Multifactorial Inheritance

PRINCIPLES OF MULTIFACTORIAL INHERITANCE

The Basic Model

- Traits in which variation is thought to be caused by the combined effects of multiple genes are called polygenic ("many genes").
- When environmental factors are also believed to cause variation in the trait, which is usually the case, the term multifactorial is used.
- Many quantitative traits (those, such as blood pressure, that are measured on a continuous numerical scale) are multifactorial.
- Because they are caused by the additive effects of many genetic and environmental factors, these traits tend to follow a normal, or "bell-shaped," distribution in populations.

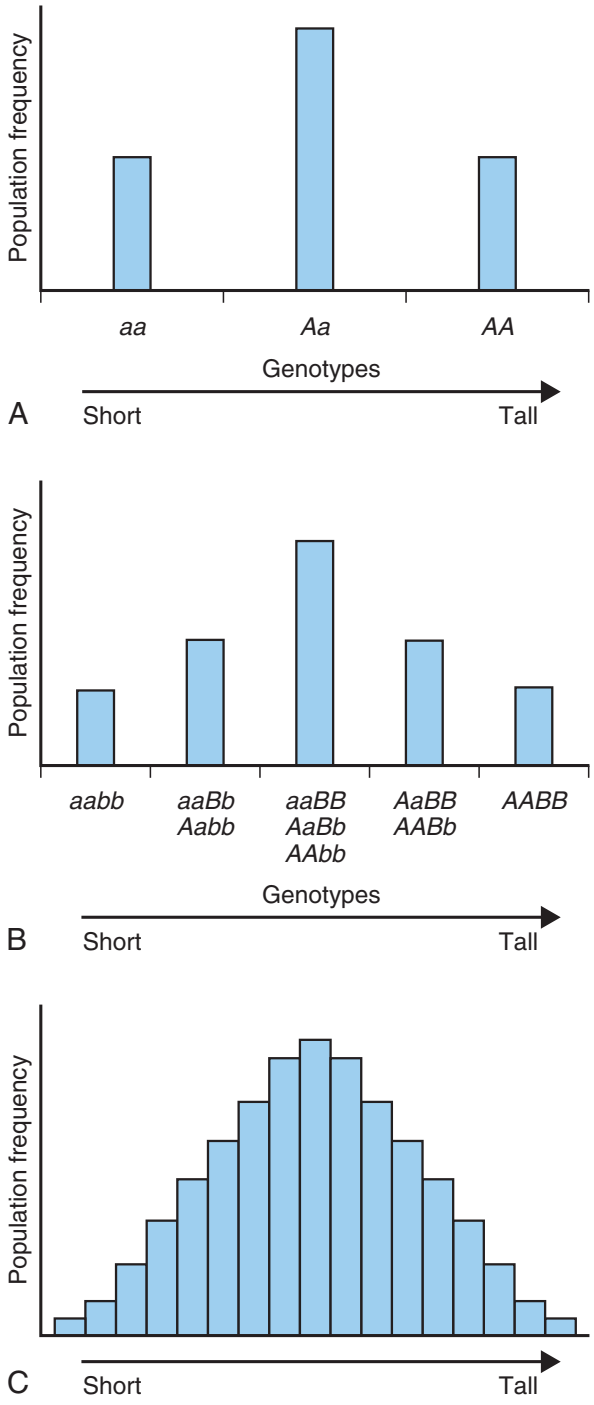


FIG 12-1 A, The distribution of height in a population, assuming that height is controlled by a single locus with genotypes AA, Aa, and aa. B, The distribution of height, assuming that height is controlled by two loci. There are now five distinct phenotypes instead of three, and the distribution begins to look more like the normal distribution. C, Distribution of height, assuming that multiple factors, each with a small effect, contribute to the trait (the multifactorial model).

The Basic Model

- Individual genes underlying a multifactorial trait such as height follow the Mendelian principles of segregation and independent assortment, just like any other genes. The only difference is that many of them *act together* to influence the trait.

- Blood pressure is another example of a multifactorial trait. There is a correlation between parents' blood pressures (systolic and diastolic) and those of their children.

