Genes and the Environment Mold Traits

› Polygenic Traits Are Continuously Varying

- For a polygenic trait, the combined action of many genes often produces a "shades of grey" or "continuously varying" phenotype, also called a **quantitative trait**. DNA sequences that contribute to polygenic traits are called **quantitative trait loci,** or **QTLs**.
- A multifactorial trait is continuously varying if it is also polygenic. That is, it is the multi-gene component of the trait that contributes the continuing variation of the phenotype. The individual genes that confer a polygenic trait follow Mendel's laws, but together they do not produce single-gene phenotypic ratios. They all contribute to the phenotype, but without being dominant or recessive to each other. Single-gene traits are instead discrete or qualitative, often providing an "all-or-none" phenotype such as "normal" versus "affected."
- A polygenic trait varies in populations, as our many nuances of hair color, body weight, and cholesterol levels demonstrate. Some genes contribute more to a polygenic trait than others.
- Within genes, alleles can have differing impacts depending upon exactly how they alter an encoded protein and how common they are in a population. For example, a mutation in the LDL receptor gene greatly raises blood serum cholesterol level. But because fewer than 1 percent of the individuals in most populations have this mutation, it contributes very little to the variation in cholesterol level at the population level. However, the mutation has a large impact on the person who has it.
- Although the expression of a polygenic trait is continuous, we can categorize individuals into classes and calculate the frequencies of the classes. When we do this and plot the frequency for each phenotype class, a bell-shaped curve results.

Even when different numbers of genes affect the trait, the curve takes the same shape, as the following examples show:

Fingerprint Patterns

- The skin on the fingertips is folded into patterns of raised skin called dermal ridges that align to form loops, whorls, and arches. This pattern is a fingerprint. A technique called dermatoglyphics ("skin writing") compares the number of ridges that comprise these patterns to identify and distinguish individuals (figure **1)**.
- **Dermatoglyphics** is part of genetics because certain disorders (such as Down syndrome) include unusual ridge patterns. Forensic fingerprint analysis is also an application of dermatoglyphics.

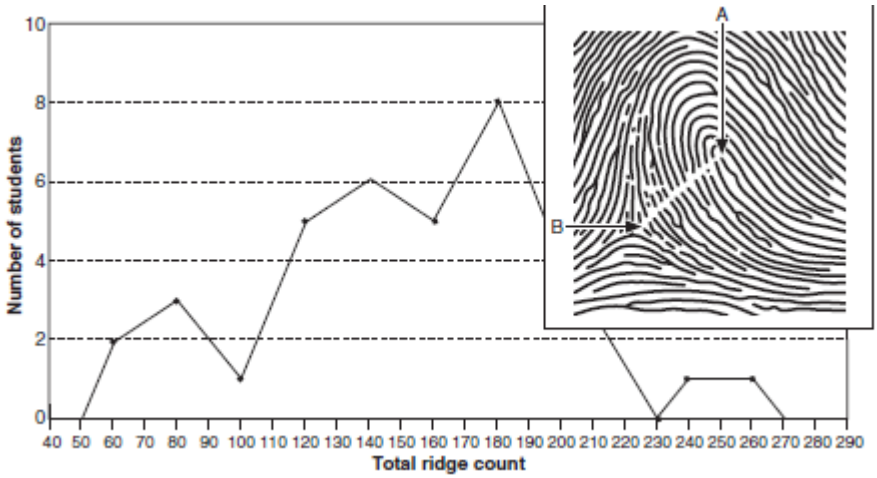

Figure 1 Anatomy of a fingerprint. Total ridge counts for a number of individuals, plotted on a bar graph, form an approximate bell-shaped curve. The number of ridges between landmark points A and B on this loop pattern is 12. Total ridge count includes the number of ridges on all fingers.

- Genes largely determine the number of ridges in a fingerprint, but the environment can affect them too. During weeks 6 through 13 of prenatal development, the ridge pattern can be altered as the fetus touches the finger and toe pads to the wall of the amniotic sac. This early environmental effect explains why the fingerprints of identical twins, who share all genes, are in some cases not exactly alike.
- We quantify a fingerprint with a measurement called a **total ridge count**, which tallies the numbers of ridges in whorls, loops, or arches. The average total ridge count in a male is 145, and in a female, 126. Plotting total ridge count reveals the bell curve of a continuously varying trait.

Methods to Investigate Multifactorial Traits

Predicting recurrence risks for polygenic traits is much more challenging than doing so for single-gene traits. Researchers use several strategies to investigate these traits.

Empiric Risk

- Using Mendel's laws, it is possible to predict the risk that a single-gene trait will recur in a family from knowing the mode of inheritance—such as autosomal dominant or recessive.
- To predict the chance that a polygenic multifactorial trait will occur in a particular individual, geneticists use **empiric risk,** which is based on incidence in a specific population. **Incidence** is the rate at which a certain event occurs, such as the number of new cases of a disorder diagnosed per year in a population of known size.
- **Prevalence** is the proportion or number of individuals in a population who have a particular disorder at a specific time, such as during one year.
- Empiric risk is not a calculation, but a population statistic based on **observation**. The population might be broad, such as an ethnic group or community, or genetically more well defined, such as families that have **cystic fibrosis**. Empiric risk increases with the severity of the disorder, the number of affected family members, and how closely related a person is to affected individuals.
- **For example**, empiric risk is used to predict the likelihood of a child being born with a neural tube defect (NTD). In the United States, the overall population risk of carrying a fetus with an NTD is about 1 in 1,000 (0.1 percent). For people of English, Irish, or Scottish ancestry, the risk is about 3 in 1,000.
- However, if a sibling has an NTD, for any ethnic group, the risk of recurrence increases to 3 percent, and if two siblings are affected, the risk to a third child is even greater.
- If a trait has an inherited component, then it makes sense that the closer the relationship between two individuals, one of whom has the trait, the greater the

probability that the second individual has the trait, too, because they share more genes. Studies of empiric risk support this logic.

- Because empiric risk is based solely on observation, it is useful to derive risks for disorders with poorly understood transmission patterns. For example, certain multifactorial disorders affect one sex more often than the other. Pyloric stenosis, an overgrowth of muscle at the juncture between the stomach and the small intestine, is five times more common among males than females.
- The condition must be corrected surgically shortly after birth, or the newborn will be unable to digest foods. Empiric data show that the risk of recurrence for the brother of an affected brother is 3.8 percent, but the risk for the brother of an affected sister is 9.2 percent. An empiric risk, then, is based on real-world observations. The cause of the illness need not be known.

Heritability

- **Charles Darwin** noted that some of the variation of a trait is due to inborn differences in populations, and some to differences in environmental influences.
- A measurement called **heritability,** designated H, estimates the proportion of the phenotypic variation for a trait that is due to genetic differences in a certain population at a certain time. The distinction between empiric risk and heritability is that empiric risk could result from nongenetic influences, whereas heritability focuses on the genetic component of the variation in a trait. Heritability refers to the degree of *variation* in a trait due to genetics, and not to the proportion of the trait itself attributed to genes.
- **Figure 7.6** outlines the factors that contribute to observed variation in a trait.

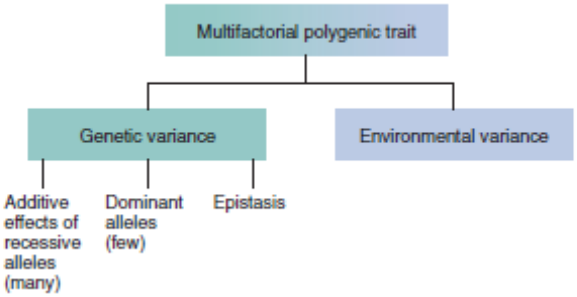

Figure 7.6 Heritability estimates the genetic contribution to the variability of a trait. Observed variance in a polygenic, multifactorial trait or illness reflects genetic and environmental contributions.

- Heritability equals 1.0 for a trait whose variability is completely the result of gene action, such as in a population of laboratory mice who share the same environment. Without environmental variability, genetic differences alone determine expression of the trait in the population. Variability of most traits, however, is due to differences among genes and environmental components.

- Heritability changes as the environment changes. For example, the heritability of skin color is higher in the winter months, when sun exposure is less likely to increase melanin synthesis. The same trait may be highly heritable in two populations, but certain variants much more common in one group due to long-term environmental differences. Populations in equatorial Africa, for example, have darker skin than sundeprived Scandinavians.

- Researchers use several statistical methods to estimate heritability. One way is to compare the actual proportion of pairs of people related in a certain manner who share a particular trait, to the expected proportion of pairs that would share it if it were inherited in a Mendelian fashion.

- The expected proportion is derived by knowing the blood relationships of the individuals and using a measurement called the **coefficient of relatedness,** which is

the proportion of genes that two people related in a certain way share A parent and child share 50 percent of their genes, because of the mechanism of meiosis.

- Siblings share on average 50 percent of their genes, because they have a 50 percent chance of inheriting each allele for a gene from each parent.

- Genetic counselors use the designations of primary (1 °), secondary (2 °), and tertiary (3 °) relatives when calculating risks (**figure 3)**.
- For extended or complicated pedigrees, the value of 1 in 2 or 50 percent between siblings and between parent-child pairs can be used to trace and calculate the percentage of genes shared between people related in other ways.

