation.
7. Distinguish between genotype and phenotype; heterozygous and homozygous; dominant and recessive.
8. Explain how a testcross can be used to determine if a dominant phenotype is homozygous or heterozygous.
9. Define random event, and explain why it is significant that allele segregation during meiosis and fusion of gametes at fertilization are random events.
10. Use the rule of multiplication to calculate the probability that a particular F_2 individual will be homozygous recessive or dominant.

11. Given a Mendelian cross, use the rule of addition to calculate the probability that a particular F_2 individual will be heterozygous.
12. Describe two alternate hypotheses that Mendel considered for how two characters might segregate during gamete formation, and explain how he tested those hypotheses.
13. State, in their own words, Mendel's law of independent assortment.
14. Use a Punnett square to predict the results of a dihybrid cross and state the phenotypic and genotypic ratios of the F_2 generation.
15. Using the laws of probability, predict from a trihybrid cross between two individuals that are heterozygous for all three traits, what expected proportion of the offspring would be:
    a. Homozygous for the three dominant traits
    b. Heterozygous for all three traits
    c. Homozygous recessive for two specific traits and heterozygous for the third
16. Give an example of incomplete dominance and explain why it is not evidence for the blending theory of inheritance.
17. Explain how the phenotypic expression of the heterozygote is affected by complete dominance, incomplete dominance and codominance.
18. Describe the inheritance of the ABO blood system and explain why the I^A and I^B alleles are said to be *codominant*.
19. Define and give examples of pleiotropy.
20. Explain, in their own words, what is meant by "one gene is epistatic to another."
21. Explain how epistasis affects the phenotypic ratio for a dihybrid cross.
22. Describe a simple model for polygenic inheritance, and explain why most polygenic characters are described in quantitative terms.
23. Describe how environmental conditions can influence the phenotypic expression of a character.
24. Given a simple family pedigree, deduce the genotypes for some of the family members.
25. Describe the inheritance and expression of cystic fibrosis, Tay-Sachs disease, and sickle-cell disease.
26. Explain how a lethal recessive gene can be maintained in a population.
27. Explain why consanguinity increases the probability of homozygosity in offspring.
28. Explain why lethal dominant genes are much more rare than lethal recessive genes.
29. Give an example of a late-acting lethal dominant in humans and explain how it can escape elimination.
30. Explain how carrier recognition, fetal testing and newborn screening can be used in genetic screening and counseling.

KEY TERMS

character
trait
true-breeding
hybridization
monohybrid cross
P generation
F_1 generation
F_2 generation
alleles
dominant allele
recessive allele
law of segregation
homozygous
heterozygous
phenotype
genotype
testcross
dihybrid cross
law of independent assortment
incomplete dominance
complete dominance
codominance
multiple alleles
pleiotropy
epistasis
quantitative character
polygenic inheritance
norm of reaction
multifactorial
carriers
cystic fibrosis
Tay-Sachs disease
sickle-cell disease
Huntington's disease

LECTURE NOTES

Listed below are a few suggestions for teaching Mendelian genetics:

1. There is a certain baseline working vocabulary that students need in order to follow your lecture, understand the text and solve problems. It is more economical to recognize this fact and just begin with some "definitions you should know." Once that is done, you can use the terms in context during the lecture and focus attention on the major points rather than on defining terms.
2. Demonstrating how to work a Punnett square and how to solve genetics problems is obviously necessary. But your students will learn best if they actively participate in the process. You can structure opportunities for students to solve problems during lecture and then let them participate in the explanation. If time does not allow this, it is highly recommended that there be an additional recitation or problem-solving session outside of class.
3. After Mendel's laws of segregation and independent assortment have been introduced, it is extremely useful to put up a transparency of meiosis and ask students to identify where in meiosis that segregation and assortment occur. Many students will not make this connection on their own.

I. Gregor Mendel's Discoveries

Based upon their observations from ornamental plant breeding, biologists in the 19th century realized that both parents contribute to the characteristics of offspring. Before Mendel, the favored explanation of heredity was the *blending theory*.

Blending theory of heredity = Pre-Mendelian theory of heredity proposing that hereditary material from each parent mixes in the offspring; once blended like two liquids in solution, the hereditary material is inseparable and the offspring's traits are some intermediate between the parental types. According to this theory:

- Individuals of a population should reach a uniform appearance after many generations.
- Once hereditary traits are blended, they can no longer be separated out to appear again in later generations.

This blending theory of heredity was inconsistent with the observations that:

- Individuals in a population do not reach a uniform appearance; inheritable variation among individuals is generally preserved.
- Some inheritable traits skip one generation only to reappear in the next.

Modern genetics began in the 1860s when Gregor Mendel, an Augustinian monk, discovered the fundamental principles of heredity. Mendel's great contribution to modern genetics was to replace the blending theory of heredity with the *particulate theory of heredity*.

Particulate theory of heredity = Gregor Mendel's theory that parents transmit to their offspring discrete inheritable factors (now called genes) that remain as separate factors from one generation to the next.

A. Mendel brought an experimental and quantitative approach to genetics: *science as a process*

While attending the University of Vienna from 1851-1853, Mendel was influenced by two professors:

- Doppler, a physicist, trained Mendel to apply a *quantitative experimental* approach to the study of natural phenomena.
- Unger, a botanist, interested Mendel in the causes of inheritable variation in plants.

