UNIT 4 - GENETIC DISORDERS

Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev

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Unit 4 Contents

Attribution

4.1 UNIT OVERVIEW

Learning Objectives

- Describe a genomic variant and the potential impacts of variants on health and development.
- Distinguish between different forms of variants.
- Explain the difference between inherited (germline) and non-inherited (somatic) variants
- Compare monogenetic and polygenic disorders.
- Examine modifiable and non-modifiable risk factors and their impacts on the genome.
- Explore factors affecting phenotype variability, including penetrance, expressivity, and anticipation.
- Describe how errors in chromosome structure occur and explore some chromosomal disorders.
- Review the impacts of mitochondrial disorders.

Outline

Topics covered in this chapter include:

- Gene variants
- Genetic disorders
- Single gene disorders
- Polygenic conditions
- Genotype-phenotype associations
- Modifiable and non-modifiable risk factors
- Disorders in chromosome number
- Mitochondrial disorders

Competencies Nurses will Develop in this Chapter

ANA (2023):

Provision of education, care, and support:

- Uses health promotion and disease prevention practices that consider genomic influences as well as personal and environmental risk factors.

NHS (2023):

Identify individuals who might benefit from genomic services and/or information as part of assessing needs and planning care:

- recognizing the key indicators of a potential genetic condition, or clinical situation where genomics-informed healthcare would be appropriate; and
- recognizing the importance of family history in assessing predisposition to a genetic condition.

Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

Provide ongoing nursing care and support to patients, carers, families and communities with genomic healthcare needs:

- promote healthy behaviours that may be beneficial to alleviate symptoms or, where applicable, implement management strategies or lifestyle changes to help reduce risk.

Key terminology

Aneuploid

An individual with an error in chromosome number.

Barr body

Early in development, when female mammalian embryos consist of just a few thousand cells, one X chromosome in each cell inactivates by condensing into a structure called a Barr body.

Codon

A codon is a DNA or RNA sequence of three nucleotides (a trinucleotide) that forms a unit of genomic information encoding a particular amino acid or signaling the termination of protein synthesis (stop signals). There are 64 different codons: 61 specify amino acids and 3 are used as stop signals.

Conditional variants

Variants that rely on the concept of phenotype = genotype + environment + interaction. Organisms with this variant express a altered phenotype, but only under specific environmental conditions.

Continuous variation

Many interesting and important traits exhibit continuous variation, meaning they exhibit a continuous range of phenotypes that are usually measured quantitatively, such as intelligence, body mass, blood pressure in animals (including humans), and yield, water use, or vitamin content in crops.

Copy number variant (CNV)

Copy number variation (abbreviated CNV) refers to a circumstance in which the number of copies of a specific segment of DNA varies among different individuals' genomes. The individual variants may be short or include thousands of bases. These structural differences may have come about through duplications, deletions or other changes and can affect long stretches of DNA. Such regions may or may not contain a gene(s).

De novo variants

Mosaicism (can be somatic or germline) refers to the presence of cells in a person that have a different genome from the body's other cells. This difference could be due to a specific genomic variant, for example, or the addition or loss of a chromosome. The condition can stem from a genetic error that occurs after fertilization of an egg, during very early embryo development, or it could occur later in development. Mosaicism can affect any type of cell and does not always cause disease.

Deletion

A deletion, as related to genomics, is a type of mutation that involves the loss of one or more nucleotides from a segment of DNA. A deletion can involve the loss of any number of nucleotides, from a single nucleotide to an entire piece of a chromosome.

Deletion-insertion

This variant occurs when a deletion and insertion happen at the same time in the same location in the gene. In a deletion-insertion variant, at least one nucleotide is removed and at least one nucleotide is inserted. However, the change must be complex enough to differ from a simple substitution. The resulting protein may not function properly. A deletion-insertion (delins) variant may also be known as an insertion-deletion (indel) variant.

Discrete variation

Most of the phenotypic traits commonly used in introductory genetics are qualitative. This means the phenotype exists in only two (or possibly a few more) discrete, alternative forms, such as purple or white flowers, or red or white eyes. These qualitative traits are therefore said to exhibit discrete variation.