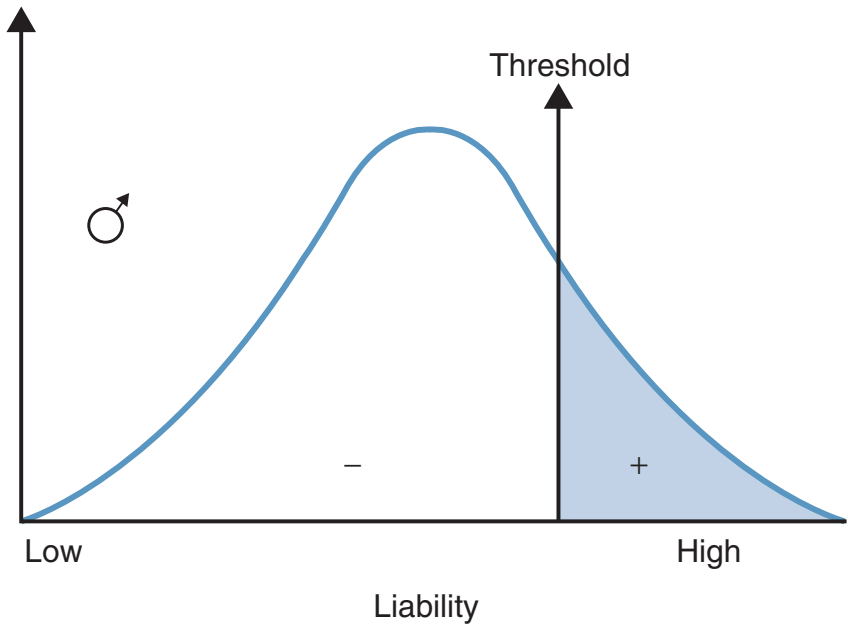
- There is good evidence that this correlation is due in part to genes. But blood pressure is also influenced by environmental factors, such as diet and stress.

The Threshold Model

- A number of diseases do not follow the bell-shaped distribution. Instead, they appear to be either present or absent in individuals.
- A commonly used explanation is that there is an underlying liability distribution for these diseases in a population.

- For multifactorial diseases that are either present or absent, it is thought that a threshold of liability must be crossed before the disease is expressed.

→ Below the threshold, the individual appears normal; above it, he or she is affected by the disease.



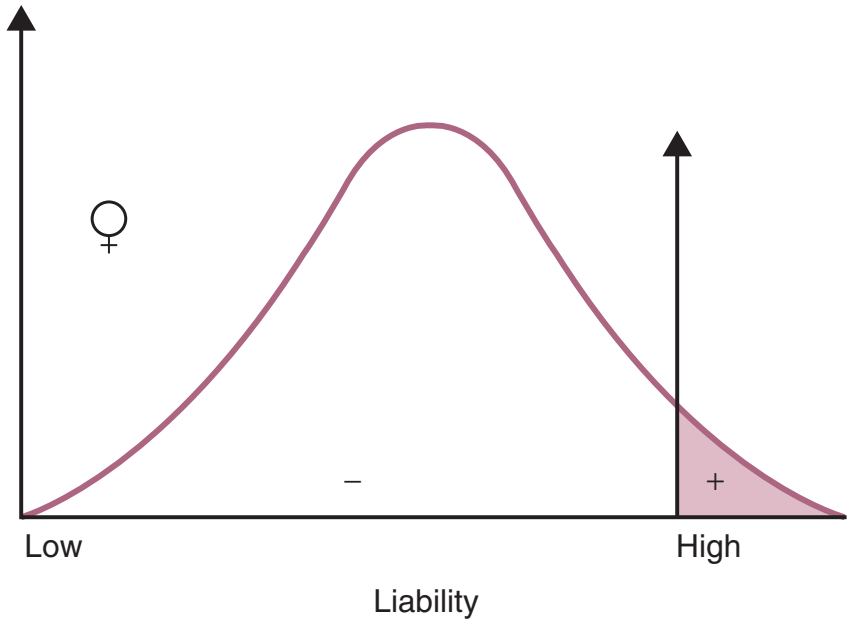


FIG 12-2 A liability distribution for a multifactorial disease in a population. To be affected with the disease, a person must exceed the threshold on the liability distribution. This figure shows two thresholds, a lower one for males and a higher one for females (as in pyloric stenosis).

The Threshold Model

- A disease that is thought to correspond to this threshold model is pyloric stenosis, a disorder that manifests shortly after birth and is caused by a narrowing or obstruction of the pylorus, the area between the stomach and intestine.

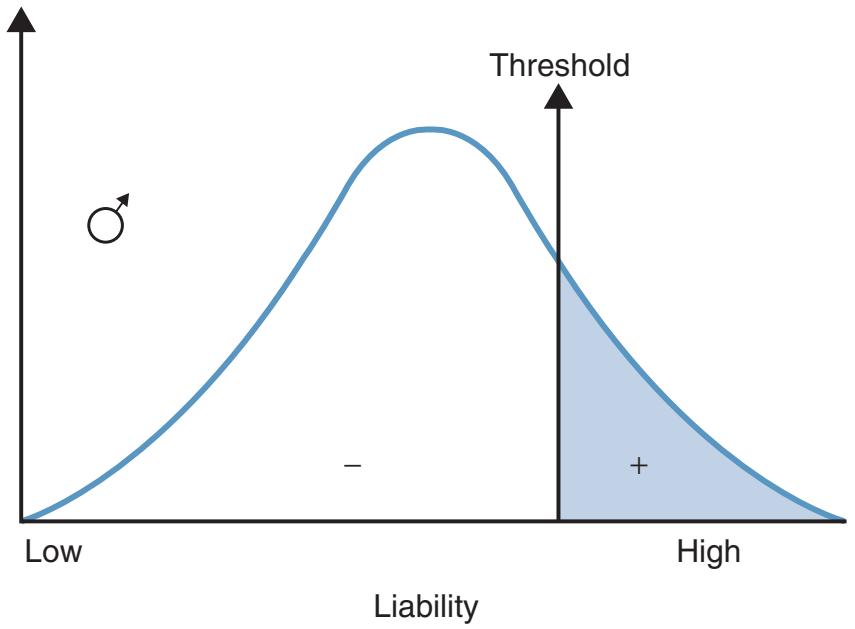
- Chronic vomiting, constipation, weight loss, and electrolyte imbalance result from the condition, but it sometimes resolves spontaneously or can be corrected by surgery.