Conclusions: From these types of experiments and observations, Mendel concluded that since the inheritable factor for white flowers was not lost in the F_1 generation, it must have been masked by the presence of the purple-flower factor. Mendel's factors are now called *genes*; and in Mendel's terms, purple flower is the *dominant trait* and white flower is the *recessive trait.*

Mendel repeated these experiments with the other six characters and found similar 3:1 ratios in the F_2 generations (see Campbell, Table 14.1). From these observations he developed a hypothesis that can be divided into four parts:

1. Alternative forms of genes are responsible for variations in inherited characters.
   - For example, the gene for flower color in pea plants exists in two alternative forms; one for purple color and one for white color.
   - Alternative forms for a gene are now called *alleles* (see Campbell, Figure 14.3).
2. For each character, an organism inherits two alleles, one from each parent.
   - Mendel deduced that each parent contributes one "factor," even though he did not know about chromosomes or meiosis.
   - We now know that Mendel's factors are genes. Each genetic locus is represented twice in diploid organisms, which have homologous pairs of chromosomes, one set for each parent. Homologous loci may have identical alleles as in Mendel's true-breeding organisms, or the two alleles may differ, as in the F_1 hybrids.\
3. If the two alleles differ, one is fully expressed (dominant allele); the other is completely masked (recessive allele).
   - Dominant alleles are designated by a capital letter: P = purple flower color.
   - Recessive alleles are designated by a lowercase letter: p = white flower color.
4. The two alleles for each character segregate during gamete production.
   - Without any knowledge of meiosis, Mendel deduced that a sperm cell or ovum carries only one allele for each inherited characteristic, because allele pairs separate (segregate) from each other during gamete production.
   - Gametes of true-breeding plants will all carry the same allele. If different alleles are present in the parent, there is a 50% chance that a gamete will receive the dominant allele, and a 50% chance that it will receive the recessive allele.
   - This sorting of alleles into separate gametes is known as Mendel's law of segregation.

Mendel's law of segregation = Allele pairs segregate during gamete formation (meiosis), and the paired condition is restored by the random fusion of gametes at fertilization (see Campbell, Figure 14.4).

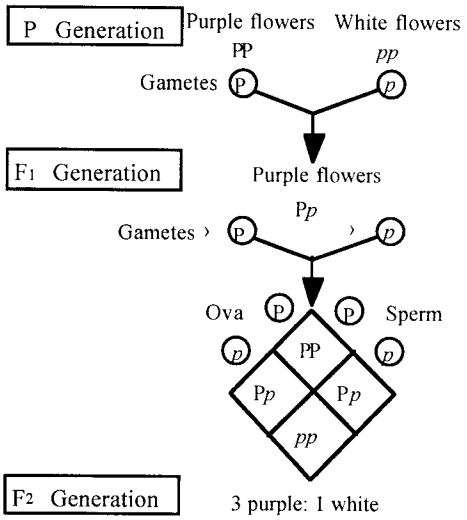
This law predicts the 3:1 ratio observed in the F_2 generation of a monohybrid cross.

- F_1 hybrids (Pp) produce two classes of gametes when allele pairs segregate during gamete formation. Half receive a purple-flower allele (P) and the other half the white-flower allele (p).
- During self-pollination, these two classes of gametes unite randomly. Ova containing purple-flower alleles have equal chances of being fertilized by sperm carrying purple-flower alleles or sperm carrying white-flower alleles.
- Since the same is true for ova containing white-flower alleles, there are four equally likely combinations of sperm and ova.

The combinations resulting from a genetic cross may be predicted by using a *Punnett square.*

The F_2 progeny would include:

- One-fourth of the plants with two alleles for purple flowers.
- One-half of the plants with one allele for purple flowers and one allele for white flowers. Since the purple-flower allele is dominant, these plants have purple flowers.
- One-fourth of the plants with two alleles for white flower color, which will have white flowers since no dominant allele is present.



The pattern of inheritance for all seven of the characteristics studied by Mendel was the same: one parental trait disappeared in the F_1 generation and reappeared in one-fourth of the F_2 generation.

1. Some useful genetic vocabulary

Homozygous = Having two identical alleles for a given trait (e.g., PP or pp).

- All gametes carry that allele.
- Homozygotes are *true-breeding*.

Heterozygous = Having two different alleles for a trait (e.g., Pp).

- Half of the gametes carries one allele (P) and the remaining half carries the other (p).
- Heterozygotes are not true-breeding.

Phenotype = An organism's expressed traits (e.g., purple or white flowers).

- In Mendel's experiment above, the F_2 generation had a 3:1 *phenotypic ratio* of plants with purple flowers to plants with white flowers.

Genotype = An organism's genetic makeup (e.g., PP, Pp, or pp).

- The *genotypic ratio* of the F_2 generation was 1:2:1 (1 PP:2 Pp:1 pp).
- Campbell, Figure 14.5 compares genotype to phenotype.

2. The testcross

Because some alleles are dominant over others, the genotype of an organism may not be apparent. For example:

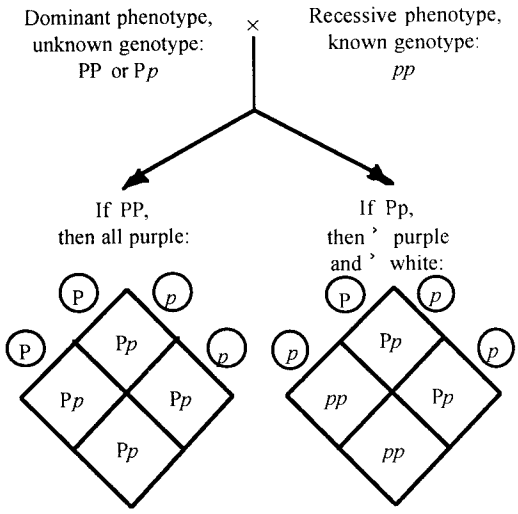
- A pea plant with purple flowers may be either homozygous dominant (PP) or heterozygous (Pp).

To determine whether an organism with a dominant phenotype (e.g., purple flower color) is homozygous dominant or heterozygous, you use a *testcross*.

Testcross = The breeding of an organism of unknown genotype with a homozygous recessive (see also Campbell, Figure 14.6).

- For example, if a cross between a purple-flowered plant of unknown genotype (P___) produced only purple-flowered plants, the parent was probably homozygous dominant since a PP × pp cross produces all purple-flowered progeny that are heterozygous (Pp).

- If the progeny of the testcross contains both purple and white phenotypes, then the purple-flowered parent was heterozygous since a Pp × pp cross produces Pp and pp progeny in a 1:1 ratio.



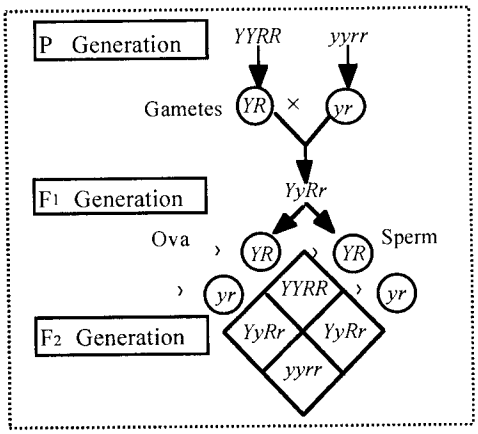
C. By the law of independent assortment, each pair of alleles segregates into gametes independently

Mendel deduced the law of segregation from experiments with *monohybrid crosses*, breeding experiments that used parental varieties differing in a single trait. He then performed crosses between parental varieties that differed in two characters or *dihybrid crosses*.