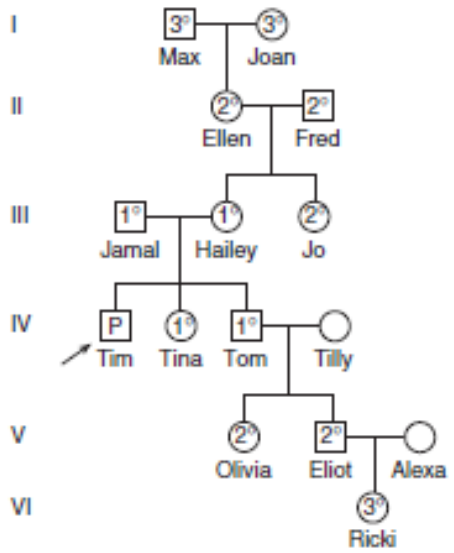

Figure 3 Tracing relatives. Tim has an inherited illness. A genetic counselor drew this pedigree to explain the approximate percentage of genes Tim shares with relatives. This information can be used to alert certain relatives to their risks.

- If the heritability of a trait is very high, then of a group of 100 sibling pairs, nearly 50 would be expected to have the same phenotype, because siblings share on average 50 percent of their genes.
- Height is a trait for which heritability reflects the environmental influence of nutrition.

- Of 100 sibling pairs in a population, for example, 40 might be the same number of inches tall. Heritability for height among this group of sibling pairs is 0.40/0.50, or 80 percent, which is the observed phenotypic variation divided by the expected phenotypic variation if environment had no influence.

("P" is the proband, or affected individual who initiated the study. See **table 7.3** for definitions of 1 ° , 2 ° , and 3 ° relationships.)

Table 7.3 Coefficient of Relatedness for Pairs of Relatives

Relationship	Degree of Relationship	Percent Shared Genes (Coefficient of Relatedness)
Sibling to sibling	1°	50% (1/2)
Parent to child	1°	50% (1/2)
Uncle/aunt to niece/ nephew	2°	25% (1/4)
Grandparent to grandchild	2°	25% (1/4)
First cousin to first cousin	3°	12 1/2% (1/8)

- Genetic variance for a polygenic trait is mostly due to the additive effects of recessive alleles of different genes. For some traits, a few dominant alleles can greatly influence the phenotype, but because they are rare, they do not contribute greatly to heritability.
- This is the case for heart disease caused by a faulty LDL receptor. Heritabilities for some traits or diseases may be underestimates if only mutations that change DNA base sequences are compared, and not also copy number variants (CNVs, which are differences in the numbers of copies of a DNA sequence).
- Epistasis (interaction between alleles of different genes) can also influence heritability. To account for the fact that different genes affect a phenotype to differing degrees, geneticists calculate a "narrow" heritability that considers only additive recessive effects, and a "broad" heritability that also considers the effects of rare dominant alleles and epistasis.

- For LDL cholesterol level, for example, the narrow heritability is 0.36, but the broad heritability is 0.96, reflecting the fact that a rare dominant allele has a large impact.
- Understanding multifactorial inheritance is important in agriculture. A breeder needs to know whether genetic or environmental influences contribute to variability in such traits as birth weight, milk yield, and egg hatchability. It is also valuable to know whether the genetic influences are additive or epistatic.
- The breeder can control the environment by adjusting the conditions under which animals are raised and crops grown, and control genetic effects by setting up crosses between particular individuals.
- Studying multifactorial traits in humans is difficult, because information must be obtained from many families. Two special types of people, however, can help geneticists to tease apart the genetic and environmental components of the variability of multifactorial traits—adopted individuals and twins.

Adopted Individuals

- An adopted person typically shares environmental influences, but not many gene variants, with the adoptive family. Conversely, adopted individuals share genes, but not the exact environment, with their biological parents.
- Therefore, biologists assume that similarities between adopted people and adoptive parents reflect mostly environmental influences, whereas similarities between adoptees and their biological parents reflect mostly genetic influences. Information on both sets of parents can reveal how heredity and the environment contribute to a trait.
- Many early adoption studies used a database of all adopted children in Denmark and their families from 1924 to 1947.
- One study examined correlations between causes of death among biological and adoptive parents and adopted children. If a biological parent died of infection before age 50, the child he or she gave up for adoption was five times more likely to die of infection at a young age than a similar person in the general population.
- This may be because inherited variants in immune system genes increase susceptibility to certain infections. In support of this hypothesis, the risk that an adopted individual would die young from infection did not correlate with adoptive parents' death from infection before age 50.
- Researchers concluded that genetics mostly determines length of life, but they did find evidence of environmental influences. For example, if adoptive parents died before age 50 of cardiovascular disease, their adopted children were three times as likely to die of heart and blood vessel disease as a person in the general population.

Twins

- Studies that use twins to separate the genetic from the environmental contribution to a phenotype provide more meaningful information than studying adopted individuals.
- Using twins to study genetic influence on traits dates to 1924, when German dermatologist **Hermann Siemens** reported that grades and teachers' comments were much more alike for identical twins than for fraternal twins. He proposed that genes contribute to **intelligence based on this observation.**
- A trait that occurs more frequently in both members of identical (**monozygotic or MZ**) twin pairs than in both members of fraternal (**dizygotic or DZ**) twin pairs is at least partly controlled by heredity.
- Geneticists calculate the **concordance** of a trait as the percentage of pairs in which both twins express the trait among pairs of twins in whom at least one has the trait.
- Twins who differ in a trait are said to be discordant for it.
- In one study, 142 MZ twin pairs and 142 DZ twin pairs took a "distorted tunes test," in which 26 familiar songs were played, each with at least one note altered. A person was considered "tune deaf" if he or she failed to detect the mistakes in three or more tunes.
- Concordance for "tune deafness" was 67 % for MZ twins, but only 44 % for DZ twins, indicating a considerable inherited component in the ability to accurately perceive musical pitch.
- **Table :** compares twin types for a variety of hard-to-measure traits.

Table 7.4 Concordance Values for Some Traits in Twins

Trait	MZ (Identical) Twins	DZ (Fraternal) Twins
Acne	14%	14%
Alzheimer disease	78%	39%
Anorexia nervosa	55%	7%
Autism	90%	4.5%
Bipolar disorder	33–80%	0–8%
Cleft lip with or without cleft palate	40%	3–6%
Hypertension	62%	48%
Schizophrenia	40–50%	10%

- Diseases caused by single genes that approach 100 % penetrance, whether dominant or recessive, also approach 100 % concordance in MZ twins.
- That is, if one identical twin has the disease, so does the other. However, among DZ twins, concordance generally is 50 % for a dominant trait and 25 % for a recessive trait. These are the Mendelian values that apply to any two non-twin siblings. For a polygenic trait with little environmental input, concordance values for MZ twins are significantly greater than for DZ twins.
- A trait molded mostly by the environment exhibits similar concordance values for both types of twins.
- Comparing twin types assumes that both types of twins share similar experiences. In fact, MZ twins are often closer emotionally than DZ twins. This discrepancy between the closeness of the two types of twins can lead to misleading results.
- A study from the 1940s, for example, concluded that **tuberculosis** is inherited because concordance among MZ twins was higher than among DZ twins. Actually, the infectious disease more readily passed between MZ twins because their parents kept them closer. However, we do inherit susceptibilities to some infectious diseases. MZ twins would share such genes, whereas DZ twins would only be as likely as any sibling pairs to do so.
- A more informative way to assess the genetic component of a multifactorial trait is to study MZ twins who were separated at birth, then raised in very different environments.
- Much of the work using this "twins reared apart" approach has taken place at the University of Minnesota. Here, since 1987, thousands of sets of twins and triplets who were separated at birth have visited the laboratories of Thomas Bouchard. For a week or more, the twins and triplets are tested for physical and behavioral traits, including 24 blood types, handedness, direction of hair growth, fingerprint pattern, height, weight, functioning of all organ systems, intelligence, allergies, and dental patterns. The participants provide DNA samples.

- Researchers videotape facial expressions and body movements in different circumstances and probe participants' fears, interests, and superstitions.
- Twins and triplets separated at birth provide natural experiments for distinguishing nature from nurture. Many of their common traits can be attributed to genetics, especially if their environments have been very different. Their differences tend to come from differences in upbringing, because their genes are identical (MZ twins and triplets) or similar (DZ twins and triplets).
- Some MZ twins separated at birth and reunited later are remarkably similar, even when they grow up in very different adoptive families (figure **4)**. Idiosyncrasies are particularly striking.

Figure 4: Identical twins have much in common. In addition to physical traits, MZ twins may share tastes, preferences, and behaviors. Studying MZ twins separated at birth and reunited is a way to assess which traits are inherited.

- One pair of twins who met for the first time when they were in their thirties responded identically to questions; each paused for 30 seconds, rotated a gold necklace she was wearing three times, and then answered the question. Coincidence or genetics?
- The “twins reared apart” approach is not an ideal way to separate nature from nurture. MZ twins and other multiples share an environment in the uterus and possibly in early infancy that may affect later development. Siblings, whether adoptive or biological, do not always share identical home environments.
- Differences in sex, general health, school and peer experiences, temperament, and personality affect each individual’s perception of such environmental influences as parental affection and discipline.