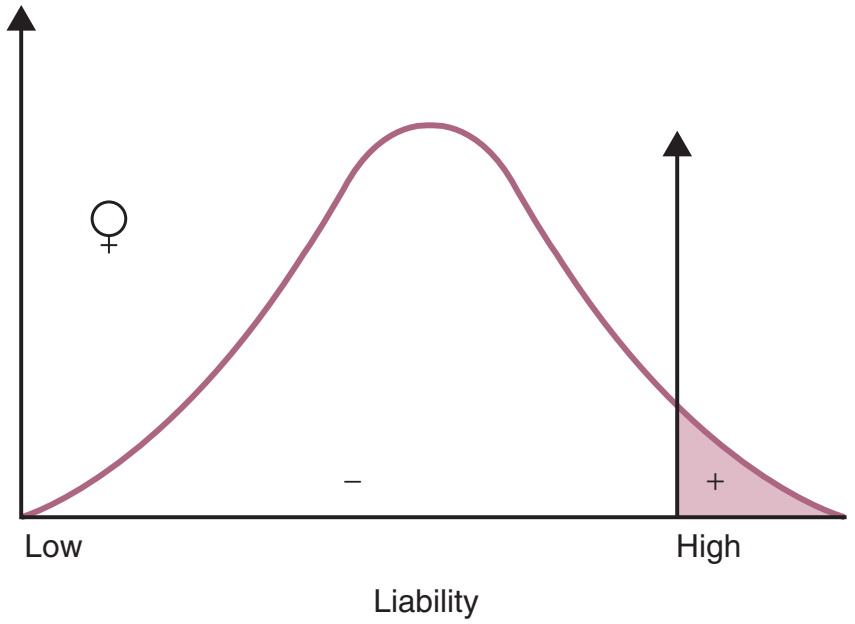
The Threshold Model

- The prevalence o f pyloric stenosis among Caucasians is about 3/1,000 live births. It is much more common in males than in females, affecting 1/200 males and 1/1,000 females.

- It is thought that this difference in prevalence reflects two thresholds in the liability distribution, a lower one in males and a higher one in females.

- A lower male threshold implies that fewer disease-causing factors are required to generate the disorder in males.





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The Threshold Model

- A number of other congenital malformations are thought to correspond to this model.

→ They include isolated* cleft lip and/or cleft palate, neural tube defects (anencephaly and spina bifida), club foot (talipes), and some forms of congenital heart disease.

- Many of the common adult diseases, such as hypertension, heart disease, stroke, diabetes mellitus (types 1 and 2), and some cancers, are caused by complex genetic and environmental factors and can thus be considered multifactorial diseases

Recurrence Risks and Transmission Patterns

- The number of genes contributing to the disease is usually not known, the precise allelic constitution of the parents is not known, and the extent of environmental effects can vary substantially!!

- For most multifactorial diseases, empirical risks (i.e., risks based on direct observation of data) have been derived.

Recurrence Risks and Transmission Patterns

- To estimate empirical risks, a large series of families is examined in which one child (the proband) has developed the disease.
- The relatives of each proband are surveyed in order to calculate the percentage who have also developed the disease.

- In contrast to most single-gene diseases, recurrence risks for multifactorial diseases can change substantially from one population to another. This is because gene frequencies as well as environmental factors can differ among populations.

Several criteria are usually used to define multifactorial inheritance:

1. The recurrence risk is higher if more than one family member is affected.
2. If the expression of the disease in the proband is more severe, the recurrence risk is higher.
3. The recurrence risk is higher if the proband is of the less commonly affected sex.
4. The recurrence risk for the disease usually decreases rapidly in more remotely related relatives.
5. If the prevalence of the disease in a population is f, the risk for offspring and siblings of probands is approximately $\sqrt{f}$.

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TABLE 12-2 Recurrence Risks for First-, Second-, and Third-Degree Relatives of Probands

DISEASE	PREVALENCE IN GENERAL POPULATION	DEGREE OF RELATION		
		FIRST DEGREE	SECOND DEGREE	THIRD DEGREE
Cleft lip/palate	0.001	0.04	0.007	0.003
Club foot	0.001	0.025	0.005	0.002
Congenital hip dislocation	0.002	0.005	0.006	0.004

Multifactorial versus Single-Gene Inheritance

- It is important to clarify the difference between a multifactorial disease and a single-gene disease in which there is locus heterogeneity. In the former case, a disease is caused by the simultaneous influence of multiple genetic and environmental factors, each of which has a relatively small effect.