Dihybrid cross = A mating between parents that are heterozygous for two characters (dihybrids).

- Mendel began his experiments by crossing true-breeding parent plants that differed in two characters such as seed color (yellow or green) and seed shape (round or wrinkled). From previous monohybrid crosses, Mendel knew that yellow seed (Y) was dominant to green (y), and that round (R) was dominant to wrinkled (r).
- Plants homozygous for round yellow seeds (RRYY) were crossed with plants homozygous for wrinkled green seeds (rryy).
- The resulting F_1 dihybrid progeny were heterozygous for both traits (RrYy) and had round yellow seeds, the dominant phenotypes.
- From the F_1 generation, Mendel could not tell if the two characters were inherited independently or not, so he allowed the F_1 progeny to self-pollinate. In the following experiment, Mendel considered two alternate hypotheses (see also Campbell, Figure 14.7):

Hypothesis 1: If the two characters segregate *together*, the F_1 hybrids can only produce the same two classes of gametes (RY and ry) that they received from the parents, and the F_2 progeny will show a 3:1 phenotypic ratio.

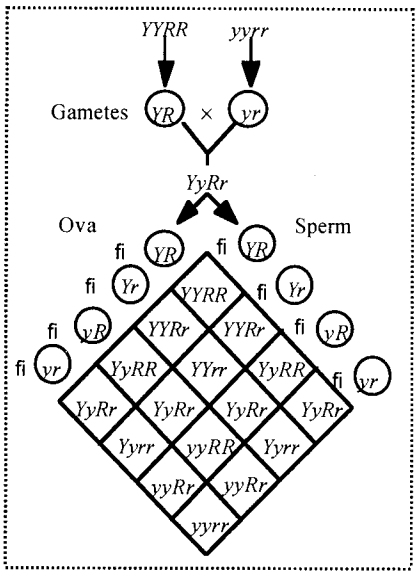


Hypothesis 2: If the two characters segregate *independently*, the F_1 hybrids will produce four classes of gametes (RY, Ry, rY, ry), and the F_2 progeny will show a 9:3:3:1 ratio.

Experiment: Mendel performed a dihybrid cross by allowing self-pollination of the F_1 plants (RrYy × RrYy).

Results: Mendel categorized the F_2 progeny and determined a ratio of 315:108:101:32, which approximates 9:3:3:1.

- These results were repeatable. Mendel performed similar dihybrid crosses with all seven characters in various combinations and found the same 9:3:3:1 ratio in each case.
- He also noted that the ratio for each individual gene pair was 3:1, the same as that for a monohybrid cross.



Conclusions: The experimental results supported the hypothesis that *each allele pair segregates independently during gamete formation.*

This behavior of genes during gamete formation is referred to as *Mendel's law of independent assortment.*

Mendel's law of independent assortment = Each allele pair segregates independently of other gene pairs during gamete formation.

D. Mendelian inheritance reflects rules of probability

Segregation and independent assortment of alleles during gamete formation and fusion of gametes at fertilization are random events. Thus, if we know the genotypes of the parents, we can predict the most likely genotypes of their offspring by using the simple *laws of probability*:

- The probability scale ranges from 0 to 1; an event that is certain to occur has a probability of 1, and an event that is certain *not* to occur has a probability of 0.
- The probabilities of all possible outcomes for an event must add up to 1.
- For example, when tossing a coin or rolling a six-sided die:

Event		Probability
Tossing heads with a two-headed coin	1	1 + 0 = 1
Tossing tails with a two-headed coin	0	
Tossing heads with a normal coin	1/2	1/2 + 1/2 = 1
Tossing tails with a normal coin	1/2	
Rolling 3 on a six-sided die	1/6	1/6 + 5/6 = 1
Rolling a number other than 3	5/6	

Random events are *independent* of one another.

- The outcome of a random event is unaffected by the outcome of previous such events.
- For example, it is possible that five successive tosses of a normal coin will produce five heads; however, the probability of heads on the sixth toss is still 1/2.

Two basic rules of probability are helpful in solving genetics problems: the *rule of multiplication* and the *rule of addition*.

1. Rule of multiplication

Rule of multiplication = The probability that independent events will occur simultaneously is the product of their individual probabilities (see Campbell, Figure 14.8). For example:

Question: In a Mendelian cross between pea plants that are heterozygous for flower color (Pp), what is the probability that the offspring will be homozygous recessive?

Answer:

Probability that an egg from the F1 (Pp) will receive a p allele = 1/2.

Probability that a sperm from the F1 will receive a p allele = 1/2.

The overall probability that two recessive alleles will unite at fertilization: $1/2 \times 1/2 = 1/4$.

This rule also applies to dihybrid crosses. For example:

Question: For a dihybrid cross, YyRr × YyRr, what is the probability of an F_2 plant having the genotype YYRR?

Answer:

Probability that an egg from a YyRr parent will receive the Y and R alleles = $1/2 \times 1/2 = 1/4$.

Probability that a sperm from a YyRr parent will receive a the Y and R alleles = $1/2 \times 1/2 = 1/4$.

The overall probability of an F_2 plant having the genotype YYRR: $1/4 \times 1/4 = \underline{\underline{1/16}}$.

2. Rule of addition

Rule of addition = The probability of an event that can occur in two or more independent ways is the sum of the separate probabilities of the different ways. For example:

Question: In a Mendelian cross between pea plants that are heterozygous for flower color (Pp), what is the probability of the offspring being a heterozygote?

Answer: There are two ways in which a heterozygote may be produced: the dominant allele (P) may be in the egg and the recessive allele (p) in the sperm, or the dominant allele may be in the sperm and the recessive in the egg. Consequently, the probability that the offspring will be heterozygous is the sum of the probabilities of those two possible ways:

Probability that the dominant allele will be in the egg with the recessive in the sperm is $1/2 \times 1/2 = 1/4$.