Genome-Wide Association Studies

- A newer tool to analyze multifactorial traits and diseases is a **genome-wide association study (GWAS),** which compares large sets of landmarks (genetic markers) across the genome between two large groups of people—one with a particular trait or disease and one without it. Identifying parts of the genome that are much more common among the people with the trait or illness can lead researchers to genes that contribute to the phenotype.
- Genome-wide association studies use genetic markers .Single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) describe the DNA base sequence.
- A SNP is a site in the genome that has a different DNA base in at least one percent of a population (figure **5)**. A CNV is a DNA sequence that repeats a different number of times in different individuals (figure **6)**. A CNV does not provide information in the way that a gene that encodes protein does, but it is another way to distinguish individuals. CNVs are very useful in forensic applications.

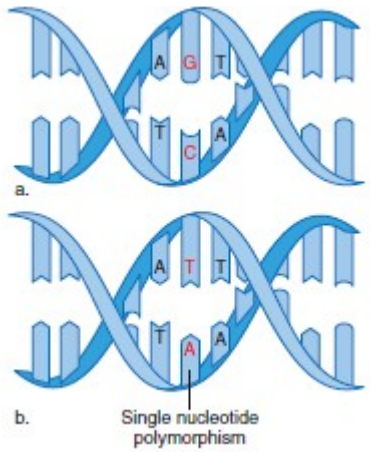

Figure 5: SNPs are sites of variability. The DNA base pair in red is a SNP—a site that differs in more than 1 percent of a population. (The percentage may change as SNPs are identified in more individuals.)

GATTACA	Allele 1
GATTACAGATTACA	Allele 2
GATTACAGATTACAGATTACA	Allele 3
GATTACAGATTACAGATTACAGATTACA	Allele 4

Figure 6: For **copy number variants**, different numbers of repeats of a short DNA base sequence are considered to be different alleles.

Table 7.5 Types of Information Used in Genome-Wide Association Studies

Marker Type	Definition
SNP	A single nucleotide polymorphism is a site in the genome that is a different DNA base in >1% of a population.
CNV	A copy number variant is a tandemly repeated DNA sequence, such as CGTA CGTA CGTA
Gene expression	The pattern of genes that are overexpressed and/or underexpressed in people with a particular trait or disease.
	Epigenetic signature of methyl groups binding

- Gene expression patterns are also used in genome-wide association studies. These patterns represent which proteins are overproduced or under produced in people with the trait or illness, compared to unaffected controls. Another way to compare genomes is by the sites to which methyl (CH 3) group's bind, shutting off gene expression.
- This is an **epigenetic change** because it doesn't affect the DNA base sequence.

- To achieve statistical significance, a genome-wide association study must include at least 100,000 markers. It is the association of markers to a trait or disease that is informative (figure 7). Typically, genome-wide association studies use a million or more SNPs, grouped into half a million or so **haplotypes.**

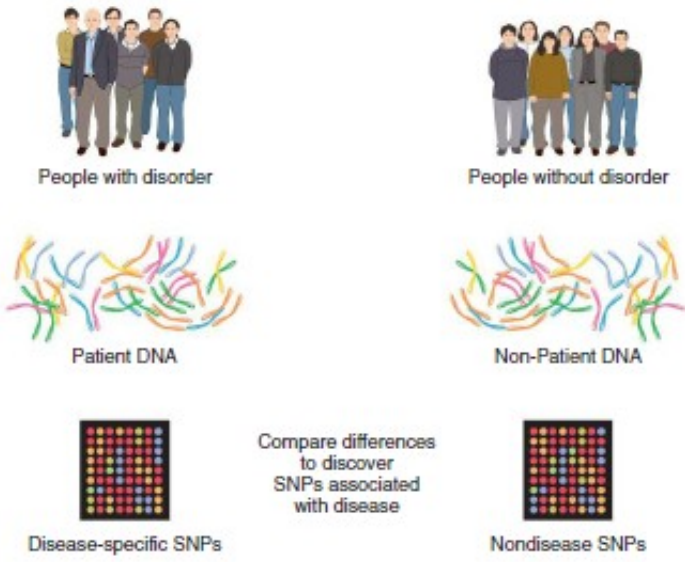

Figure 7: Tracking genes in groups. Genome-wide association studies seek DNA sequence variants that are shared with much greater frequency among individuals with the same illness or trait than among others. The squares are DNA microarrays, which display short, labeled DNA pieces.

- A specific "tag SNP" is used to identify a **haplotype**. A GWAS is a stepwise focusing in on parts of the genome responsible to some degree for a trait (figure **8)**.

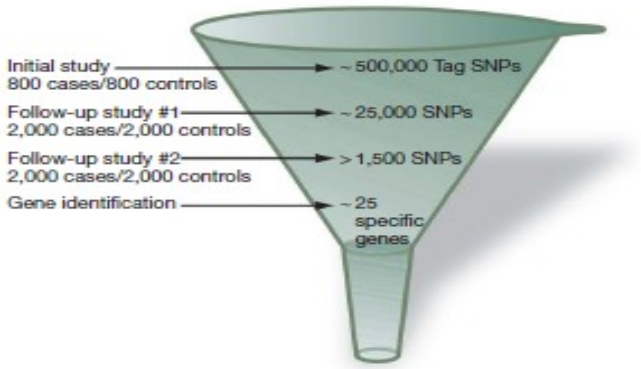

Figure 8: A stepwise approach to gene discovery. Genome-wide association study results must be validated in several different populations. Further research is necessary to go beyond association to demonstrate correlation and cause.

- In general, a group of people with the same condition or trait and a control group have their DNA isolated and genotyped for the 500,000 tag SNPs.

- Statistical algorithms identify the uniquely shared SNPs in the group with the trait or disorder. Repeating the process on additional populations narrows the SNPs and strengthens the association. It is important to validate a SNP association in different population groups, to be certain that it is the trait of interest that is being tracked, and not another part of the genome that members of one population share due to their common ancestry.

- Several study designs are used in these investigations (table 7.6**)**. In a **cohort study,** researchers follow a large group of individuals over time and measure many aspects of their health.
- The most famous is the Framingham Heart Study, which began tracking thousands of people and their descendants in Massachusetts in 1968. Nine thousand of them are participating in a genome-wide association study.
- In a **case-control study,** each individual in one group is matched to an individual in another group who shares as many characteristics as possible, such as age, sex, activity level, and Environmental exposures.
- SNP differences are then associated with the presence or absence of the disorder or trait. For example, if 5,000 individuals with hypertension (high blood pressure) have particular DNA bases at six sites in the genome, and 5,000 matched individuals who do not have hypertension have different bases at only these six sites, then these genome regions may include genes whose protein products control blood pressure.
- The **affected sibling pair** strategy follows the logic that because siblings share 50 percent of their genes, a trait or condition that many siblings share is likely to be inherited.
- Researchers scan genomes for SNPs that most siblings who have the same condition share, but that siblings who do not both have the condition do not often share.

Such genome regions may have genes that contribute to the condition.

- A variation on the affected sibling pair strategy is **homozygosity mapping,** which is performed on families that are **consanguineous**—that is, the parents are related. The genomes of children whose parents share recent ancestors have more homozygous regions than do other children, and therefore greater likelihood that they have inherited two copies of a susceptibility or disease causing mutation.
- After a SNP association has been validated in diverse and large populations, the next step is gene identification.
- The human genome sequence near the SNPs might reveal "candidate" genes whose known functions explain the condition.
- Common characteristics, such as height and body mass index, are also investigated with genome-wide association studies. One study examined facial features.
- Researchers measured eye and nose positions and dimensions, twenty lip descriptors, and the length of the space between the nose and the upper lip. The study identified variants of several genes already known to be mutant in specific syndromes that disrupt development of facial features.

- A genome-wide association study can explore the multifactorial aspects of traits and medical conditions. Consider a form of lung cancer for which several chromosomes have susceptibility genes.

- An ongoing GWAS is seeking to identify smoking-related behaviors that may indicate an increased risk of inherited susceptibility leading to the clinical reality of lung cancer. These possibly informative behaviors include age at which smoking began, number of years smoking, number of years since quitting, and number of cigarettes smoked per day.
- Genome-wide association studies have limitations, and are being replaced by direct analysis of the human genome sequence, as the functions of genes are being discovered.

- A conceptual limitation of genome-wide association studies is that they reveal associations between sets of information, and not causes. An *association* only means that one event or characteristic occurs when another occurs.
- A *correlation* is a directional association: If one measurement increases, so does the other, such as stress and blood pressure. In contrast, establishing a cause requires that a specific mechanism explains how one event makes another happen: *How* does stress elevate blood pressure? An association study does not provide information on a gene's function—it is more a discovery tool.
- A practical limitation of genome-wide association studies is that they often identify parts of the genome that contribute only slightly to the risk of developing a disease. A genetic test that indicates a 1 percent increase in risk of developing cancer, for example, would not matter much to a smoker whose environmental risk is much higher. A gene that contributes so little risk of a cancer, for example, that it is not detected in a GWAS, may nonetheless cause that cancer in a particular family.

- The way that a patient population is selected can introduce bias into a genome-wide association study. Samples drawn from clinics, for example, would not include the very mildly affected who are not ill enough to show up, or those who have died. Another source of error is that individuals in the control population might not actually be healthy. They might have problems other than the one being investigated.