Down syndrome

Down syndrome (also called Trisomy 21) is a genetic condition caused by an error in the process that replicates and then divides up the pairs of chromosomes during cell division, resulting in the inheritance of an extra full or partial copy of chromosome 21 from a parent. This extra chromosomal DNA causes the intellectual disabilities and physical features characteristic of Down syndrome, which vary among individuals.

Duplication

Duplication, as related to genomics, refers to a type of mutation in which one or more copies of a DNA segment (which can be as small as a few bases or as large as a major chromosomal region) is produced. Duplications occur in all organisms. For example, they are especially prominent in plants, although they can also cause genetic diseases in humans. Duplications have been an important mechanism in the evolution of the genomes of humans and other organisms.

Essential genes

Variants in essential genes create recessive lethal alleles that arrest or derail the development of an individual at an immature (embryonic, larval, or pupal) stage. This type of variant may, therefore, go unnoticed in a typical variant screen because they are absent from the progeny being screened.

Expressivity

The variability in mutant phenotypes observed in individuals with a particular phenotype.

Euploid

An individual with the appropriate number of chromosomes for their species (22 pairs autosomes and one pair of sex chromosomes in humans).

Frameshift

A frameshift mutation in a gene refers to the insertion or deletion of nucleotide bases in numbers that are not multiples of three. This is important because a cell reads a gene's code in groups of three bases when making a protein. Each of these "triplet codons" corresponds to one of 20 different amino acids used to build a protein. If a mutation disrupts this normal reading frame, then the entire gene sequence following the mutation will be incorrectly read. This can result in the addition of the wrong amino acids to the protein and/or the creation of a codon that stops the protein from growing longer.

Gain-of-function variants

Some variants can have a positive effects, such as producing new proteins that help an individual better adapt to changes is the environment.

Genetic disorder

Genetic disorders are caused by variants that alter or eliminate a gene's function leading to morphological or physiological changes.

Genetic redundancy

The lack of phenotypic change from a loss-of-function variant by be attributed to genetic redundancy.

That is, the mutant gene's lost function is compensated by another gene, at another locus, encoding a similarly functioning product. Thus, the loss of one gene is compensated by the presence of another. The concept of genetic redundancy is an important consideration in genetic screens. A gene whose function can be compensated for my another gene, cannot be easily identified in a genetic screen for loss-of-function variants.

Germline variants (inherited)

Are passed from parent to child and are present throughout a person's life in virtually every cell in the body. These variants are also called germline variants because they are present in the parent's egg or sperm cells, which are also called germ cells. When an egg and a sperm cell unite, the resulting fertilized egg cell contains DNA from both parents. Any variants that are present in that DNA will be present in the cells of the child that grows from the fertilized egg.

Insertion

An insertion, as related to genomics, is a type of mutation that involves the addition of one or more nucleotides into a segment of DNA. An insertion can involve the addition of any number of nucleotides, from a single nucleotide to an entire piece of a chromosome.

Karyotype

A karyotype is an individual's complete set of chromosomes. The term also refers to a laboratory-produced image of a person's chromosomes isolated from an individual cell and arranged in numerical order. A karyotype may be used to look for abnormalities in chromosome number or structure.

Klinefelter syndrome

The XXY chromosome complement, corresponding to one type of Klinefelter syndrome, corresponds to male individuals with small testes, enlarged breasts, and reduced body hair.

Intergenic regions

Intergenic regions are the stretches of DNA located between genes. In humans, intergenic regions are non-protein-coding and comprise a large majority of the genome. Some intergenic DNA is known to regulate the expression of nearby genes.

Introns

An intron is a region that resides within a gene but does not remain in the final mature mRNA molecule following transcription of that gene and does not code for amino acids that make up the protein encoded by that gene. Most protein-coding genes in the human genome consist of exons and introns.

Inversion

An inversion in a chromosome occurs when a segment breaks off and reattaches within the same chromosome, but in reverse orientation. DNA may or may not be lost in the process.

Lethal variants

Variants that cause the premature death of an organism.

Loss-of-function variant

Variants that cause the loss-of-function of a gene, yet do not cause a change in phenotype, even when the mutant allele is homozygous.