Probability that the dominant allele will be in the sperm and the recessive in the egg is $1/2 \times 1/2 = 1/4$.

Therefore, the probability that a heterozygous offspring will be produced is $1/4 + 1/4 = \underline{\underline{1/2}}$.

3. Using rules of probability to solve genetics problems

The rules of probability can be used to solve complex genetics problems. For example, Mendel crossed pea varieties that differed in three characters (*trihybrid crosses*).

Question: What is the probability that a trihybrid cross between two organisms with the genotypes AaBbCc and AaBbCc will produce an offspring with the genotype aabbcc?

Answer: Because segregation of each allele pair is an independent event, we can treat this as three separate monohybrid crosses:

Aa × Aa:	probability for aa offspring	=	1/4
Bb × Bb:	probability for bb offspring	=	1/4
Cc × Cc:	probability for cc offspring	=	1/4

The probability that these independent events will occur simultaneously is the product of their independent probabilities (rule of multiplication). So the probability that the offspring will be aabbcc is:

1/4 aa × 1/4 bb × 1/4 cc = 1/64

For another example, consider a trihybrid cross of garden peas, where:

Character	Trait & Genotype
Flower Color	Purple: PP, Pp
	White: pp
Seed Color	Yellow: YY, Yy
	Green: yy
Seed Shape	Round: RR, Rr
	Wrinkled: rr

Question: phenotypes for *at least* two of the three traits?

PpYyRr × Ppyyrr

Answer: First list those genotypes that are homozygous recessive for at least two traits, (note that this includes the homozygous recessive for all three traits). Use the *rule of multiplication* to calculate the probability that offspring would be one of these genotypes. Then use the *rule of addition* to calculate the probability that two of the three traits would be homozygous recessive.

Genotypes with at least two homozygous recessives			Probability of genotype
ppyyRr	1/4 × 1/2 × 1/2	=	1/16
ppYyrr	1/4 × 1/2 × 1/2	=	1/16
Ppyyrr	1/2 × 1/2 × 1/2	=	2/16
PPyyrr	1/4 × 1/2 × 1/2	=	1/16
ppyyrr	1/4 × 1/2 × 1/2	=	1/16
		=	6/16 or 3/8 chance of two recessive traits

D. Mendel discovered the particulate behavior of genes: *a review*

If a seed is planted from the F_2 generation of a monohybrid cross, we cannot predict with absolute certainty that the plant will grow to produce white flowers (pp). We *can* say that there is a 1/4 chance that the plant will have white flowers.

- Stated in statistical terms: among a large sample of F_2 plants, 25% will have white flowers.
- The larger the sample size, the closer the results will conform to predictions.

Mendel's quantitative methods reflect his understanding of this statistical feature of inheritance. Mendel's laws of segregation and independent assortment are based on the premise that:

- Inheritance is a consequence of discrete factors (genes) that are passed on from generation to generation.
- Segregation and assortment are random events and thus obey the simple laws of probability.

II. Extending Mendelian Genetics

A. The relationship between genotype and phenotype is rarely simple

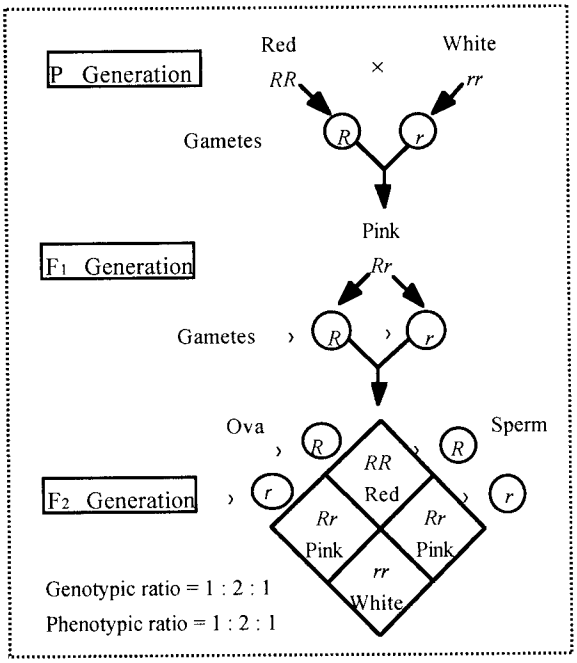
As Mendel described it, characters are determined by one gene with two alleles; one allele completely dominant over the other. There are other patterns of inheritance not described by Mendel, but his laws of segregation and independent assortment can be extended to these more complex cases.

1. Incomplete dominance

In cases of *incomplete dominance*, one allele is not completely dominant over the other, so the heterozygote has a phenotype that is intermediate between the phenotypes of the two homozygotes (see Campbell, Figure 14.9).

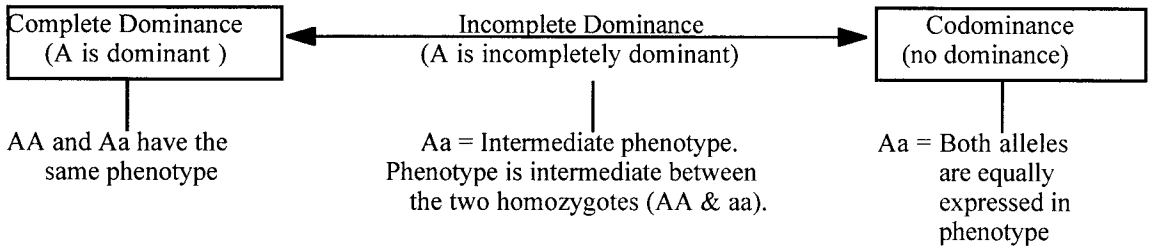
Incomplete dominance = Pattern of inheritance in which the dominant phenotype is not fully expressed in the heterozygote, resulting in a phenotype intermediate between the homozygous dominant and homozygous recessive.

- For example, when red snapdragons (RR) are crossed with white snapdragons (rr), all F_1 hybrids (Rr) have pink flowers. (The heterozygote produces half as much red pigment as the homozygous red-flowered plant.)
- Since the heterozygotes can be distinguished from homozygotes by their phenotypes, the phenotypic and genotypic ratios from a monohybrid cross are the same—1:2:1.
- Incomplete dominance is *not* support for the blending theory of inheritance, because alleles maintain their integrity in the heterozygote and segregate during gamete formation. Red and white phenotypes reappear in the F_2 generation.



