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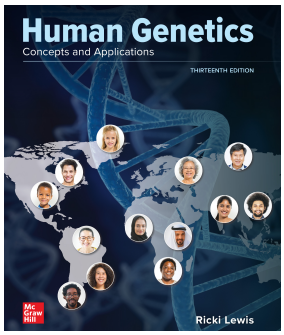

Chapter 7
Complex Traits
Thirteenth Edition

Ricki Lewis

1

Learning Outcomes

1. Distinguish between single-gene and polygenic traits.
2. Define *complex traits*.
3. Explain how continuously varying traits reflect genetic and environmental influences.
4. Explain how determining empiric risk differs from calculating a Mendelian frequency.
5. Define *heritability*.
6. Discuss how studies on adopted individuals and twins can indicate the extent to which a trait is inherited.
7. Explain the type of information that a genome-wide association study can reveal.
8. Discuss how the methods discussed in the chapter can be applied to investigate variation in body weight.

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Genes, Environment, and Traits 1

Few genes act alone

Environmental factors and other genes may modify expression

Traits can be described as

- **Mendelian**—Caused by a single gene
- **Polygenic**—Caused by multiple genes

Both can be **complex** (also called multifactorial) due to an interaction between genes and the environment

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Genes, Environment, and Traits 2

Lung cancer is a complex trait

- Variants of genes that increase the risk of becoming addicted to nicotine and of developing cancer come into play
- However, these may not ever be expressed if a person never smokes and breathes only fresh air.

Purely polygenic traits—those not influenced by the environment at all—are rare.

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Genes, Environment, and Traits 3

Polygenic complex traits include common ones, such as height, skin color, body weight, many illnesses, and behavioral conditions & tendencies.

A polygenic complex trait or condition is the consequence of contributions of several genes.

- Each gene confers a degree of susceptibility, but not necessarily equally.

Different genes may contribute different parts of a phenotype

- This is the case for migraine.

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Polygenic Traits Are Continuously Varying

Single-gene traits are discrete or qualitative.

- Often produce an all-or-none effect

Polygenic traits produce a continuously varying phenotype.

- Also called quantitative traits
- DNA sequences involved are termed **Quantitative Trait Loci (QTLs)**

Frequency of distribution of phenotypes forms a bell-shaped curve.

- Even when different numbers of genes affect the trait, the curve takes the same shape

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Fingerprint Patterns 1

Skin on the fingertips is folded into raised patterns called dermal ridges that align to form loops, whorls, and arches.

- This pattern is a fingerprint.

Dermatoglyphics is the study of fingerprints.

Number of ridges is largely determined by genes and prenatal contact.

- Average total ridge count is 145 in a male and 126 in a female.

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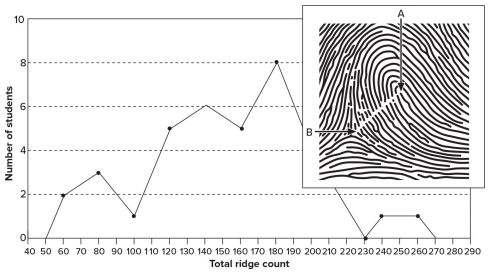
Fingerprint Patterns 2



Data from Gordon Mendenhall, Thomas Mertens, and Jon Hendrix, "Fingerprint Ridge Count" in The American Biology Teacher, vol. 51, no. 4, April 1989, pp. 204 to 206

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Height 1

The effect of the environment on height is obvious—people who do not eat enough do not reach their genetic potential for height

Difference in height between the students of the yesteryears and today are attributed to improved diet and better overall health.

Height is a continuously, varying polygenic trait

- At least 50 genes affect variation in height, some with large effects and some with lesser effects.

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Height 2

 David Hyde/Wayne Falda/McGraw-Hill Education 10

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Skin Color 1

Melanin protects against DNA damage from UV radiation, and exposure to the sun increases melanin synthesis.

Humans have same number of melanocytes per unit area of skin.