- Genetic heterogeneity, in which different genes cause the same trait or condition, could also be a source of error. Epistasis, when one gene masks the effect of another, also confounds these studies, but as we learn more, such interactions are being taken into account.
- Another limitation of genome-wide association studies is that people who share symptoms and a SNP pattern may share something *else* that accounts for the

association, such as an environmental exposure that then can generate a false positive result.

- For example, mutations contribute to atherosclerosis risk, but so do infection, smoking, lack of exercise, and a fatty diet. These environmental factors are so common that if a GWAS isn't large enough, it might not correctly identify a genetic influence.
- The success of a GWAS may depend on the quality of the question asked. The technique was very helpful, for example, in explaining why some people who live on the Solomon Islands have blond hair (figure **9)**.

Figure 9: A striking phenotype. Blond hair among the residents of the Solomon Islands is due to a single base difference in a single gene.

- Most people living on these equatorial islands have dark hair and skin, similar to people who live in equatorial Africa. A case-control genome-wide association study on 43 blond Solomon Islanders and 42 dark-haired islanders clearly showed that the blonds were much more likely to have a particular SNP on chromosome 9.
- When researchers consulted the human genome sequence, they discovered in that interval a gene called tyrosine-related protein 1 (*TYRP1*). Its protein product controls melanin pigmentation in all vertebrate animals and the mutant gene causes a form of

human albinism. A single DNA base change is responsible for the unusual blond hair of some Solomon Islanders.

- Often, the old and the new techniques for dissecting multifactorial traits work well together. This is the case for stuttering. Concordance for MZ twins ranges from 20 to 83 percent, and for DZ twins, from 4 to 9 percent, suggesting a large inherited component.
- The risk of a first-degree relative of a person who stutters also stuttering is 15 percent based on empiric evidence, compared to the lifetime risk of stuttering in the general population of 5 percent, although part of that increase could be due to imitating an affected relative. A genome-wide association study on 100 families who have at least two members who stutter identified candidate genes on three chromosomes that contribute to the trait.

Q How can skin color have a different heritability at different times of the year?
Q: Do all genes that contribute to a polygenic trait do so to the same degree?
Q: Describe the type of information in a empiric risk calculation.
Q: What is a limitation of a genome-wide association study?
Q: Choose a single-gene disease and describe how environmental factors may affect the phenotype.
Q: What is the difference between a Mendelian multifactorial trait and a polygenic multifactorial trait?
Q: How will genome sequencing ultimately make a genome wide association study unnecessary?
Q: In a large, diverse population, why are medium brown skin colors more common than very white or very black skin?

1. How do leptin, ghrelin, and other proteins affect weight?
2. What is the significance of the difference in heritability for BMI and obesity?
3. What can populations that suddenly become sedentary and switch to a high-calorie diet reveal about environmental influences on weight?

Review Questions

1. Explain how Mendel's laws apply to multifactorial traits.
2. Choose a single-gene disease and describe how environmental factors may affect the phenotype.
3. What is the difference between a Mendelian multifactorial trait and a polygenic multifactorial trait?
4. Do all genes that contribute to a polygenic trait do so to the same degree?
5. Explain why figures 7.2 , 7.3 , and 7.4 have the same bell shape, even though they represent different traits.
6. How can skin color have a different heritability at different times of the year?
7. Explain how the twins in figure 7.4 have such different skin colors.
8. In a large, diverse population, why are medium brown skin colors more common than very white or very black skin?
9. Which has a greater heritability—eye color or height? State a reason for your answer.
10. Describe the type of information in a(n)
a. empiric risk calculation.
b. twin study.
c. adoption study.
d. genome-wide association study.
11. Name three types of proteins that affect cardiovascular functioning and three that affect body weight.
12. What is a limitation of a genome-wide association study?
13. How will genome sequencing ultimately make a genomewide association study unnecessary?

Summary

7.1 Genes and the Environment Mold Traits

1. **Multifactorial traits** reflect influences of the environment and genes. A **polygenic trait** is determined by more than one gene and varies continuously in expression.
2. Single-gene traits are rare. For most traits, many genes contribute to a small, but not necessarily equal, degree.

7.2 Polygenic Traits Are Continuously Varying

3. Genes that contribute to polygenic traits are called **quantitative trait loci**. The frequency distribution of phenotypes for a polygenic trait forms a bell curve.

7.3 Methods to Investigate Multifactorial Traits

4. **Empiric risk** measures the likelihood that a multifactorial trait will recur based on **prevalence**. The risk rises with genetic closeness, severity, and number of affected relatives.
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7.4 A Closer Look: Body Weight

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Applied Questions

1. "Heritability" is often used in the media to refer to the degree to which a trait is inherited. How is this definition different from the scientific one?
2. Would you take a drug that was prescribed to you based on your race? Cite a reason for your answer.
3. The incidence of obesity in the United States has doubled over the past two decades. Is this due more to genetic or environmental factors? Cite a reason for your answer.
4. One way to calculate heritability is to double the difference between the concordance values for MZ versus DZ twins. For multiple sclerosis, concordance for MZ twins is 30 percent, and for DZ twins, 3 percent. What is the heritability? What does the heritability suggest about the relative contributions of genes and the environment in causing MS?
5. In chickens, high body weight is a multifactorial trait. Several genes contribute small effects additively, and a few genes exert a great effect. Do the several genes provide broad heritability and the few genes narrow heritability, or vice versa?
6. Devise a genome-wide association study to assess whether restless legs syndrome is inherited, and if it is, where susceptibility or causative genes may be located.
7. The environmental epigenetics hypothesis states that early negative experiences, such as neglect, abuse, and extreme stress, increase the risk of developing depression, anxiety disorder, addictions, and obesity later in life, through effects on gene expression that persist.
Suggest an experiment to test this hypothesis.
8. Guidelines from the American Academy of Ophthalmology support genetic tests for single-gene eye diseases such as the many types of retinitis pigmentosa, but do not advise use of genome-wide association study results to counsel patients who have age-related macular degeneration, which is multifactorial. What is the reasoning behind the recommendation?
9. Three large pharmaceutical companies are developing drugs based on a very few cases of people who have extremely low LDL levels, due to a homozygous recessive mutation in a gene called proprotein convertase subtilisin/ kexin type 9 (PCSK9) . The idea is that mimicking the effects of the mutation in people who don't have it will

lower LDL level enough to combat elevated risk of heart disease. What other information would you like to have before enrolling in a clinical trial to test whether one of the new drugs can prevent heart disease?

10. Lung scarring due to idiopathic pulmonary fibrosis affects more than 50,000 people in the United States and is often fatal within a few years of diagnosis. "Idiopathic" means "cause unknown," but the condition is set into motion by mutations in several genes (transforming growth factor B, surfactant protein C, mucin 5B, and human telomerase reverse transcriptase). Environmental influences are important too. These include certain viral infections and exposure to inhaled irritants including cigarette smoke. How do these contributing factors explain why idiopathic pulmonary fibrosis is considered to be a disease of aging?

11. Suggest a way to mimic the effects of weight-loss surgery.

Body Weight

- Weight is a multifactorial trait. Body weight reflects energy balance, which is the rate of food taken in versus the rate at which the body uses it for fuel. Excess food means, ultimately, excess weight.
- Being overweight or obese raises the risk of developing hypertension, diabetes, stroke, gallstones, sleep apnea, and some cancers.
- Scientific studies of body weight use a measurement called body mass index (BMI), which is weight in proportion to height (figure **1)**. BMI makes sense—a person who weighs 170 pounds and is 6 feet tall is slim, whereas a person of the same weight who is 5 feet tall is obese.
- The tall person's BMI is 23; the short person's is 33.5.
- Heritability for BMI is 0.55, which leaves room for environmental influences on our appetites and sizes. Dozens of genes affect how much we eat, how we use calories, and how fat is distributed in the body. The biochemical pathways and hormonal interactions that control weight may reveal points for drug intervention.

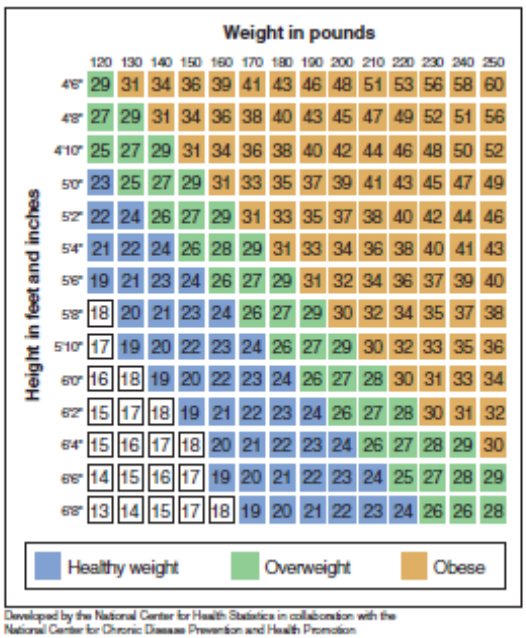

Figure 1: Body mass index (BMI). BMI equals weight/ height 2 , with weight measured in kilograms and height measured in meters. This chart provides a shortcut—the calculations have been done and converted to the English system of measurement. Squares that are not filled in indicate underweight.