Missense

A missense mutation is a DNA change that results in different amino acids being encoded at a particular position in the resulting protein. Some missense mutations alter the function of the resulting protein

Mitochondrial DNA

Mitochondrial DNA is the circular chromosome found inside the cellular organelles called mitochondria. Located in the cytoplasm, mitochondria are the site of the cell's energy production and other metabolic functions. Offspring inherit mitochondria — and as a result mitochondrial DNA — from their mother.

Mitochondrial encephalomyopathies

Mitochondrial disorders that cause both muscular and neurological problems.

Mitochondrial myopathies

Mitochondrial disorders that mostly cause muscular problems.

Monogenic disorder

Multifactorial inheritance disorder or polygenic inheritance.

Morphological variants

Variants that cause changes in the visible form of the organism as they give rise to altered forms of a trait.

Mutation

A mutation is a change in the DNA sequence of an organism. Mutations can result from errors in DNA replication during cell division, exposure to mutagens or a viral infection. Germline mutations (that occur in eggs and sperm) can be passed on to offspring, while somatic mutations (that occur in body cells) are not passed on. The preferred term is “variant,” though mutation can be used to refer to a pathogenic variant.

Nonsense

A nonsense mutation occurs in DNA when a sequence change gives rise to a stop codon rather than a codon specifying an amino acid. The presence of the new stop codon results in the production of a shortened protein that is likely non-functional.

Penetrance

The proportion of individuals with a particular genotype that display a corresponding phenotype.

Permissive conditions

Under permissive conditions, conditional variants show a wild type phenotype.

Pleiotropic

Pleiotropy occurs when one gene influences two or more seemingly unrelated phenotypic traits. Such a gene that exhibits multiple phenotypic expression is called a pleiotropic gene.

Polymorphisms

One of two or more variants of a particular DNA sequence.

Polyploid

An individual with more than the correct number of chromosome sets (two for diploid species).

Reciprocal translocation

Result from the exchange of chromosome segments between two nonhomologous chromosomes such that there is no gain or loss of genetic information.

Repeat expansion

Some regions of DNA contain short sequences of nucleotides that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of sequences of three nucleotides, and a tetranucleotide repeat is made up of sequences of four nucleotides. A repeat expansion is a variant that increases the number of times that the short DNA sequence is repeated. This type of variant can cause the resulting protein to function improperly.

Restrictive conditions

Under restrictive conditions, conditional variants express the altered phenotype.

Silent variants

When the variant does not have an obvious effect on the phenotype. This could be because the change occurs in the DNA sequence in a non-coding region such as intergenic regions or introns. Alternatively, a change in a single nucleotide may result in a codon that produces the same amino acid.

Single nucleotide polymorphisms (SNP – pronounced “snip)

A single nucleotide polymorphism (abbreviated SNP, pronounced snip) is a genomic variant at a single base position in the DNA. Scientists study if and how SNPs in a genome influence health, disease, drug response and other traits.

Somatic variants (non-inherited)

Occur at some time during a person’s life and are present only in certain cells, not in every cell in the body. Because non-inherited variants typically occur in somatic cells (cells other than sperm and egg cells), they are often referred to as **somatic variants**. These variants cannot be passed to the next generation. Non-inherited variants can be caused by environmental factors such as ultraviolet radiation from the sun or can occur if an error is made as DNA copies itself during cell division.

Substitution

Substitution, as related to genomics, is a type of mutation in which one nucleotide is replaced by a different nucleotide. The term can also refer to the replacement of one amino acid in a protein with a different amino acid.

Translocation

A translocation, as related to genetics, occurs when a chromosome breaks and the (typically two) fragmented pieces re-attach to different chromosomes. The detection of chromosomal translocations can be important for the diagnosis of certain genetic diseases and disorders.

Turner syndrome

Characterized by the presence of only one X chromosome in women instead of two.

Variant

A difference in the DNA sequence. See mutation.

Attribution & References

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4.2 GENE VARIANTS

What is a Gene Variant and how do Variants Occur?

Variant vs. Mutation

In Unit 2, we discussed gene variants and inheritance patterns. In our discussion of genetic conditions, we will revisit these concepts in this Unit. Recall that prior practice was to use the term "**mutation**." However, due to the negative connotations associated with this word, the preferred term is "**variant**." Not all variants cause a change in phenotype. The term mutation refers to a pathogenic variant which causes a change in the end product. The preferred term is "pathogenic variant."

What is a genomic variant?