- In contrast, a disease with locus heterogeneity, such as osteogenesis imperfecta, requires only a single mutation to cause it. Because of locus heterogeneity, a single mutation at either of two or more loci can cause disease; some affected persons have one mutation while others have the other mutation.

- In some cases, a trait may be influenced by the combination of both a single gene with large effects and a multifactorial background in which additional genes and environmental factors have small individual effects (Fig. 12-4).

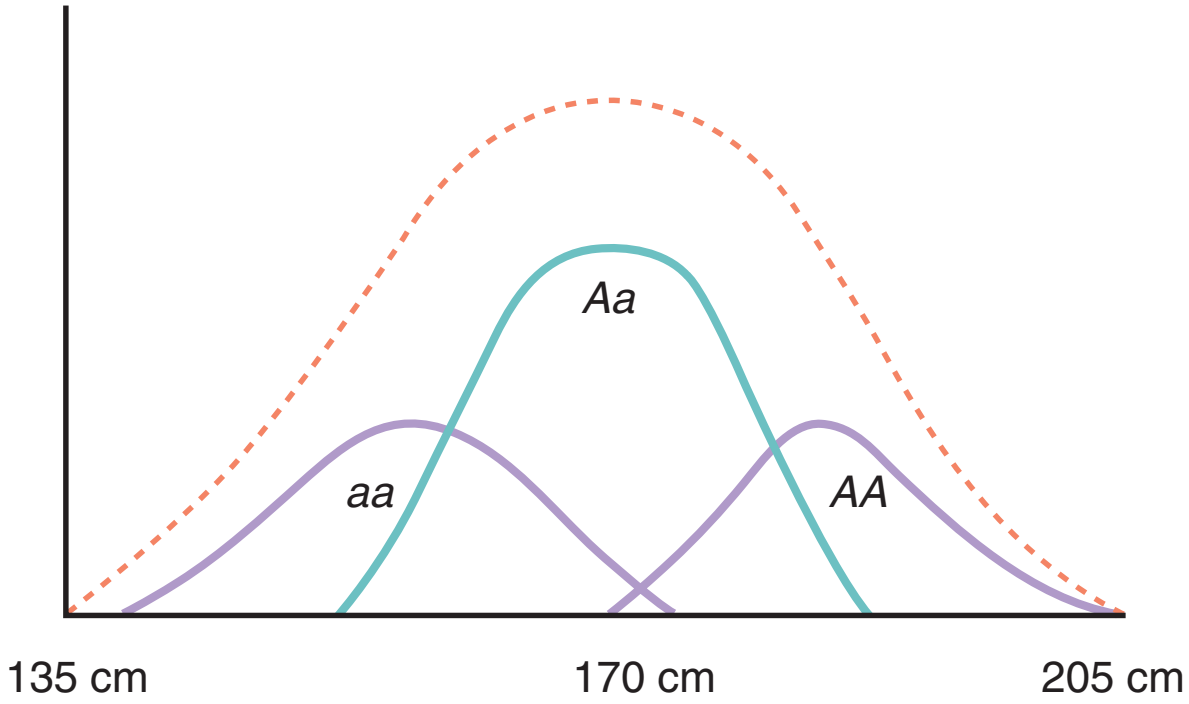

FIG 12-4 The distribution of height, assuming the presence of a major gene (genotypes *AA, Aa,* and *aa*) combined with a multifactorial background. The multifactorial background causes variation in height among individuals of each genotype. If the distributions of each of the three genotypes were superimposed, then the overall distribution of height would be approximately normal, as shown by the dotted line.

- Many of the diseases to be discussed later can be caused by a major gene and/or multifactorial inheritance.

- That is, there are subsets of the population in which diseases such as colon cancer, breast cancer, or heart disease are inherited as single-gene disorders (with additional variation in disease susceptibility contributed by other genetic and environmental factors).

- These subsets usually account for only a small percentage of the total number of disease cases. It is nevertheless important to identify the responsible major genes, because their function can provide important clues to the pathophysiology and treatment of the disease.

THE GENETICS OF COMMON DISEASES
Congenital Malformations

- Congenital malformations are seen in roughly **1** of every 50 live births. Most of them are considered to be multifactorial disorders.
- Specific genes and environmental causes have been detected for some congenital malformations, but the causes of most congenital malformations remain largely unknown.
- In general, sibling recurrence risks for most of these disorders range from 1% to 5%.

TABLE 12-4 Prevalence Rates of Common Congenital Malformations in Persons of European Descent

DISORDER	APPROXIMATE PREVALENCE PER 1000 BIRTHS
Cleft lip/palate	1.0
Club foot	1.0
Congenital heart defects	4.0-8.0
Hydrocephaly	0.5-2.5
Isolated cleft palate	0.4
Neural tube defects	1.0-3.0
Pyloric stenosis	3.0

- Some congenital malformations, such as cleft lip/palate and pyloric stenosis, are relatively easy to repair and thus do not cause lasting problems.
- Others, such as neural tube defects, usually have more severe consequences.
- Although some cases of congenital malformations can occur in the 'absence of any other problems, it is quite common for them to be associated with other disorders.