Genes That Affect Weight

- Genetics became prominent in obesity research in 1994, when Jeffrey Friedman at Rockefeller University discovered a gene that encodes the protein hormone leptin in mice and in humans.
- Normally, eating stimulates fat cells (adipocytes) to secrete **leptin**, which travels in the bloodstream to a region of the brain's hypothalamus, where it binds to receptors on nerve cells (neurons). Leptin binding signals the neurons to release another type of hormone that binds yet other types of receptors, which ultimately function as an appetite "brake," while speeding digestion of food already eaten. When a person hasn't eaten in several hours, leptin levels fall, which triggers the release of an appetite "accelerator."
- The discovery of genes and proteins that affect appetite led to great interest in targeting them with drugs to either lose or gain weight. When Friedman gave mice extra leptin, they ate less and lost weight.
- Headlines soon proclaimed the new magic weight loss elixir, a biotech company paid $20 million for rights to the hormone, and clinical trials ensued.
- The idea was to give obese people leptin, assuming that they had a deficiency, to trick them into feeling full. Only about 15 percent of the people lost weight, but the other 85 percent didn't actually lack leptin. Instead, most of them had leptin resistance, which is a diminished ability to recognize the hormone due to defective leptin receptors. Giving these people leptin had no effect on their appetites. However, the discovery helped a few severely obese children with true leptin deficiency attain normal weights after years of daily leptin injections.
- The stomach is another source of weight-related proteins. Ghrelin is a peptide (small protein) hormone produced in the stomach that responds to hunger, signaling the hypothalamus to produce more of the appetite accelerator. One of the ways that weight loss surgery may work is by decreasing ghrelin secretion by making the stomach smaller.

- While leptin acts in the long term to maintain weight, the stomach's appetite control hormones function in the short term.
- All of these hormonal signals are integrated to finely control appetite in a way that maintains weight.

- Identifying single genes that influence weight paved the way for considering the trait to be multifactorial. Researchers are investigating how combinations of genes control weight.
- One study looked at 21 genes in which mutations cause syndromes that include obesity, as well as 37 genes whose products participate in biochemical pathways related to weight.
- This approach identified many rare gene variants that could, in combinations, explain many people's tendency to gain weight.
- Genome-wide association studies that compare gene expression patterns have also enhanced understanding of body weight. One study compared the sets of genes that are expressed in adipose (fat) tissue to other tissues. Samples from more than 1,600 people in Iceland revealed a set of genes whose products take part in inflammation and the immune response, but also contribute obesity-related traits.

Environmental Influences on Weight

- Many studies on adopted individuals and twins suggest that obesity has a heritability of 75 percent. Because the heritability for BMI is lower than this, the discrepancy suggests that genes play a larger role in those who tend to gain weight easily. The role of genes in obesity is seen when populations that have an inherited tendency to easily gain weight experience a large and sudden plunge in the quality of the diet.
- On the tiny island of Naura, in Western Samoa, the residents' lifestyles changed greatly when they found a market for the tons of bird droppings on their island as commercial fertilizer.

- The money led to inactivity and a high-calorie, high-fat diet, replacing an agricultural lifestyle and diet of fish and vegetables.
- Within a generation, two-thirds of the population had become obese, and a third had type 2 diabetes.
- The Pima Indians offer another example of environmental effects on body weight. These people separated into two populations during the Middle Ages, one group settling in the Sierra Madre mountains of Mexico, the other in southern Arizona. By the 1970s, the Arizona Indians no longer farmed nor ate a low-calorie, low-fat diet, but instead consumed 40 percent of their calories from fat. With this extreme change in lifestyle, they developed the highest prevalence of obesity of any population on earth. Half of the Arizona group had diabetes by age 35, weighing, on average, 57 pounds (26 kilograms) more than their southern relatives, who still eat a low-fat diet and are very active.

- The Pima Indians demonstrate that future obesity is not sealed in the genes at conception, but instead is much more likely to occur if the environment provides too many calories and too much fat.

- Geneticist **James Neel** expressed this idea as the “thrifty gene hypothesis” in 1962. He suggested that long ago, the hunter-gatherers who survived famine had genes that enabled them to store fat. Today, with food plentiful, the genetic tendency to retain fat is no longer healthful, but harmful. Unfortunately, for many of us, our genomes hold an energy-conserving legacy that works too well—it is much easier to gain weight than to lose it, for a sound evolutionary reason: survival.

- The **thrifty gene hypothesis** also applies: to people who were born after a full-term pregnancy, but were very low weight. To compensate for starvation conditions in the uterus, metabolism shifts, before birth, in a way that conserves calories—and the person later faces elevated risk of heart disease, stroke, obesity, osteoporosis, and type 2 diabetes. These are multifactorial conditions that, instead of arising from mutations, reflect epigenetic alterations of gene expression.

- Another environmental influence on weight is the "**gut microbiome**," the types of bacteria that normally live in our digestive tracts. Bacterial cells in our bodies actually outnumber our own cells. The actions of certain types of bacteria affect the number of calories that we extract from particular foods. An obese person has a different gut microbiome than a person who easily stays thin. The gut microbiome changes dramatically after weight-loss surgery, and finding a way to recreate this changed microbiome might one day provide an alternative to the surgery.

- Perhaps nowhere are the complexities and challenges of gene-environment interactions more profound than in behavioral characteristics, nuances, quirks, and illnesses.

Summary

7.1 Genes and the Environment Mold Traits

1. **Multifactorial traits** reflect influences of the environment and genes. A **polygenic trait** is determined by more than one gene and varies continuously in expression.

2. Single-gene traits are rare. For most traits, many genes contribute to a small, but not necessarily equal, degree.

7.2 Polygenic Traits Are Continuously Varying

3. Genes that contribute to polygenic traits are called **quantitative trait loci**. The frequency distribution of phenotypes for a polygenic trait forms a bell curve.

7.3 Methods to Investigate Multifactorial Traits

4. **Empiric risk** measures the likelihood that a multifactorial trait will recur based on **prevalence**. The risk rises with genetic closeness, severity, and number of affected relatives.

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Q1: Suggest a way to mimic the effects of weight-loss surgery.

Q2: One way to calculate heritability is to double the difference between the concordance values for MZ versus DZ twins. For multiple sclerosis, concordance for MZ twins is 30 percent, and for DZ twins, 3 percent. What is the heritability? What does the heritability suggest about the relative contributions of genes and the environment in causing MS?

Q3: The incidence of obesity in the United States has doubled over the past two decades. Is this due more to genetic or environmental factors?

Reproductive Technologies

1- Infertility and Subfertility

- **Infertility** is the inability to conceive a child after a year of frequent intercourse without the use of contraceptives. Some specialists use the term *subfertility* to distinguish those individuals and couples who can conceive unaided, but for whom this may take longer than average.
- On a more personal level, infertility is a seemingly endless monthly cycle of raised hopes and crushing despair. In addition to declining fertility, as a woman ages, the incidence of pregnancy-related problems rises, including chromosomal anomalies, fetal deaths, premature births, and low-birth-weight babies. Older fathers are at increased risk of having children who have autism or schizophrenia. Sperm motility declines with age.
- One in six couples has difficulty conceiving or giving birth to children. Physicians who specialize in infertility treatment can identify a physical cause in 90 percent of cases.
- Of these cases, 30 percent of the time the problem is primarily in the male, and 60 percent of the time it is primarily in the female. When a physical problem is not obvious, the cause is usually a mutation or chromosomal aberration that impairs fertility in the male.
- The statistics are somewhat unclear, because in 20 percent of the 90 percent, both partners have a medical condition that could contribute to infertility or subfertility. A common combination is a woman with an irregular menstrual cycle and a man with a low sperm count.

Male Infertility

- Infertility in the male is easier to detect but sometimes harder to treat than female infertility. Four in 100 men in the general population are infertile, and half of them do not make any sperm, a condition called **azoospermia**.
- Some men have difficulty fathering a child because they produce fewer than the average 20 to 200 million sperm cells per milliliter of ejaculate. This condition, **called oligospermia**, has several causes:

❖ If a low sperm count is due to a hormonal imbalance, administering the appropriate hormones may boost sperm output.

❖ Sometimes a man's immune system produces IgA antibodies that cover the sperm and prevent them from binding to oocytes.

❖ Male infertility can also be due to a varicose vein in the scrotum. This enlarged vein emits heat near developing sperm, which prevents them from maturing. Surgery can remove a scrotal varicose vein.

- **Most cases of male infertility are genetic**:

❖ About a third of infertile men have small deletions of the Y chromosome that remove the only copies of key genes whose products control spermatogenesis.

❖ Other genetic causes of male infertility include mutations in genes that encode androgen receptors or protein fertility hormones, or that regulate sperm development or motility.

- For many men with low sperm counts, if they have at least 60 million sperm cells per ejaculate, fertilization is likely eventually.
- To speed conception, a man with a low sperm count can donate several semen samples over a period of weeks at a fertility clinic.

  ❖ The samples are kept in cold storage, and then pooled. Some of the seminal fluid is withdrawn to leave a sperm cell concentrate, which is then placed in the woman's body. It is highly effective at achieving pregnancy.