2. What is a dominant allele?

Dominance/recessiveness relationships among alleles vary in a continuum from *complete dominance* on one end of the spectrum to *codominance* on the other, with various degrees of incomplete dominance in between these extremes.



Complete dominance = Inheritance characterized by an allele that is fully expressed in the phenotype of a heterozygote and that masks the phenotypic expression of the recessive allele; state in which the phenotypes of the heterozygote and dominant homozygote are indistinguishable.

Codominance = Inheritance characterized by full expression of both alleles in the heterozygote.

- For example, the MN blood-group locus codes for the production of surface glycoproteins on the red blood cell. In this system, there are three blood types: M, N and MN.

Blood Type	Genotype
M	MM
N	NN
MN	MN

- The MN blood type is the result of full phenotypic expression of *both* alleles in the heterozygote; both molecules, M and N, are produced on the red blood cell.

Apparent dominance/recessiveness relationships among alleles reflect the level at which the phenotype is studied. For example:

- *Tay-Sachs disease* is a recessively inherited disease in humans; only children who are homozygous recessive for the Tay-Sachs allele have the disease.
- Brain cells of Tay-Sachs babies lack a crucial lipid-metabolizing enzyme. Thus, lipids accumulate in the brain, causing the disease symptoms and ultimately leading to death.
- At the *organismal level*, since heterozygotes are symptom free, it appears that the normal allele is completely dominant and the Tay-Sachs allele is recessive.
- At the *biochemical level*, inheritance of Tay-Sachs seems to be incomplete dominance of the normal allele, since there is an intermediate phenotype. Heterozygotes have an enzyme activity level that is intermediate between individuals homozygous for the normal allele and individuals with Tay-Sachs disease.
- At the *molecular level*, the normal allele and the Tay-Sachs allele are actually codominant. Heterozygotes produce equal numbers of normal and dysfunctional enzymes. They lack disease symptoms, because half the normal amount of functional enzyme is sufficient to prevent lipid accumulation in the brain.

Dominance/recessiveness relationships among alleles:

- Are a consequence of the mechanism that determines phenotypic expression, not the ability of one allele to subdue another at the level of the DNA
- Do not determine the relative abundance of alleles in a population
  - In other words, dominant alleles are not necessarily more common and recessive alleles more rare.

- For example, the allele for polydactyly is quite rare in the U.S. (1 in 400 births), yet it is caused by a dominant allele. (Polydactyly is the condition of having extra fingers or toes.)

3. Multiple alleles

Some genes may have *multiple alleles*; that is, more than just two alternative forms of a gene. The inheritance of the ABO blood group is an example of a locus with three alleles (see Campbell, Figure 14.10).

Paired combinations of three alleles produce four possible phenotypes:

- Blood type A, B, AB, or O.
- A and B refer to two genetically determined polysaccharides (A and B antigens) which are found on the surface of red blood cells different from the (different from the MN characters).

There are three alleles for this gene: I^A, I^B, and i.

- The I^A allele codes for the production of A antigen, the I^B allele codes for the production of B antigen, and the i allele codes for *no* antigen production on the red blood cell (neither A or B).
- Alleles I^A and I^B are *codominant* since both are expressed in heterozygotes.
- Alleles I^A and I^B are dominant to allele i, which is recessive.
- Even though there are three possible alleles, every person carries only two alleles which specify their ABO blood type; one allele is inherited from each parent.

Since there are three alleles, there are six possible genotypes:

Blood Type	Possible Genotypes	Antigens on the Red Blood Cell	Antibodies in the Serum
A	I^AI^A I^Ai	A	anti-B
B	I^BI^B I^Bi	B	anti-A
AB	I^AI^B	A, B	----
O	ii	----	anti-A anti-B

Foreign antigens usually cause the immune system to respond by producing *antibodies*, globular proteins that bind to the foreign molecules causing a reaction that destroys or inactivates it. In the ABO blood system:

- The antigens are located on the red blood cell and the antibodies are in the serum.
- A person produces antibodies against foreign blood antigens (those not possessed by the individual). These antibodies react with the foreign antigens causing the blood cells to clump or *agglutinate*, which may be lethal.
- For a blood transfusion to be successful, the red blood cell *antigens of the donor* must be compatible with the *antibodies of the recipient.*

4. Pleiotropy

Pleiotropy = The ability of a single gene to have multiple phenotypic effects.

- There are many hereditary diseases in which a single defective gene causes complex sets of symptoms (e.g., sickle-cell anemia).

- One gene can also influence a combination of seemingly unrelated characteristics. For example, in tigers and Siamese cats, the gene that controls fur pigmentation also influences the connections between a cat's eyes and the brain. A defective gene causes both abnormal pigmentation and cross-eye condition.

5. Epistasis

Different genes can interact to control the phenotypic expression of a single trait. In some cases, a gene at one locus alters the phenotypic expression of a second gene, a condition known as *epistasis* (see Campbell, Figure 14.12).

Epistasis = (Epi=upon; stasis=standing) Interaction between two nonallelic genes in which one modifies the phenotypic expression of the other.

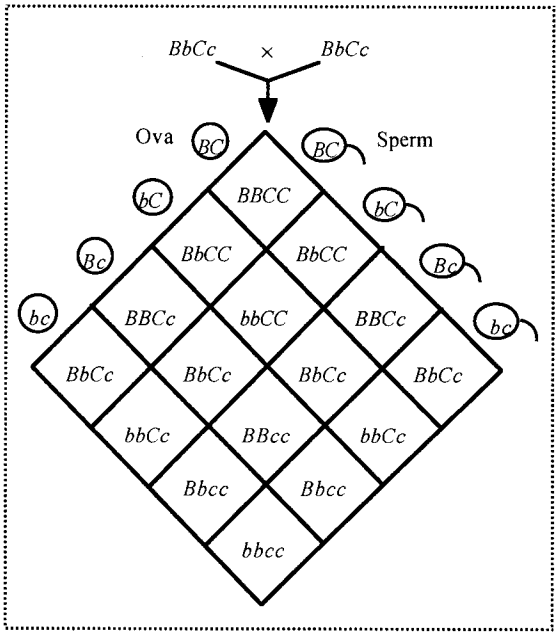
- If one gene suppresses the phenotypic expression of another, the first gene is said to be *epistatic* to the second.
- If epistasis occurs between two nonallelic genes, the phenotypic ratio resulting from a dihybrid cross will deviate from the 9:3:3:1 Mendelian ratio.
- For example, in mice and other rodents, the gene for pigment deposition (C) is epistatic to the gene for pigment (melanin) production. In other words, whether the pigment can be deposited in the fur determines whether the coat color can be expressed. Homozygous recessive for pigment deposition (cc) will result in an albino mouse regardless of the genotype at the black/brown locus (BB, Bb or bb):