All humans have near-identical DNA sequences across the estimated six billion-letter code for their genome. Slight differences exist between individuals, making each of us unique. These differences, called genomic variants, occur at specific locations within the DNA. DNA is read like a code. Recall this code is made up of four types of chemical building blocks – adenine, thymine, cytosine and guanine, abbreviated with the letters A, T, C and G. A genomic variant occurs in a location within the DNA where that code differs among people. For example, in Person One below, the location shows a "C" base. But in the exact location in Person Two, it is a "T."

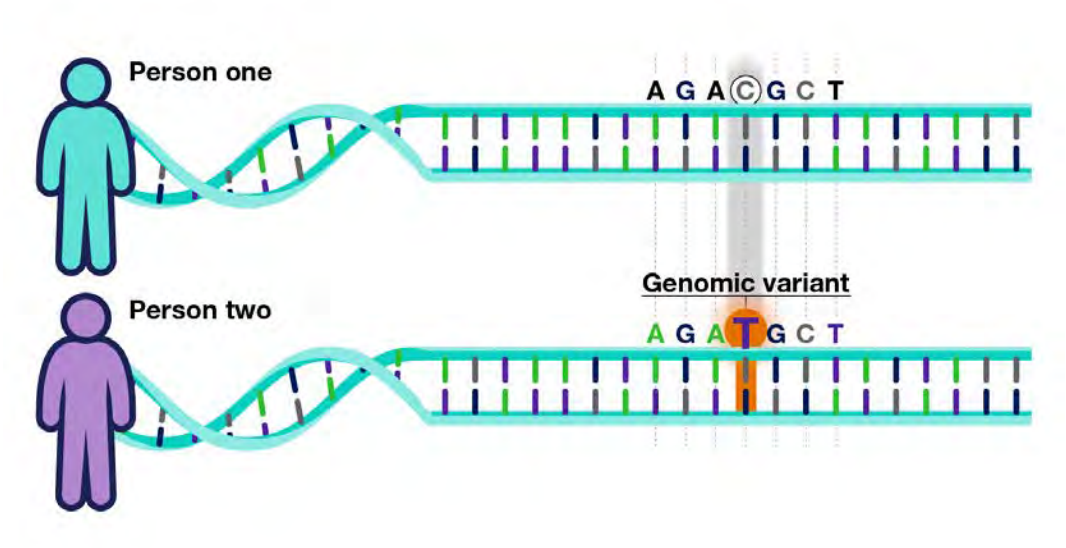

Figure 4.1 courtesy: National Human Genome Research Institute, PDM with attribution

An individual's genome has roughly 4 to 5 million such genomic variants. These variants may be unique to that individual or occur in others. Some variants increase the risk of developing diseases, while others may reduce such risk; others do not affect disease risk. In other words,

The question is: How do these genomic variants influence the risk for specific diseases?