- Sperm quality is more important than quantity. Sperm cells that are unable to move or are shaped abnormally cannot reach an oocyte. Inability to move may be due to a

hormone imbalance, and abnormal shapes may reflect impaired apoptosis (programmed cell death) that normally removes such sperm.

- **The genetic package** of an immobile or abnormally shaped sperm cell can be injected into an oocyte and sometimes this leads to fertilization. However, even sperm that look and move normally may be unable to fertilize an oocyte.

Female Infertility

- Abnormalities in any part of the female reproductive system can cause infertility (figure **-2)**. Many women with subfertility or infertility have irregular menstrual cycles, making it difficult to pinpoint when conception is most likely. In an average menstrual cycle of 28 days, ovulation usually occurs around the 14th day after menstruation begins. At this time a woman is most likely to conceive.

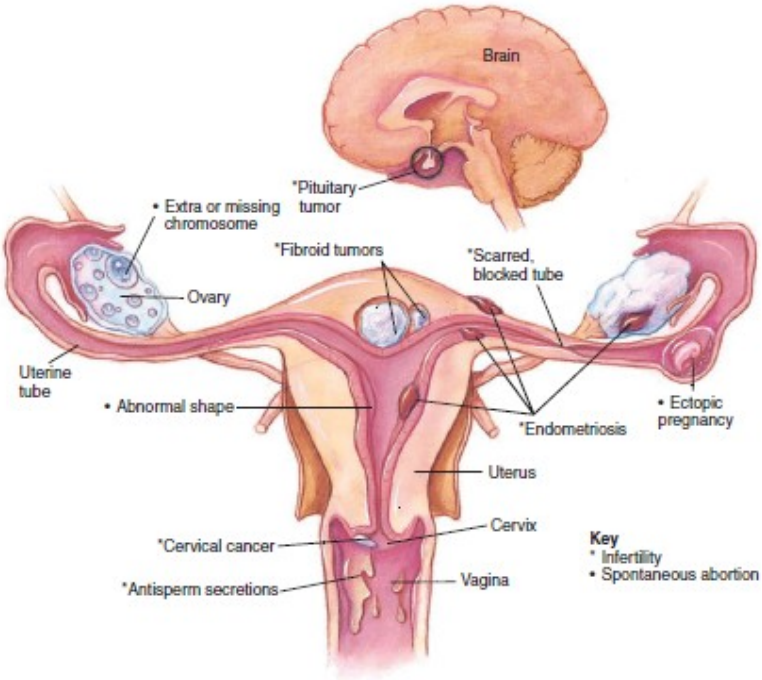

Figure.2 Sites of reproductive problems in the female.

- For a woman with regular menstrual cycles who is under 30 years old and not using birth control, pregnancy typically happens within 3 or 4 months. A woman with

irregular menstrual periods can tell when she is most fertile by using an ovulation predictor test, which detects a peak in the level of **luteinizing hormone** that precedes ovulation by a few hours.

- Another way to detect the onset of ovulation is to record body temperature each morning using a digital thermometer with subdivisions of hundredths of a degree Fahrenheit, which can indicate the 0.4 to 0.6 rise in temperature when ovulation starts.
- Several apps track a woman's menstrual cycle, enabling her to predict the time of ovulation. Sperm can survive in a woman's body for up to 5 days, but the oocyte is only viable for 24 to 48 hours after ovulation.
- **The hormonal imbalance that usually underlies irregular ovulation has various causes:** These include a tumor in the ovary or in the pituitary gland in the brain that controls the reproductive system, an underactive thyroid gland, or use of steroid-based drugs such as cortisone. If a nonpregnant woman produces too much prolactin, the hormone that promotes milk production and suppresses ovulation in new mothers, she will not ovulate.
- Fertility drugs can stimulate ovulation, but they can also cause women to "**superovulate**," producing and releasing more than one oocyte each month.
- A commonly used drug, **clomiphene,** raises the chance of having twins from 1 to 2 percent to 4 to 6 percent. If a woman's ovaries are completely inactive or absent (due to a birth defect or surgery), she can become pregnant only if she uses a **donor oocyte.** Some cases of female infertility are due to "**reduced ovarian reserve**"—too few oocytes.
- This is typically discovered when the ovaries do not respond to fertility drugs. Signs of reduced ovarian reserve are an ovary with too few follicles (observed on an ultrasound scan) or elevated levels of **follicle-stimulating hormone on the third day of the menstrual cycle.**

❖ The uterine tubes are a common site of female infertility because fertilization usually occurs in open tubes. Blockage can prevent sperm from reaching the

oocyte, or entrap a fertilized ovum, keeping it from descending into the uterus. If an embryo begins developing in a blocked tube and is not removed and continues to enlarge, the tube can burst and the woman can die. Such a **"tubal pregnancy**" is called an ectopic pregnancy.

- ❖ Uterine tubes can also be blocked due to a **birth defect** or, more likely, from an infection such as pelvic inflammatory disease. A woman may not know she has blocked uterine tubes until she has difficulty conceiving and medical tests uncover the problem. Surgery can open blocked uterine tubes.
- ❖ **Excess tissue growing in the uterine lining may make it inhospitable to an embryo.** This tissue can include benign tumors called fibroids or areas of thickened lining from a condition called endometriosis. The tissue can grow outside of the uterus too, in the abdominal cavity. In response to the hormonal cues to menstruate, the excess lining bleeds, causing cramps. Endometriosis can hamper conception, but curiously, if a woman with endometriosis conceives, the cramps and bleeding usually disappear after the birth.

- Secretions in the vagina and cervix may be hostile to sperm. Cervical mucus that is thick or sticky due to infection can entrap sperm, keeping them from moving far enough to encounter an oocyte.
- Vaginal secretions may be so acidic or alkaline that they weaken or kill sperm. Douching daily with an acidic solution such as acetic acid (vinegar) or an alkaline solution such as bicarbonate, can alter the pH of the vagina so that in some cases it is more receptive to sperm cells.
- Too little mucus can prevent conception too; this is treated with low daily doses of oral estrogen. Sometimes mucus in a woman's body has antibodies that attack sperm. Infertility may also result if the oocyte does not release sperm-attracting biochemicals.

- One reason the incidence of female infertility increases with **age is that older women** are more likely to produce oocytes that have an abnormal chromosome number, which

often causes spontaneous abortion because defects are too severe for development to proceed for long. The cause is usually misaligned spindle fibers when the second meiotic division begins, causing aneuploidy (extra or missing chromosomes).

- Perhaps the longer exposure of older oocytes to harmful chemicals, viruses, and radiation contributes to the risk of meiotic errors. Losing very early embryos may appear to be infertility because the bleeding accompanying the aborted embryo resembles a heavy menstrual flow.

Infertility Tests

- A number of medical tests can identify causes of infertility. The man is checked first, because it is easier, less costly, and less painful to obtain sperm than oocytes.
- Sperm are checked for number (sperm count), motility, and morphology (shape).
- An ejaculate containing up to 40 percent unusual forms is still considered normal, but many more than this can impair fertility. A urologist performs sperm tests.
- A genetic counselor can evaluate Y chromosome deletions associated with lack of sperm. If a male cause of infertility is not apparent, a gynecologist checks the woman to see that reproductive organs are present and functioning.
- Some cases of subfertility or infertility have no clear explanation. Psychological factors may be at play, or it may be that inability to conceive results from consistently poor timing.
- Sometimes a subfertile couple adopts a child, only to conceive one of their own shortly thereafter; many times, infertility remains a lifelong mystery.

2. Assisted Reproductive Technologies

- Many people with fertility problems who do not choose to adopt children use alternative ways to conceive. Several of the ARTs were developed in nonhuman animals.
- In the United States, slightly more than 1 percent of the approximately 4 million births a year are from ARTs and worldwide ART accounts for about 250,000 births a year.
- This section describes types of ARTs. The different procedures can be performed on material from the parents-to-be ("nondonor") or from donors, and may be "fresh" (collected just prior to the procedure) or "frozen" (preserved in liquid nitrogen). Except for intrauterine insemination, the ARTs cost thousands of dollars and are not typically covered by health insurance in the United States.

Donated Sperm—Intrauterine Insemination

- The oldest assisted reproductive technology is **intrauterine insemination (IUI),** in which a doctor place donated sperm into a woman's cervix or uterus. (It used to be called artificial insemination.) The success rate is 5 to 15% per attempt.
- The sperm are first washed free of seminal fluid, which can inflame female tissues.
- A woman might seek IUI if her partner is infertile or has a mutation that the couple wishes to avoid passing to their child. Women also undergo IUI to be a single parent without having sex, or a lesbian couple may use it to have a child.
- The first documented IUI in humans was done in **1790**. For many years, physicians donated sperm, and this became a way for male medical students to earn a few extra dollars.
- **By 1953**, sperm could be frozen and stored and IUI became much more commonplace. Today, donated sperm are frozen and stored in sperm banks, which provide the cells to obstetricians who perform the procedure. IUI costs on average $865 per cycle, according to the American Society of Reproductive Medicine, with higher charges from some facilities for sperm from donors who have professional degrees because those men are paid more for their donations.