→ For example, cleft lip/ palate is often seen in babies with trisomy 13, and congenital heart defects are seen in many syndromes, including trisomy of chromosomes 13, 18, and 21.

THE GENETICS OF COMMON DISEASES

Multifactorial Disorders in the Adult Population

Heart Disease

- The most common underlying cause of heart disease is coronary artery disease (CAD), which is caused by atherosclerosis.
- A number of risk factors for CAD have been identified, including obesity, cigarette smoking, hypertension, elevated cholesterol level, and positive family history
- Studies showed that the risk is higher if there are more affected relatives, if the affected relative is female (the less commonly affected sex) rather than male, and if the age of onset in the affected relative is early (before 55 years of age).

- As lipids play a major role in atherosclerosis, studies have focused on the genetic determination of variation in circulating lipoprotein levels.
- An important advance was the identification of the gene that encodes the low-density lipoprotein (LDL) receptor.

→ Heterozygosity for a mutation in this gene roughly doubles LDL cholesterol levels and is seen in approximately 1 in 500 persons.

- Mutations in the gene encoding apolipoprotein B, which are seen in about 1 in 1000 persons, are another genetic cause of elevated LDL cholesterol.

TABLE 12-5 Lipoprotein Genes Known to Contribute to Coronary Heart Disease Risk

GENE	CHROMOSOME LOCATION	FUNCTION OF PROTEIN PRODUCT
Apolipoprotein A-I	11q	HDL component; LCAT cofactor
Apolipoprotein A-IV	11q	Component of chylomicrons and HDL; may influence HDL metabolism
Apolipoprotein C-III	11q	Allelic variation associated with hypertriglyceridemia
Apolipoprotein B	2p	Ligand for LDL receptor; involved in formation of VLDL, LDL, IDL, and chylomicrons
Apolipoprotein D	2p	HDL component
Apolipoprotein C-I	19q	LCAT activation
Apolipoprotein C-II	19q	Lipoprotein lipase activation
Apolipoprotein E	19q	Ligand for LDL receptor
Apolipoprotein A-II	1p	HDL component
LDL receptor	19p	Uptake of circulating LDL particles
Lipoprotein(a)	6q	Cholesterol transport
Lipoprotein lipase	8p	Hydrolysis of lipoprotein lipids
Hepatic triglyceride lipase	15q	Hydrolysis of lipoprotein lipids
LCAT	16q	Cholesterol esterification
Cholesterol ester transfer protein	16q	Facilitates transfer of cholesterol esters and phospholipids between lipoproteins

Adapted in part from King RA, Rotter JI, eds. *The Genetic Basis of Common Diseases*. 2nd ed. New York: Oxford University Press; 2002.
HDL, High-density lipoprotein; *IDL,* Intermediate-density lipoprotein; *LCAT,* lecithin cholesterol acyltransferase; *LDL,* low-density lipoprotein; *VLDL,* very-low-density lipoprotein.

- Environmental factors, many of which are easily modified, are also important causes of CAD.

→ There is abundant epidemiological evidence that cigarette smoking and obesity increase the risk of CAD, whereas exercise and a diet low in saturated fats decrease the risk.

- The approximate 60% reduction in age-adjusted mortality due to CAD and stroke in the United States since 1950 is usually attributed to a decrease in the percentage of adults who smoke cigarettes, decreased consumption of saturated fats, improved medical care, and increased emphasis on healthy lifestyle factors such as exercise.

THE GENETICS OF COMMON DISEASES
Hypertension

- Systemic hypertension is a key risk factor for heart disease, stroke, and kidney disease. It is estimated that hypertension is responsible for approximately half of all cardiovascular mortality.
- Studies of blood pressure correlations within families yield heritability estimates of approximately 30% to 50% for both systolic and diastolic blood pressure.
- As the heritability estimates are less than 100%, it indicates that environmental factors must also be significant causes of blood pressure variation.
- The most important environmental risk factors for hypertension are increased sodium intake, decreased physical activity, psychosocial stress, and obesity

- Blood pressure regulation is a highly complex process that is influenced by many physiological systems, including various aspects of kidney function, cellular ion transport, vascular tone, and heart function.
- Much research is now focused on specific components that might influence blood pressure variation, such as the renin-angiotensin system (involved in sodium reabsorption and vasoconstriction); vasodilators such as nitric oxide and the kallikrein-kinin system; and ion transport systems such as adducin and sodium-lithium countertransport.

→ Linkage and association studies have implicated several genes involved in the renin-angiotensin system (e.g., the genes that encode angiotensinogen, angiotensin-converting enzyme type I, and angiotensin II type I receptor) in causing hypertension.