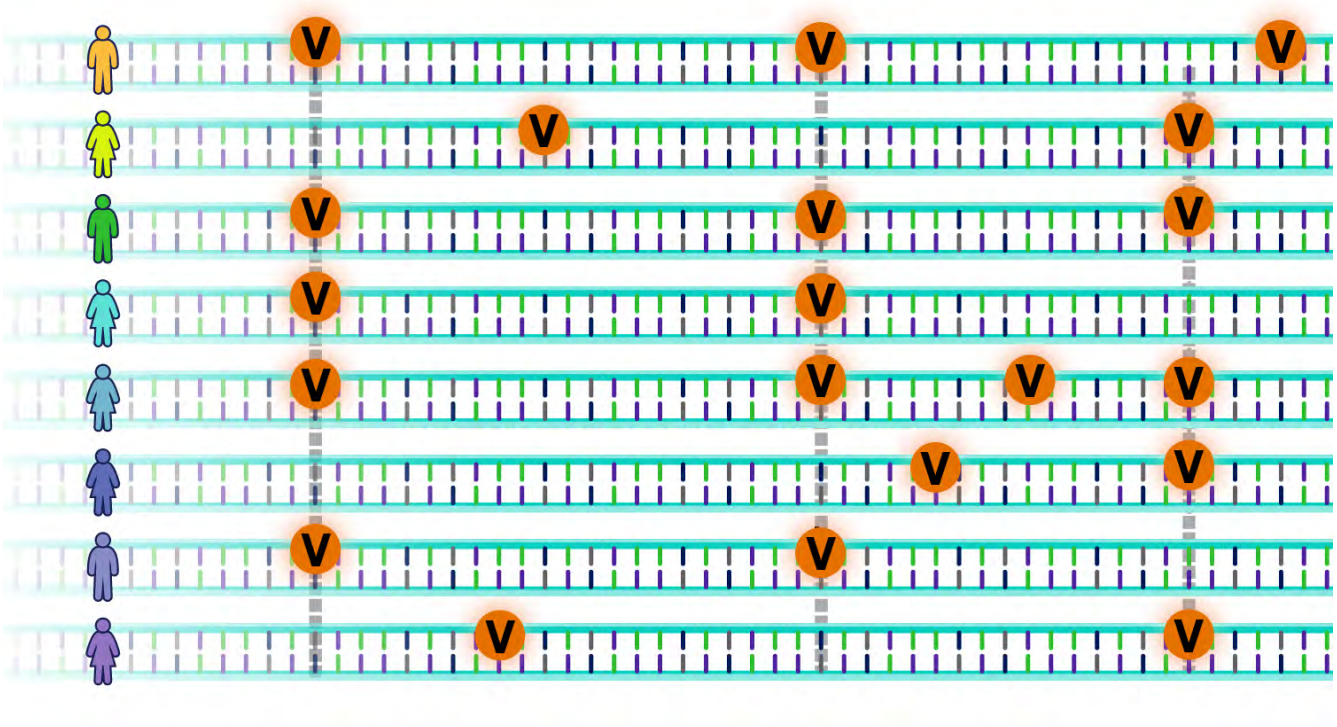

Figure 4.2 Image shows genomic variants represented by the letter "V." Some are shared among individuals, while others are specific to one person. **Courtesy:** National Human Genome Research Institute, PDM with attribution

Morphological Variants

Morphological variants cause changes in the visible form of the organism as they give rise to altered forms of a trait, e.g., change in size, shape (normal wing vs. curly wing in fruit flies), colour, number, etc.

Figure 4.3 Examples of Morphological Variants in Dogs. Six different dogs, each of different species, display a wide range of physical attributes that point to morphological mutations, such as differences in fur colour and texture, tail length, height of limbs, facial features, ear presentation, etc. **Source:** Dog morphological variation by Mary Bloom, American Kennel Club, CC0.

Lethal Variants

A **lethal variant** causes the premature death of an organism. For example, in Drosophila (fruit flies), lethal variants can result in death during the embryonic, larval, or pupal stages. Lethal variants are usually recessive, so both gene copies must be lost for premature death (homozygous lethal alleles will not be viable). Heterozygotes, which have one lethal allele and one wild-type allele, are typically viable. In the example shown in the figure below regarding yellow coat colour in mice, the lethal allele is recessive because it causes death only in homozygotes. Unlike its effect on survival, the effect of the allele on colour is dominant. A single copy of the allele in heterozygotes produces a yellow colour in mice. These examples illustrate the point that the type of dominance depends on the aspect of the phenotype examined.