- Differ in melanosome number, size, and density distribution

More than 100 genes affect pigmentation in skin, hair, and the irises

- A simplified three-gene model is presented next

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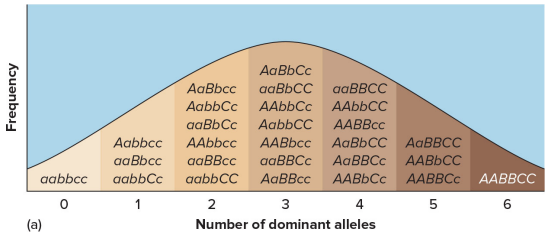
Skin Color 2



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Skin Color 3

Definition of race based largely on skin color is a social construct more than a biological concept.

Skin color is not a reliable indicator of ancestry.

- 93% of varying inherited traits are no more common in people of one skin color than any other.

(b)

(b): SWNS/South West News Service Ltd.
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Investigating Complex Traits 1

Empiric risk measures the likelihood that a trait will recur based on incidence.

Incidence is the rate at which a certain event occurs.

Prevalence is the proportion or number of individuals who have a particular trait at a specific time.

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Investigating Complex Traits 2

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:

- Severity of the disease
- Number of affected family members
- How closely related a person is to affected persons.

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Investigating Complex Traits 3

Cleft lip is more likely in a person who has a relative with the condition.

Source: Centers of Disease Control and Prevention (CDC)
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Empiric Risk of Recurrence for Cleft Lip

Table 7.1 Empiric Risk of Recurrence for Cleft Lip

Relationship to Affected Person	Empiric Risk of Recurrence
Identical twin	40.0%
Sibling	4.1%
Child	3.5%
Niece/nephew	0.8%
First cousin	0.3%
General population risk (no affected relatives)	0.1%

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Heritability 1

Heritability (denoted H) estimates the proportion of variation in a complex trait due to genetics in a particular population at a certain time.

- 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.

Heritability equals 1.0 for a trait whose variability is completely the result of gene action

- Variability of most traits, however, is due to differences among genes and environmental influences.

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Heritability 2

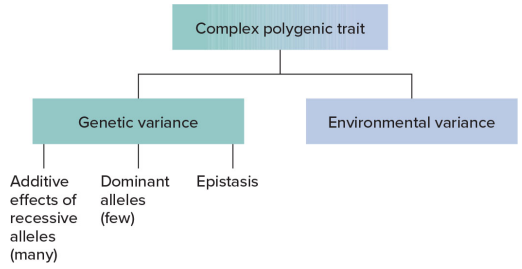

Figure 7.6 Heritability estimates the genetic contribution to the variability of a trait. Observed variance in a complex polygenic trait or illness reflects genetic and environmental contributions.

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Heritability 3

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 sun-deprived Scandinavians.

Missing heritability occurs when identified genes cannot account for all of the variability in a trait or illness.

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Heritability for Some Human Traits

Table 7.2 Heritabilities for Some Human Traits

Trait	Heritability
Clubfoot	0.8
Height	0.8
Blood pressure	0.6
Body mass index	0.4 to 0.7
Verbal aptitude	0.7
Mathematical aptitude	0.3
Spelling aptitude	0.5
Total fingerprint ridge count	0.9
Intelligence	0.5 to 0.8
Total serum cholesterol	0.6

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Estimating Heritability

- Researchers use several statistical methods to estimate heritability.
- One way is to compare the proportion of people sharing a trait to the proportion predicted to share the trait.
- Expected proportion is derived by knowing the blood relationships of the individuals.

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Coefficient of Relatedness

- The proportion of genes that two people related in a certain way share

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)
Uncl/aunt to niece/nephew	2°	25% (1/4)
Half-siblings	2°	25% (1/4)
Grandparent to grandchild	2°	25% (1/4)
First cousin to first cousin	3°	12.5% (1/8)

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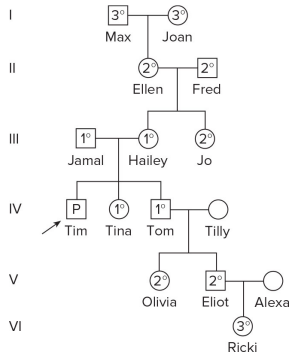
Tracing Relatives



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Adopted Individuals

- Similarities between adopted people and adopted parents reflect mostly environmental influences.
- Similarities between adoptees and their biological parents reflect mostly genetic influences.
- Information on both sets of parents can reveal how heredity and the environment both contribute to a trait.