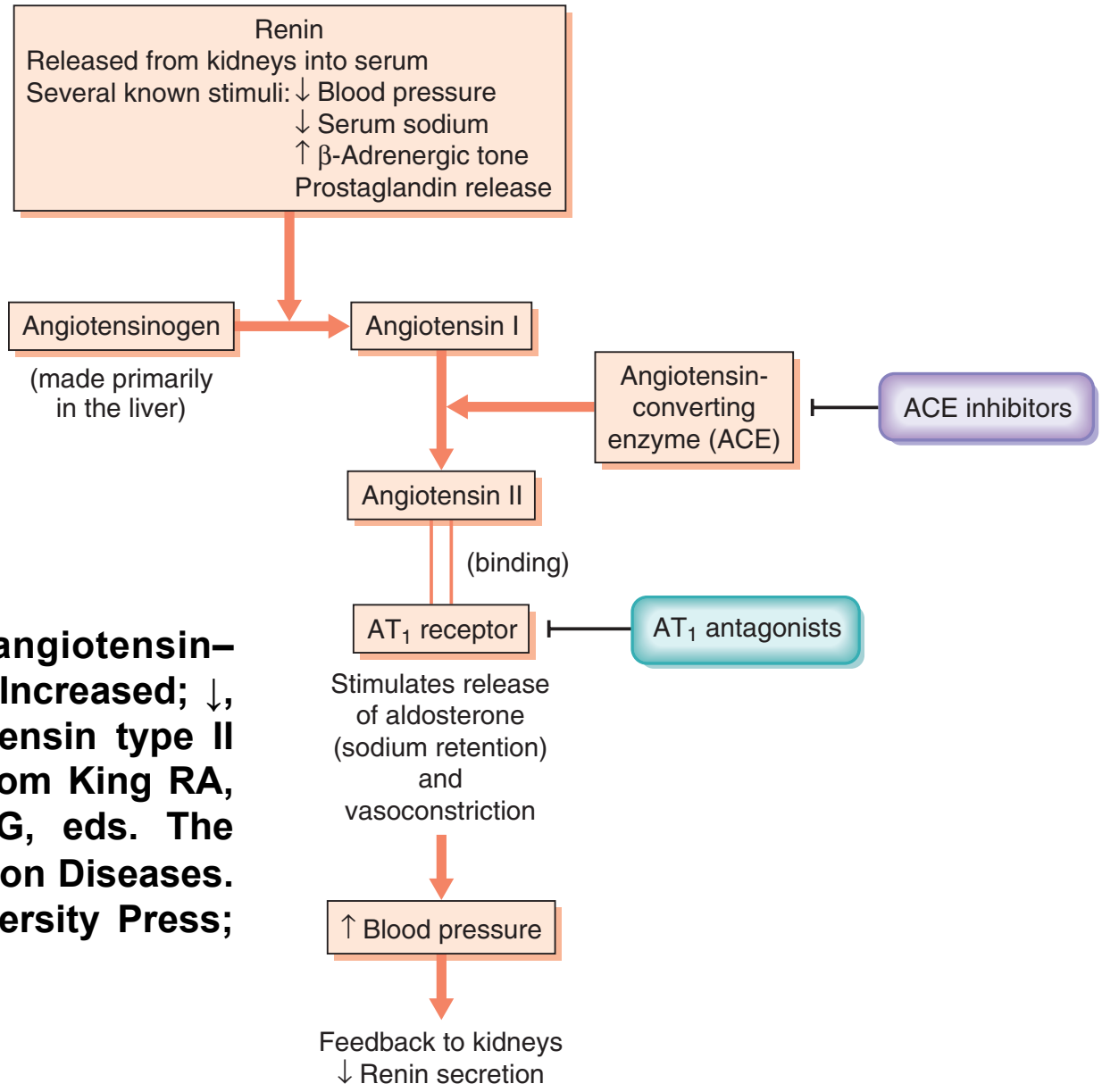

FIG 12-8 The renin–angiotensin–aldosterone system. ↑, Increased; ↓, decreased; AT_1, angiotensin type II receptor 1. (Modified from King RA, Rotter JI, Motulsky AG, eds. The Genetic Basis of Common Diseases. New York: Oxford University Press; 1992.)

THE GENETICS OF COMMON DISEASES
Cancer

- Most common cancers have genetic components Recurrence risks tend to be higher if there are multiple affected relatives and if those relatives developed cancer at an early age

- Specific genes have been discovered that cause inherited colon, breast, and prostate cancer in some families.

THE GENETICS OF COMMON DISEASES

Cancer

- Many major types of cancer (e.g., breast, colon, prostate, ovarian) cluster strongly in families. This is due both to shared genes and shared environmental factors.
- Environmental factors play an important role in causing cancer by inducing somatic mutations.

→ Tobacco use is estimated to account for one third of all cancer cases in developed countries, making it the most important known cause of cancer.

→ Diet (i.e., carcinogenic substances and the lack of "anticancer" components such as fiber, fruits, and vegetables) is another leading cause of cancer and may also account for as much as one third of cancer cases.