  CC, Cc = Melanin deposition

  cc = Albino

  BB, Bb = Black coat color

  bb = Brown coat color



- Even though both genes affect the same character (coat color), they are inherited separately and will assort independently during gamete formation. A cross between black mice that are heterozygous for the two genes results in a 9:3:4 phenotypic ratio:

  9 Black (B_C_)

  3 Brown (bbC_)

  4 Albino (_cc)

6. Polygenic inheritance

Mendel's characters could be classified on an either-or basis, such as purple versus white flower. Many characters, however, are *quantitative characters* that vary in a continuum within a population.

Quantitative characters = Characters that vary by degree in a continuous distribution rather than by discrete (either-or) qualitative differences.

- Usually, continuous variation is determined not by one, but by many segregating loci or *polygenic inheritance*.

Polygenic inheritance = Mode of inheritance in which the additive effect of two or more genes determines a single phenotypic character.

For example, skin pigmentation in humans appears to be controlled by at least three separately inherited genes. The following is a simplified model for the polygenic inheritance of skin color:

- Three genes with the dark-skin allele (*A*, *B*, *C*) contribute one "unit" of darkness to the phenotype. These alleles are incompletely dominant over the other alleles (*a*, *b*, *c*).
- An *AABBCC* person would be very dark and an aabbcc person would be very light.
- An *AaBbCc* person would have skin of an intermediate shade.
- Because the alleles have a cumulative effect, genotypes *AaBbCc* and *AABbcc* make the same genetic contribution (three "units") to skin darkness. (See Campbell, Figure 14.12)
- Environmental factors, such as sun exposure, could also affect the phenotype.

7. Nature versus nurture: the environmental impact on phenotype

Environmental conditions can influence the phenotypic expression of a gene, so that a single genotype may produce a range of phenotypes. This environmentally-induced phenotypic range is the *norm of reaction* for the genotype.

Norm of reaction = Range of phenotypic variability produced by a single genotype under various environmental conditions (see Campbell, Figure 14.13). Norms of reaction for a genotype:

- May be quite limited, so that a genotype only produces a specific phenotype, such as the blood group locus that determines ABO blood type.
- May also include a wide range of possibilities. For example, an individual's blood cell count varies with environmental factors such as altitude, activity level or infection.
- Are generally broadest for polygenic characters, including behavioral traits.

The expression of most polygenic traits, such as skin color, is *multifactorial*; that is, it depends upon many factors - a variety of possible genotypes, as well as a variety of environmental influences.

8. Integrating a Mendelian view of heredity and variation

These patterns of inheritance that are departures from Mendel's original description, can be integrated into a comprehensive theory of Mendelian genetics.

- Taking a holistic view, an organism's entire phenotype reflects its overall genotype and unique environmental history.
- Mendelism has broad applications beyond its original scope; extending the principles of segregation and independent assortment helps explain more complex hereditary patterns such as epistasis and quantitative characters.

III. Mendalian Inheritance in Humans

A. Pedigree analysis reveals Mendelian patterns in human inheritance

Mendelian inheritance in humans is difficult to study because:

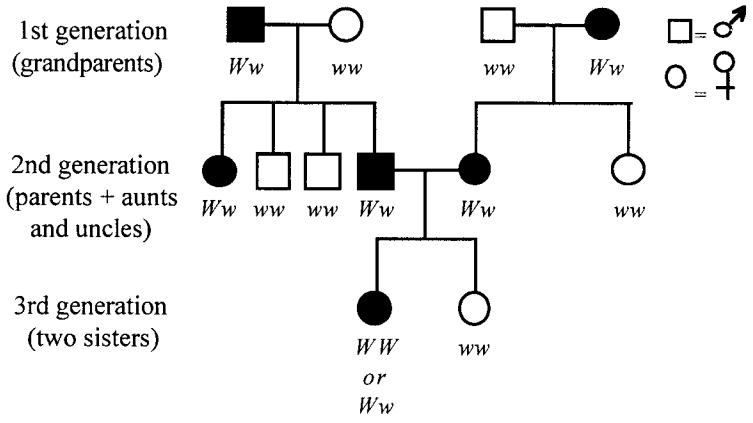
- The human generation time is about 20 years.
- Humans produce relatively few offspring compared to most other species.
- Well-planned breeding experiments are impossible.

Our understanding of Mendelian inheritance in humans is based on the analysis of family pedigrees or the results of matings that have already occurred.

Pedigree = A family tree that diagrams the relationships among parents and children across generations and that shows the inheritance pattern of a particular phenotypic character (see Campbell, Figure 14.14). By convention:

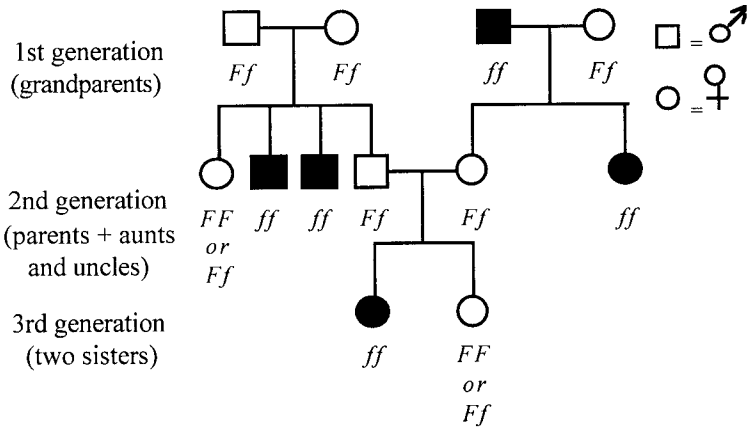
- Squares symbolize males and circles represent females.
- A horizontal line connecting a male and female indicates a mating; offspring are listed below in birth order, from left to right.
- Shaded symbols indicate individuals showing the trait being traced.