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Twins 1

Twin studies have largely replaced adoption methods.

Concordance: Measures the frequency of expression of a trait in both members of monozygotic (MZ) or dizygotic (DZ) twins.

- Twins who differ in a trait are said to be discordant.

The more influence genes exert over a trait, the higher the differences in concordance between MZ and DZ twins.

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Twins 2

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% to 80%	0% to 8%
Cleft lip with or without cleft palate	40%	3% to 6%
Hypertension	62%	48%
Schizophrenia	40% to 50%	10%

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Twins 3

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Separating Genetic and Environmental Influences

- **Dizygotic twins**—Shared environment and 50% of genes
- **Monozygotic twins**—Identical genotype and shared environment
- **Twins raised apart**—Shared genotype but not environment
- **Adopted individuals**—Shared environment but not genes

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Genome-Wide Association Studies

A **genome-wide association study (GWAS)** compares many genetic markers across the genome between two large groups of people

- One with a particular trait or disease and one without it.

Identifying DNA sequences that are much more common in affected people can enable researchers to identify genes that contribute to the phenotype

GWAS uses several types of genetic markers, including **single nucleotide polymorphisms (SNPs)** and **copy number variants (CNVs)**

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Types of Information Used in GWAS

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 has 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 under expressed in people with a particular trait or disease.
	Epigenetic signature of methyl groups binding DNA.

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Single Nucleotide Polymorphisms (SNPs) 1

Sites in a genome where the DNA base varies in at least 1% of the population

In these studies, SNPs span the genome, rather than define a single gene

- SNP can be *anywhere* among our roughly 3.2 billion base pairs

To achieve statistical significance, a GWAS must include at least 100,000 markers.

Typically, a GWAS uses a million or more SNPs, grouped into half a million or so haplotypes.

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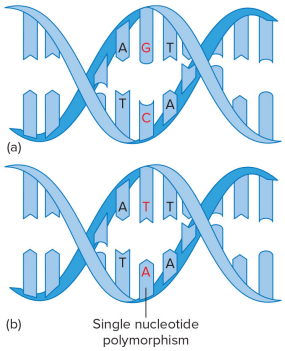
Single Nucleotide Polymorphisms (SNPs) 2



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Copy Number Variants (CNVs) 1

A CNV is a DNA sequence that repeats a different number of times in different individuals

A CNV does not provide information in the same way as a gene that encodes protein does

- But comparing CNVs is another way to distinguish individuals.

CNVs are useful in forensic applications

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Copy Number Variants (CNVs) 2

For CNVs, different numbers of repeats of a short DNA base sequence are considered to be different alleles.

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

Figure 7.10 Copy number variants provide a different type of genetic information. For copy number variants, different numbers of repeats of a short DNA base sequence are considered to be different alleles.

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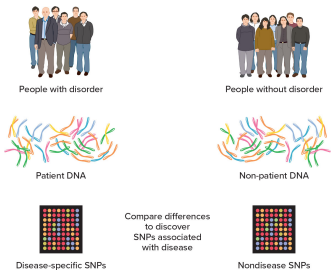
Tracking Genes in Groups

- Genome-wide association study is a stepwise focusing-in on parts of a genome that are associated to some degree with a particular trait or illness



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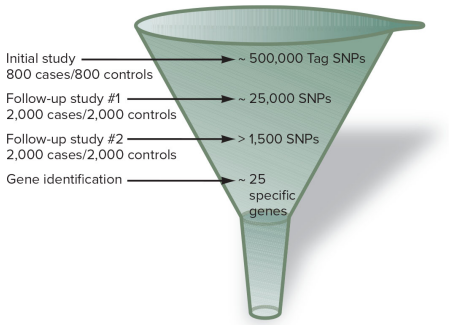
Step-Wise Approach to Gene Discovery



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Study Designs in GWAS 1

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

Case-control study: Pairs of individuals are matched so that they share as many characteristics as possible.