→ Approximately 15% of worldwide cancer cases are caused primarily by infectious agents (e.g., human papilloma virus for cervical cancer, hepatitis B and C for liver cancer).

Breast Cancer

- If a woman has one affected first-degree relative her risk developing breast cancer doubles.
- The risk increases further with additional affected relatives, and it increases if those relatives developed cancer at a relatively early age (before 50 years of age).

- Several genes are now known to predispose women to developing hereditary breast cancer.

→ Most important among these are *BRCA1* and *BRCA2*, two genes involved in DNA repair.

→ Germline mutations in the *TP53* and *CHK2* genes can cause Li-Fraumeni syndrome, which also predisposes to breast cancer.

→ Cowden disease, Ataxia-telangiectasia, Mutations in the *MSH2* and *MLH* 1 DNA repair genes.

- Despite the significance of these genes, it should be emphasized that more than 90% of breast cancer cases are not inherited as mendelian diseases.

- A number of environmental factors are known to increase the risk of developing breast cancer. These include:

→ nulliparity (never bearing children),

→ bearing the first child after 30 years of age,

→ a high-fat diet, alcohol use, and

→ estrogen replacement therapy.

Colorectal cancer

- 1 in 20 Americans will develop colorectal cancer, and roughly one third of those with this cancer will die from it.
- It is also clusters in families. The risk of colorectal cancer in people with one affected first-degree relative is two to three times higher than that of the general population.

- Familial colorectal cancer can be the result of mutations in the *APC* tumor suppressor gene or in one of several DNA mismatch-repair genes (HNPCC).

- Most colorectal cancer cases (>90%) are not inherited as mendelian conditions and are likely to be caused by a complex interaction of inherited and somatic genetic alterations and environmental factors.
- The latter risk factors include a lack of physical activity and a high-fat, low-fiber diet.

Prostate cancer

- Having an affected first-degree relative increases the risk of developing prostate cancer by a factor of two to three, and the heritability of prostate cancer is estimated to be approximately 40%.

- The relatively late age of onset of most prostate cancer cases (median age, 72 years) makes genetic analysis especially difficult.

- Genome scans have identified several dozen polymorphisms associated with prostate cancer risk.

- Several of these are located in chromosome 8q24, which contains polymorphisms associated with several other cancers as well (colon, pancreas, and esophagus).

- Although the 8q24 region contains no protein-coding genes, it contains enhancer elements that affect expression of the *MYC* oncogene, located about 250 kb from 8q24.

- Nongenetic risk factors for prostate cancer may include a high-fat diet.

- Because prostate cancer usually progresses slowly and because it can be detected by digital examination and by the prostate-specific antigen (PSA) test, fatal metastasis can usually be prevented. usually be prevented.

THE GENETICS OF COMMON DISEASES

Diabetes

- Three major types of diabetes:

- Type 1 (formerly termed insulin-dependent diabetes mellitus, or IDDM),
- Type 2 (formerly termed non-insulin-dependent diabetes mellitus, or NIDDM), and
- Maturity-onset diabetes of the young MODY).

THE GENETICS OF COMMON DISEASES

Diabetes

- ***Type 1 diabetes***.

- Characterized by destruction of the insulin-producing beta cells,
- usually manifests before 40 years of age.
- Patients with type 1 diabetes must receive exogenous insulin to survive.
- Autoantibodies are formed against pancreatic cells, insulin, and enzymes such as glutamic acid decarboxylase.
- A strong association with the presence of several human leukocyte antigen (HLA) class II alleles.
- Over the past few decades, the incidence of type I diabetes has increased substantially.

THE GENETICS OF COMMON DISEASES

Diabetes

- ***Type 1 diabetes***.

- Siblings of persons with type 1 diabetes face a substantial elevation in risk: approximately 6%, as opposed to a risk of about 0.3% to 0.5% in the general population.
- The recurrence risk is also elevated when there is a diabetic parent, although this risk varies with the sex of the affected parent.

→ The risk for offspring of diabetic mothers is only 1% to 3%, but it is 4% to 6% for the offspring of diabetic fathers.

- Approximately 95% of whites with type 1 diabetes have the *HLA DR3* and/or *DR4* alleles, whereas only about 50% of the general white population has either of these alleles.
- If an affected proband and a sibling are both heterozygous for the *DR3* and *DR4* alleles, the sibling's risk of developing type 1 diabetes is nearly 20% (i.e., about 40 times higher than the risk in the general population).
-

THE GENETICS OF COMMON DISEASES

Diabetes

- ***Type 1 diabetes***.

- The insulin gene, which is located on the short arm of chromosome 11, is another logical candidate for type 1 diabetes susceptibility.
- Polymorphisms within and near this gene have been tested for association with type 1 diabetes.

→ A strong risk association is seen with allelic variation in a VNTR polymorphism located just 5' of the insulin gene.

→ Differences in the number of VNTR repeat units might affect transcription of the insulin gene, which would result in variation in susceptibility.