- Additional fees are charged for a more complete medical history of the donor, for photos of the man at different ages, and for participation in a "**consent program**" in which the donor's identity is revealed when his offspring turns 18 years old. If ovulation is induced to increase the chances of success of IUI, additional costs may exceed $3,000.
- A couple who chooses IUI can select sperm from a catalog that lists the personal characteristics of donors, such as blood type, hair and eye color, skin color, build, educational level, and interests. Some traits have nothing to do with genetics.
- If a couple desires a child of one sex—such as a daughter to avoid passing on an X-linked disorder—sperm can be separated into fractions enriched for X-bearing or Y-bearing sperm.
- Problems can arise in IUI if a donor learns that he has an **inherited disease**. For example, a man developed **cerebellar ataxia**, a movement disorder, years after he donated sperm. Eighteen children conceived using his sperm face a 1 in 2 risk of having inherited the mutant gene. Overenthusiastic sperm donors can lead to problems. One man, listed in the Fairfax Cryobank as "Donor 401," earned $40,000 donating sperm while in law school. He was quite attractive and popular, and forty-five children were conceived with his sperm.
- When a few of the families he started appeared on a talk show, several other families tuning in were shaken to see so many children who resembled their own. Cases came to light of males fathering more than 150 offspring, prompting sperm banks to limit sales of a particular male's sperm cells.
- A male's role in reproductive technologies is simpler than a woman's. A man can be a genetic parent, contributing half of his genetic self in his sperm, but a woman can be both a genetic parent (donating an oocyte) and a gestational parent (donating the uterus).

A Donated Uterus—Surrogate Motherhood

- If a man produces healthy sperm but his partner's uterus cannot maintain a pregnancy, a surrogate mother may help by being inseminated with the man's sperm. When the child is born, the surrogate mother gives the baby to the couple. In this variation of the technology, the surrogate is both the genetic and the gestational mother. Attorneys usually arrange surrogate relationships.
- The surrogate mother signs a statement signifying her intent to give up the baby. In some U.S. states, and in some nations, she is paid for her 9-month job, but in the United Kingdom compensation is illegal. This is to prevent wealthy couples from taking advantage of women who become surrogates for the money.

- A problem with surrogate **motherhood** is that a woman may not be able to predict her responses to pregnancy and childbirth in a lawyer's office months before she must hand over the baby. When a surrogate mother changes her mind, the results are wrenching for all.
- A prominent early case involved **Mary Beth Whitehead**, who carried the child of a married man for a fee and then changed her mind about giving up the baby. The courts eventually awarded custody to the father and his wife. The woman who raises the baby may feel badly too, especially when people say she is not the "real" mother.
- Another type of surrogate mother lends only her uterus, receiving a fertilized ovum conceived from a man and a woman who has healthy ovaries but lacks a functional uterus.
- This variation is an "embryo transfer to a host uterus," and the pregnant woman is a "gestational-only surrogate mother."
- She turns the child over to the biological parents. About 1,600 babies are born in the United States to gestational surrogates each year.

In Vitro Fertilization

- In ***in vitro*** **fertilization** (IVF**)**, which means "fertilization in glass," sperm and oocyte join in a laboratory dish. Soon after, the embryo that forms is placed in a uterus. If all goes well, it implants into the uterine lining and continues development until a baby is born.
- **Louise Joy Brown, the first "test-tube baby**," was born in 1978, amid great attention and sharp criticism. A prominent bioethicist said that IVF challenged "the idea of humanness and of our human life and the meaning of our embodiment and our relation to ancestors and descendants."
- Yet Louise is, despite her unusual beginnings, an ordinary young woman. More than 5 million children have been born following IVF.
- A woman might undergo IVF if her ovaries and uterus work but her uterine tubes are blocked. Using a laparoscope, which is a lit surgical instrument inserted into the body through a small incision, a physician removes several of the largest oocytes from an ovary and transfers them to a culture dish. If left in the body, only one oocyte would exit the ovary, but in culture, many oocytes can mature sufficiently to be fertilized *in vitro*. Chemicals, sperm, and other cell types similar to those in the female reproductive tract are added to the culture. An acidic solution may be applied to the zona pellucida, which is the layer around the egg, to thin it to ease the sperm's penetration.
- Sperm that cannot readily enter the oocyte may be sucked up into a tiny syringe and microinjected into the female cell.
- This technique, called **intracytoplasmic sperm injection** (**ICSI**), is more effective than IVF alone and has become standard at some facilities (**figure 21.3**). ICSI is very helpful for men who have low sperm counts or many abnormal sperm.

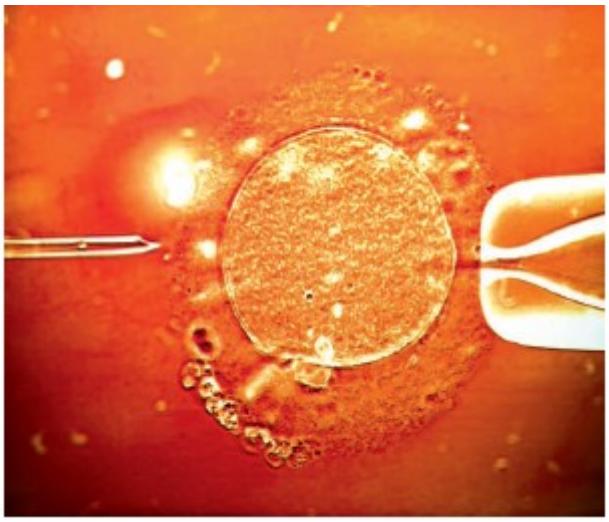

Figure 21.3 ICSI. Intracytoplasmic sperm injection (ICSI) enables some infertile men, men with spinal cord injuries, or men with certain illnesses to become fathers. A single sperm cell is injected into the cytoplasm of an oocyte.

- It makes fatherhood possible for men who cannot ejaculate, such as those who have suffered spinal cord injuries. ICSI has been performed on thousands of men with about a 30 percent success rate.
- Two to five days after sperm wash over the oocytes in the dish, or are injected into them, a blastocyst is transferred to the uterus. If the hormone human chorionic gonadotropin appears in the woman's blood a few days later, and its level rises, she is pregnant.
- IVF costs from on average $8,158 per cycle. Medications can add $3,000 to $5,000 to the cost. ICSI adds another $1,544 on average.
- **Children born following IVF have a slight increase in the rate of birth defects** (about 8 percent) compared to children conceived naturally (about 3 percent). This difference may be due to the medical problems that caused the parents to seek IVF, the tendency of IVF to interfere with the parting of chromosome pairs during meiosis, closer scrutiny of IVF pregnancies, and/or effects on imprinting from the time spent in culture.
- **Children born after IVF on average have higher birth weights**. An increase in birth defects among multiple births since 1984 is possibly due to an increase in the use of ARTs. In the past, several embryos were implanted to increase the success rate of

IVF, but this led to many multiple births, which are riskier than single births. In some cases, physicians had to remove embryos to make room for others to survive.

- To avoid the multiples problem, and because IVF has become more successful as techniques have improved, guidelines now suggest transferring only one embryo.
- Embryos resulting from IVF that are not soon implanted in the woman can be frozen in liquid nitrogen ("cryopreserved" or "vitrified") for later use.
- Cryoprotectant chemicals are used to prevent salts from building up or ice crystals from damaging delicate cell parts. Freezing takes a few hours; thawing about a half hour. The longest an embryo has been frozen, stored, and then successfully revived is 13 years; the "oldest" pregnancy using a frozen embryo occurred 9 years after the freezing.
- So many people have had IVF since Louise Joy Brown was born that researchers have developed algorithms to predict the chances that the procedure will be successful and lead to a birth for a particular couple. Overall the chances of a live birth following IVF are about 25 percent, but this prediction varies greatly, depending on certain risk factors that lower the likelihood of success. These include:

■ maternal age—success is 30 to 40 percent for women (oocyte donors) under age 34, but only 5 to 10 percent for women over 40;
■ increased time being infertile;
■ number of previous failed IVF attempts;
■ number of previous IVF attempts;
■ use of a woman's own oocytes rather than a donor's; and
■ infertility with a known cause.

- A website (http://www.ivfpredict.com) assesses these risks. In one example, a couple had been infertile for 11 years.
- They attempted IVF four times that resulted in two failures and two spontaneous abortions. They had used the woman's eggs and ICSI because too many sperm were abnormal. The chance of success per IVF attempt is about 8 percent, but if they use a donor oocyte, the likelihood of success doubles.

- Gamete and Zygote Intrafallopian Transfer IVF may fail because of the artificial environment for fertilization.
- A procedure called **GIFT,** which stands for **gamete intrafallopian transfer,** improves the setting. (Uterine tubes are also called fallopian tubes.) Fertilization is assisted in GIFT, but it occurs in the woman's body rather than in glassware.
- In GIFT, several of a woman's largest oocytes are removed. The man submits a sperm sample, and the most active cells are separated from it. The collected oocytes and sperm are deposited together in the woman's uterine tube, at a site past any obstruction that might otherwise block fertilization. GIFT is about 22 percent successful.
- A variation of GIFT is **ZIFT,** which stands for **zygote intrafallopian transfer**. In this procedure, an IVF ovum is introduced into the woman's uterine tube. Allowing the fertilized ovum to make its own way to the uterus increases the chance that it will implant. ZIFT is also 22 percent successful.
- GIFT and ZIFT are done less frequently than IVF. These procedures may not work for women who have scarred uterine tubes. The average cost of GIFT or ZIFT is $15,000 to $20,000.
- *Bioethics: Choices for the Future* on page 416 considers the unusual situation of collecting gametes from a person shortly after the person has died.