Following a dominant trait. For example, family members' genotypes can be deduced from a pedigree that traces the occurrence of widow's peak, the expression of a dominant allele.



- If a widow's peak results from a dominant allele, *W*, then all individuals that do not have a widow's peak hairline must be homozygous recessive (*ww*). The genotypes of all recessives can be written on the pedigree.
- If widow's peak results from a dominant allele, W, then individuals that have a widow's peak hairline must be either homozygous dominant (*WW*) or heterozygous (*Ww*).
- If only some of the second generation offspring have a widow's peak, then the grandparents that show the trait must be heterozygous (*Ww*). (Note: if the grandparents with widow's peak were homozygous dominant, then all their respective offspring would show the trait.)
- Second generation offspring with widow's peaks must be heterozygous, because they are the result of *Ww* × *ww* matings.
- The third generation sister with widow's peak may be either homozygous dominant (*WW*) or heterozygous (*Ww*), because her parents are both heterozygous.

Following a recessive trait. For example, the same family can be used to trace a recessive trait such as attached ear lobes.



- If attached earlobes is due to a recessive allele (*f*), then all individuals with attached earlobes must be homozygous recessive (*ff*).
- Since attached earlobes appears in second generation offspring, the grandparents with free earlobes are heterozygous (*Ff*) since they must be capable of passing on a recessive allele (*f*).
- Since one of the third generation sisters has attached earlobes (ff), her parents are heterozygous; they have free earlobes (dominant trait) and yet must be able to contribute a recessive allele to their daughter. The other sister shows the dominant trait, so her genotype is unknown; it is possible that she may be either homozygous dominant or heterozygous.

Pedigree analysis can also be used to:

- Deduce whether a trait is determined by a recessive or dominant allele. Using the example above:
  - The first-born third generation daughter has attached earlobes. Since both parents *lack* the trait, it must not be determined by a dominant allele.
- Predict the occurrence of a trait in future generations. For example, if the second generation couple decide to have another child,
  - What is the probability the child will have a widow's peak? From a mating of *Ww* × *Ww*:

    Probability of a child being *WW* = 1/4
    Probability of a child being *Ww* = 2/4
    Probability of widow's peak = 3/4
  - What is the probability the child will have attached earlobes? From a mating of *Ff* × *Ff*:

    probability of a child being *ff* = 1/4
  - What is the probability the child will have a widow's peak and attached earlobes? From a cross of *WwFf* × *WwFf*, use the rule of multiplication:

    3/4 (probability of widow's peak) × 1/4 (probability of attached earlobes) = 3/16

This type of analysis is important to geneticists and physicians, especially when the trait being analyzed can lead to a disabling or lethal disorder.

B. Many human disorders follow Mendelian patterns of inheritance

1. Recessively inherited disorders

Recessive alleles that cause human disorders are usually defective versions of normal alleles.

- Defective alleles code for either a malfunctional protein or no protein at all.
- Heterozygotes can be phenotypically normal, if one copy of the normal allele is all that is needed to produce sufficient quantities of the specific protein.

Recessively inherited disorders range in severity from nonlethal traits (e.g., albinism) to lethal diseases (e.g., cystic fibrosis). Since these disorders are caused by recessive alleles:

- The phenotypes are expressed only in homozygotes (aa) who inherit one recessive allele from each parent.
- Heterozygotes (Aa) can be phenotypically normal and act as *carriers*, possibly transmitting the recessive allele to their offspring.

Most people with recessive disorders are born to normal parents, both of whom are carriers.

- The probability is 1/4 that a mating of two carriers (Aa × Aa) will produce a homozygous recessive zygote.
- The probability is 2/3 that a normal child from such a mating will be a heterozygote, or a carrier.

Human genetic disorders are not usually evenly distributed among all racial and cultural groups due to the different genetic histories of the world's people. Three examples of such recessively inherited disorders are *cystic fibrosis*, *Tay-Sachs disease* and *sickle-cell disease*.

Cystic fibrosis, the most common lethal genetic disease in the United States, strikes 1 in every 2,500 Caucasians (it is much rarer in other races).

- Four percent of the Caucasian population are carriers.
- The dominant allele codes for a membrane protein that controls chloride traffic across the cell membrane. Chloride channels are defective or absent in individuals that are homozygous recessive for the cystic fibrosis allele.
- Disease symptoms result from the accumulation of thickened mucus in the pancreas, intestinal tract and lungs, a condition that favors bacterial infections.

Tay-Sachs disease occurs in 1 out of 3,600 births. The incidence is about 100 times higher among Ashkenazic (central European) Jews than among Sephardic (Mediterranean) Jews and non-Jews.

- Brain cells of babies with this disease are unable to metabolize gangliosides (a type of lipid), because a crucial enzyme does not function properly.
- As lipids accumulate in the brain, the infant begins to suffer seizures, blindness and degeneration of motor and mental performance. The child usually dies after a few years.

Sickle-cell disease is the most common inherited disease among African Americans. It affects 1 in 400 African Americans born in the United States (see Campbell, Figure 14.15).

- The disease is caused by a single amino acid substitution in hemoglobin.
- The abnormal hemoglobin molecules tend to link together and crystallize, especially when blood oxygen content is lower than normal. This causes red blood cells to deform from the normal disk-shape to a sickle-shape.

- The sickled cells clog tiny blood vessels, causing the pain and fever characteristic of a sickle-cell crisis.

About 1 in 10 African Americans are heterozygous for the sickle-cell allele and are said to have the *sickle-cell trait.*

- These carriers are usually healthy, although some suffer symptoms after an extended period of low blood oxygen levels.
- Carriers can function normally because the two alleles are codominant (heterozygotes produce not only the abnormal hemoglobin but also normal hemoglobin).
- The high incidence of heterozygotes is related to the fact that in tropical Africa where malaria is endemic, heterozygotes have enhanced resistance to malaria compared to normal homozygotes. Thus, heterozygotes have an advantage over both homozygotesÑthose who have sickle cell disease and those who have normal hemoglobin.