- It is estimated that inherited genetic variation in the insulin region accounts for approximately 10% of the familial clustering of type 1 diabetes.

THE GENETICS OF COMMON DISEASES

Diabetes

- ***Type 2 diabetes***.

- Accounts for more than 90% of all diabetes cases, and its incidence is rising rapidly in populations with access to high-calorie diets.
- Affects approximately 10% to 20% of the adult populations of many developed countries.
- Usually have some degree of endogenous insulin production, and can sometimes be treated successfully with dietary modification, oral drugs, or both.
- Patients usually have insulin resistance (i.e., their cells have difficulty using insulin) and are more likely to be obese.

THE GENETICS OF COMMON DISEASES

Diabetes

- ***Type 2 diabetes***.

- Usually seen in patients older than 40 years, but because of increasing obesity among adolescents and young adults, it is now increasing rapidly in this segment of the population.
- The recurrence risks for first-degree relatives of patients with type 2 diabetes are higher than those for type 1 patients, generally ranging from 15% to 40%.
- The two most important risk factors for type 2 diabetes are a positive family history and obesity; the latter increases insulin resistance.
- Extensive linkage and genome-wide association analyses have identified more than 70 genes that contribute to type 2 diabetes susceptibility.

→ The most significant gene identified thus far is *TCF7L2*, which encodes a transcription factor involved in secreting insulin.

THE GENETICS OF COMMON DISEASES

Diabetes

- ***Maturity-onset diabetes of the young (MODY)**:*

- Accounts for 1% to 5% of all diabetes cases, typically occurs before 25 years of age and follows an autosomal dominant mode of inheritance.
- Is not associated with obesity.
- About 50% of cases are caused by mutations in the gene that encodes glucokinase, a rate-limiting enzyme in the conversion of glucose to glucose-6-phosphate in the pancreas.
- Another 40% of MODY cases are caused by mutations in any of five genes that encode transcription factors involved in pancreatic development or insulin regulation: hepatocyte nuclear factor-1α *(HNFlα),* hepatocyte nuclear factor-1*β (HNF1β),* hepatocyte nuclear factor-4α *(HNF4α),* insulin promoter factor-1 *(IPF1),* and neurogenic differentiation 1 *(NEUROD1).*

THE GENETICS OF COMMON DISEASES
Obesity

- The worldwide prevalence of obesity is increasing rapidly among adults and children.
- Approximately 70% of American adults and 60% of British adults are overweight (body mass index [BMI) >25), and about half of these overweight persons are obese (BMI >30).
- Although obesity itself is not a disease, it is an important risk factor for several common diseases, including heart disease, stroke, type 2 diabetes, and cancers of the prostate, breast, and colon.

THE GENETICS OF COMMON DISEASES
Obesity

- There is a strong correlation between obesity in parents and obesity in their children.

→ Common environmental effects: parents and children usually share similar diet and exercise habits.

- Genetic components:

- adoption studies each showed that the body weights of adopted persons correlated significantly with their natural parents' body weights but not with those of their adoptive parents.
- The heritability of fatness" (measured, for example, by skinfold thickness) is approximately 0.50.
- Genes that encode leptin (Greek, "thin") and its receptor.

THE GENETICS OF COMMON DISEASES
Obesity

- The leptin hormone is secreted by adipocytes and binds to receptors in the hypothalamus, the site of the body's appetite control center.

→ Increased fat stores lead to an elevated leptin level, which produces satiety and a loss of appetite.

→ Lower leptin levels lead to increased appetite.

- Leptin participates in important interactions with other components of appetite control, such as neuropeptide Y, α-melanocyte-stimulating hormone and its receptor, the melanocortin-4 receptor (MC4R).
- Mutations in the gene that encodes MC4R have been found in 3% to 5% of severely obese individuals.

THE GENETICS OF COMMON DISEASES

Alzheimer's Disease

- Affects approximately 10 % of the population older than 65 years and 40% of the population older than 85 years.
- Alzheimer disease is characterized by progressive dementia and memory loss and by the formation of amyloid plaques and neurofibrillary tangles in the brain, particularly in the cerebral cortex and hippocampus.
- The plaques and tangles lead to progressive neuronal loss, and death usually occurs within 7 to 10 years after the first appearance of symptoms.
- The risk of developing AD doubles in persons who have an affected first-degree relative.
- About 3% to 5% of AD cases occur before age 65 years and are considered early onset; these are much more likely to be inherited in autosomal dominant fashion.

THE GENETICS OF COMMON DISEASES
Alzheimer's Disease

- Approximately 10% of AD cases are caused by autosomal dominant genes. Early-onset cases cluster more strongly in families and are more likely to follow an autosomal dominant inheritance pattern.
- This disease is genetically heterogeneous: at least four AD susceptibility genes have been identified.
- Three of the genes (encoding presenilin 1, presenilin 2, and amyloid-β precursor protein) cause early-onset AD and affect the cleavage and processing of the amyloid precursor protein.
- A fourth encodes the apolipoprotein E protein and is strongly associated with late-age onset of AD.