Q:

1-Why men are typically tested for infertility before women?

3. What are some of the causes of infertility among older women?

4. Cite a situation in which both man and woman contribute to subfertility.

5. How does ZIFT differ from GIFT and IVF?

6-Why is it much easier to freeze and revive early embryos than oocytes?

7- Some ARTs were invented to help people who could not have children for medical reasons, or to avoid conceiving a child with a genetic disease in the family. With time,
as the technologies became more familiar, in the United States people with economic means began to use them for other reasons, such as a celebrity who does not wish to lose her shape during pregnancy. Remembering that the U.S. government does not regulate ARTs, do you
think that any measures should be instituted to select candidates for ARTs? How can these technologies be made more affordable?

Sequential polar body analysis

- A technique called **sequential polar body analysis** may substitute for PGD and provides genetic information even earlier in development. The approach is based on the fact that meiosis completes in the female only as a secondary oocyte is fertilized (see figure 3.10). If a woman is heterozygous for a mutation, then an oocyte would inherit the mutation and its associated polar bodies would inherit the wild type allele, or vice versa. This is in accordance with Mendel's first law, gene segregation. The timetable of female meiosis is important, too. The first polar body forms as the developing oocyte leaves the ovary.
- That polar body is not accessible, and it would not show the effects of crossing over. A second polar body, however, which forms at fertilization, can be tested (figure**.5)**. Researchers can sequence linked markers or even entire genomes of polar bodies to determine whether crossing over has occurred, to be certain that the fertilized ovum has not inherited the mutation.

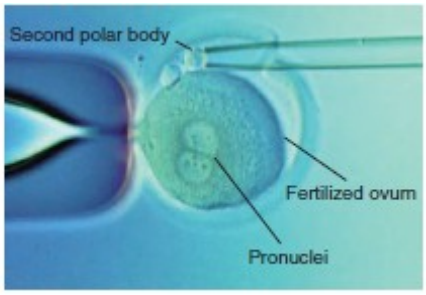

Figure.5 deducing a fertilized ovum's genotype by testing a polar body. Because of Mendel's law of Segregation, if a polar body associated with a fertilized ovum has a mutation that the woman carries, wild type for that gene is inferred for the secondary oocyte.

- Because sequential polar body analysis is still experimental, researchers follow it up with PGD to test their predictions and ensure that IVF embryos transferred to the woman's uterus to develop are free of the family's mutation. The idea of probing polar bodies dates from the 1980s, but the technique first led to results in 2011. So far mutations behind more than 150 single-gene diseases have been detected at this initial stage of prenatal development—the very first cell.

3 -Extra Embryos

- Sometimes assisted reproductive technologies leave "extra" oocytes, fertilized ova, or very early embryos. **Table 1** lists the possible fates of this biological material.
- In the United States, nearly half a million embryos derived from IVF sit in freezers; some have been there for years. Most couples who donate embryos to others do so anonymously, with no intention of learning how their genetic offspring are raised. Scott and Glenda Lyons chose a different path when they learned that their attempt at IVF had yielded too many embryos.

- In 2001, two of Glenda's eighteen embryos were transferred to her uterus, and developed into twins Samantha and Mitchell. Through a website where couples chat about fertility issues, Scott and Glenda met and selected Bruce and Susan Lindeman to receive fourteen remaining embryos. This second couple had tried IVF three times, with no luck. The Lyons's frozen embryos were shipped cross-country to a clinic where two were implanted in Susan's uterus. In July 2003, Chase and Jack Lindeman were born—genetic siblings of Samantha and Mitchell Lyons. But there were still embryos left. The Lyonses allowed the Lindemans to send twelve embryos to a third couple, who used two to have twin daughters in August 2004. They are biological siblings of Samantha and Mitchell Lyons and Chase and Jack Lindeman (figure**.6)**.

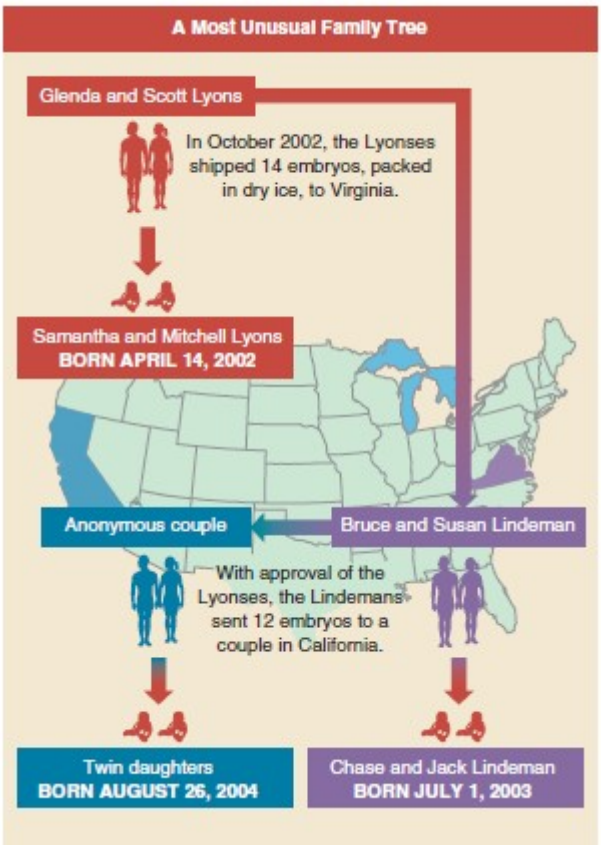

Figure.6 Using extra embryos. Six children resulted from Glenda and Scott Lyons's embryos. The Lyonses had a boy and a girl, then donated embryos to the Lindemans, who had twin boys. Finally, a couple in California used the Lyons's embryos to have twin daughters.

- Another alternative to disposing of fertilized ova and embryos is to donate them for use in research. The results of experiments sometimes challenge long-held ideas, indicating that we still have much to learn about early human prenatal development. This was the case for a study from Royal Victoria Hospital in Montreal.
- Researchers examined the chromosomes of sperm from a man with XXY syndrome. Many of the sperm would be expected to have an extra X chromosome, due to nondisjunction (see figure 13.12), which could lead to a preponderance of XXX and XXY offspring. Surprisingly, only 3.9 percent of the man's *sperm* had extra chromosomes, but five out of ten of his spare *embryos* had an abnormal X, Y, or chromosome 18. That is, even though most of the man's sperm were normal, his embryos weren't. The source of reproductive problems in XXY syndrome, therefore, might not be in the sperm, but in early embryos—a finding that was previously

unknown and not expected, and was only learned because of observing early human embryos.

- In another study, Australian researchers followed the fates of single blastomeres that had too many or too few chromosomes.
- They wanted to see whether the abnormal cells preferentially ended up in the inner cell mass, which develops into the embryo, or the trophectoderm, which becomes extra-embryonic membranes. The study showed that cells with extra or missing chromosomes become part of the inner cell mass much more frequently than expected by chance. This finding indicates that the ability of a blastomere sampled for PGD to predict health may depend on whether it is fated to be part of the inner cell mass.
- Using fertilized ova or embryos designated for discard in research is controversial. Without regulations on privately funded research, ethically questionable experiments can happen.
- For example, researchers reported at a conference that they had mixed human cells from male embryos with cells from female embryos, to see if the normal male cells could "save" the female cells with a mutation. Sex was chosen as a marker because the Y chromosome is easy to detect, but the idea of human embryos with mixed sex parts caused a public outcry.
- ARTs introduce ownership and parentage issues (table **1)**. Another controversy is that human genome information is providing more traits to track and perhaps control in coming generations. When we can routinely scan the human genome in gametes, fertilized ova, or early embryos, who will decide which traits are worth living with, and which aren't?
- ARTs operate on molecules and cells, but affect individuals and families. Ultimately, by introducing artificial selection, these interventions may affect the gene pool.

Table 21.3 Assisted Reproductive Disasters

1. A physician used his own sperm to perform intrauterine insemination on 15 patients, telling them that he had used sperm from anonymous donors.
2. A plane crash killed the wealthy parents of two early embryos stored at −320°F (−195°C) in a hospital. Adult children of the couple were asked to share their estate with two 8-celled siblings-to-be.
3. Several couples planning to marry discovered that they were half-siblings. Their mothers had been inseminated with sperm from the same donor.
4. Two Rhode Island couples sued a fertility clinic for misplacing several embryos.
5. Several couples sued a fertility clinic for implanting their oocytes or embryos in other women without donor consent. One woman requested partial custody of the resulting children if her oocytes were taken, and full custody if her embryos were used, even though the children were of school age and she had never met them.
6. A man sued his ex-wife for possession of their frozen fertilized ova. He won, and donated them for research. She had wanted to be pregnant.
7. The night before *in vitro* fertilized embryos were to be implanted in a 40-year-old woman's uterus after she and her husband had spent 4 years trying to conceive, the man changed his mind, and wanted the embryos destroyed.