The probability of inheriting the same rare harmful allele from both parents, is greater if the parents are closely related.

Consanguinity = A genetic relationship that results from shared ancestry

- The probability is higher that consanguinous matings will result in homozygotes for harmful recessives, since parents with recently shared ancestry are more likely to inherit the same recessive alleles than unrelated persons.
- It is difficult to accurately assess the extent to which human consanguinity increases the incidence of inherited diseases, because embryos homozygous for deleterious mutations are affected so severely that most are spontaneously aborted before birth.
- Most cultures forbid marriage between closely related adults. This may be the result of observations that stillbirths and birth defects are more common when parents are closely related.

2. Dominantly inherited disorders

Some human disorders are dominantly inherited.

- For example, *achondroplasia* (a type of dwarfism) affects 1 in 10,000 people who are heterozygous for this gene.
- Homozygous dominant condition results in spontaneous abortion of the fetus, and homozygous recessives are of normal phenotype (99.9% of the population).

Lethal dominant alleles are much rarer than lethal recessives, because they:

- Are always expressed, so their effects are not masked in heterozygotes.
- Usually result from new genetic mutations that occur in gametes and later kill the developing embryo.

Late-acting lethal dominants can escape elimination if the disorder does not appear until an advanced age after afflicted individuals may have transmitted the lethal gene to their children. For example,

- *Huntington's disease*, a degenerative disease of the nervous system, is caused by a late-acting lethal dominant allele. The phenotypic effects do not appear until 35 to 40 years of age. It is irreversible and lethal once the deterioration of the nervous system begins.
- Molecular geneticists have recently located the gene for Huntington's near the tip of chromosome #4.
- Children of an afflicted parent have a 50% chance of inheriting the lethal dominant allele. A newly developed test can detect the Huntington's allele before disease symptoms appear.

3. Multifactorial disorders

Not all hereditary diseases are simple Mendelian disorders; that is, diseases caused by the inheritance of certain alleles at a single locus. More commonly, people are afflicted by *multifactorial* disorders, diseases that have both genetic and environmental influences.

- Examples include heart disease, diabetes, cancer, alcoholism and some forms of mental illness.
- The hereditary component is often polygenic and poorly understood.
- The best public-health strategy is to educate people about the role of environmental and behavioral factors that influence the development of these diseases.

C. Technology is providing new tools for genetic testing and counseling

Genetic counselors in many hospitals can provide information to prospective parents concerned about a family history for a genetic disorder.

- This preventative approach involves assessing the risk that a particular genetic disorder will occur.
- Risk assessment includes studying the family history for the disease using Mendel's law of segregation to deduce the risk.

For example, a couple is planning to have a child, and both the man and woman had siblings who died from the same recessively inherited disorder. A genetic counselor could deduce the risk of their first child inheriting the disease by using the laws of probability:

Question: What is the probability that the husband and wife are each carriers?

Answer: The genotypic ratio from an Aa × Aa cross is 1 AA:2 Aa:1 aa. Since the parents are normal, they have a 2/3 of being carriers.

Question: What is the chance of two carriers having a child with the disease?

Answer: 1/2 (mother's chance of passing on the gene) × 1/2 (father's chance of passing on the gene) = 1/4

Question: What is the probability that their firstborn will have the disorder?

Answer: (Chance that the father is a carrier) × (chance that mother is a carrier) × (chance of two carriers having a child with the disease).

$2/3 \times 2/3 \times 1/4 = 1/9$

If the first child is born with the disease, what is the probability that the second child will inherit the disease?

- If the first child is born with the disease, then it is certain that both the man and the woman are carriers. Thus, the probability that other children produced by this couple will have the disease is 1/4.
- The conception of each child is an independent event, because the genotype of one child does not influence the genotype of the other children. So there is a 1/4 chance that any additional child will inherit the disease.

1. Carrier recognition

Several tests are available to determine if prospective parents are carriers of genetic disorders.

- Tests are currently available that can determine heterozygous carriers for the Tay-Sachs allele, cystic fibrosis, and sickle-cell disease.
- Tests such as these enable people to make informed decisions about having children, but they could also be abused. Ethical dilemmas about how this information should be used points to the immense social implications of such technological advances.

2. **Fetal testing**

A couple that learns they are both carriers for a genetic disease and decide to have a child can determine if the fetus has the disease. Between the fourteenth and sixteenth weeks of pregnancy, *amniocentesis*. can be done to remove amniotic fluid for testing (see Campbell, Figure 14.17).

- During amniocentesis, a physician inserts a needle into the uterus and extracts about ten milliliters of amniotic fluid.
- The presence of certain chemicals in amniotic fluid indicate some genetic disorders.
- Some tests (including one for Tay-Sachs) are performed on cells grown in culture from fetal cells sloughed off in the amniotic fluid. These cells can also be karyotyped to identify chromosomal defects.

Chorionic villus sampling (CVS) is a newer technique during which a physician suctions off a small amount of fetal tissue from the chorionic villi of the placenta.

- These rapidly dividing embryonic cells can be karyotyped immediately, usually providing results in 24 hoursÑa major advantage over amniocentesis which may take several weeks. (Amniocentesis requires that the cells must first be cultured before karyotyping can be done.)
- Another advantage of CVS is that it can be performed at only eight to ten weeks of pregnancy.

Other techniques such as *ultrasound* and *fetoscopy* allow physicians to examine a fetus for major abnormalities.

- Ultrasound is a non-invasive procedure which uses sound waves to create an image of the fetus.
- Fetoscopy involves inserting a thin fiber-optic scope into the uterus.

Amniocentesis and fetoscopy have a 1% risk of complication such as maternal bleeding or fetal death. Thus, they are used only when risk of genetic disorder or birth defect is relatively high.

3. **Newborn screening**

In most U.S. hospitals, simple tests are routinely performed at birth, to detect genetic disorders such as *phenylketonuria* (PKU).

- PKU is recessively inherited and occurs in about 1 in 15,000 births in the United States.
- Children with this disease cannot properly break down the amino acid phenylalanine.
- Phenylalanine and its by-product (phenylpyruvic acid) can accumulate in the blood to toxic levels, causing mental retardation.
- Fetal screening for PKU can detect the deficiency in a newborn and retardation can be prevented with a special diet (low in phenylalanine) that allows normal development.

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