- SNP differences are then associated with the presence or absence of the disease or trait

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Study Designs in GWAS 2

Affected sibling pair strategy: Scans genomes of siblings for SNPs shared by those with the condition, but not by those who don't have it

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

Homozygosity mapping: Performed on families that are consanguineous

- Children in this case are more likely to inherit two copies of the mutation

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Study Designs for Complex Traits

Table 7.6 Study Designs for Complex Traits

Type of Study	Definition
Cohort	Researchers follow many people over time and measure several traits.
Case-control	People in two groups are individually matched for several characteristics, and differences in SNP patterns are identified.
Affected sibling pair	Tests identify SNPs that siblings with the same condition share but that siblings who do not both have the condition do not share.
Homozygosity mapping	Disease-causing mutations are identified in homozygous genome regions that children inherit from parents who are related to each other.

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Limitations of Genome-Wide Association Studies 1

- Include so many data points and so are prone to error
- Reveal associations between two types of information, not causes
- Bias can be introduced in the way the patient population is selected
- Accuracy is affected by complicating factors, such as phenocopy and epistasis
- May miss extremely rare SNPs

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Limitations of Genome-Wide Association Studies 2

The success of a GWAS may depend on the quality of the question asked.

- The technique was helpful, for example, in explaining why some people who live on the Solomon Islands have blond hair
  - A single base change in a gene called *TYRP1*

 Danyi Lenkukiga fotostock 42

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Terms Used in Evaluating Multifactorial Traits

Table 7.7 Terms Used in Evaluating Complex Traits

Coefficient of relatedness The proportion of genes shared by two people related in a particular way. Used to calculate heritability.

Concordance The percentage of twin pairs in which both twins express a trait.

Empiric risk The risk of recurrence of a trait or illness based on known incidence in a population.

Genome-wide association study (GWAS) Detecting any association between marker patterns and increased risk of a condition.

Heritability The percentage of phenotypic variation for a trait that is attributable to genetic differences. It equals the ratio of the observed phenotypic variation to the expected phenotypic variation for a population of individuals.

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Body Weight

Weight is a complex trait that can be studied

- Determined by the rate at which food is taken in versus the rate at which the body uses it for fuel

Scientific studies use a measurement called **body mass index (BMI)**

- BMI = weight (kg)/height^2 (m^2)

Heritability for BMI ranges in various studies from 0.4 to 0.7, which leaves room for environmental influences on our appetites and sizes.

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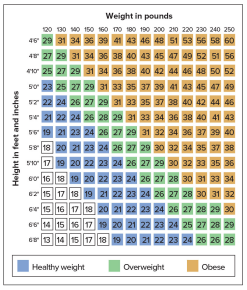
Body Mass Index (BMI)



(Source: CDC.gov)

Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion

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Genes that Affect Weight

Leptin—Protein hormone produced by fat cells

- Signals the hypothalamus to decrease appetite
- Acts in the long term to maintain weight

Ghrelin—Peptide hormone produced in the stomach

- Responds to hunger by increasing appetite
- Functions in the short term to regulate weight

Many more genes are involved in weight regulation

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Genetic Control of Body Weight

Table 7.8 Some Sites of Genetic Control of Body Weight

Protein	Function	Effect on Appetite
Leptin	Stimulates cells in hypothalamus to decrease appetite and metabolize nutrients	↓
Leptin transporter	Enables leptin to cross from bloodstream into brain	↓
Leptin receptor	Binds leptin on hypothalamus cell surfaces, triggering hormone's effects	↓
Neuropeptide Y	Produced in hypothalamus when leptin levels are low and the individual loses weight	↑
Melanocortin-4 receptor	Activated when leptin levels are high and the individual gains weight	↓
Ghrelin	Signals hunger from stomach to brain in the short term, stimulating neuropeptide Y	↑
PYY	Signals satiety from stomach to brain	↓
Stearoyl-CoA desaturase-1	Controls whether body stores or uses fat	↑

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Environmental Influences on Weight

Heritability studies of obesity and BMI suggest that genes play a larger role in those who tend to gain weight easily.

Populations that switch to a high-fat, high-calorie diet and a less-active lifestyle reveal effects of the environment on body weight.

- The Arizona Pima Indians developed the highest prevalence of obesity on earth

Another environmental influence on weight is the "gut microbiome"

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