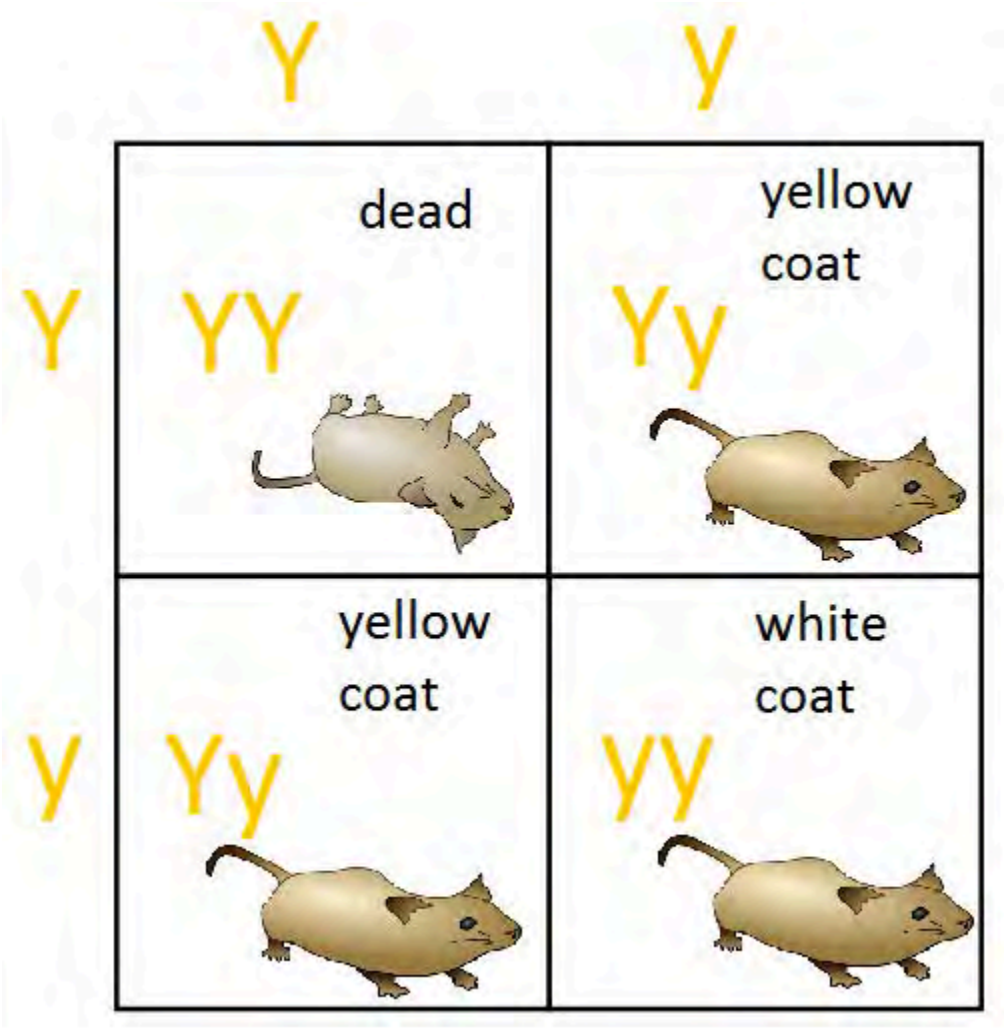

Figure 4.4 A Punnett square shows the production of offspring from two parents, both of which carry the allele dominant for coat colour but recessive for lethality. Both parents are genotype Yy; both display a yellow coat colour. In the offspring, there is a 3:1 ratio of living to dead progeny, with the accumulation of the YY alleles in one-out-of-four offspring results in death. Yy in the offspring (50%) display yellow coat colour and are alive, and yy offspring (25%) display white coat colour, which is recessive to yellow, and are alive. **Source:** Lethal alleles punnett square by Dead_mouse.svg and Mouse.svg: Madprime derivative work: Adabow, CC BY-SA 3.0.

Conditional Variants

Conditional variations rely on phenotype = genotype + environment + interaction. Organisms with this variant express an altered phenotype, but only under specific environmental conditions. Under **restrictive conditions**, they express the altered phenotype; under permissive conditions, they show a wild-type phenotype. One example of a conditional variant is the temperature-sensitive pigmentation of Siamese cats. Siamese cats have a temperature-sensitive fur colour; their fur appears unpigmented (light-coloured) when grown in a warm environment. The hair appears pigmented (dark) when grown at a cooler temperature. This is seen at the peripheral regions of the feet, snout, and ears. This is because, in warm temperatures, the enzyme needed for melanin pigment synthesis becomes nonfunctional. However, in cooler temperatures, the enzyme required for melanin synthesis is functional, and the deposition of melanin makes the fur look dark.

Figure 4.5 Two Siamese cats display temperature sensitive colour, which is an example of conditional mutations, whereby the environment dictates the phenotype expressed. Their fur appears unpigmented (light coloured) when grown in a warm temperature environment. The fur appears pigmented (dark) when grown at a cooler temperature. This is seen at the peripheral regions of the feet, snout, and ears. **Source:** Two Siamese Cats by Steve Gilham, CC BY-NC-SA 2.0

Do all gene variants affect health and development?

Only a small percentage of variants cause genetic disorders—most have no impact on health or development. For example, some variants alter a gene's DNA sequence but do not change the function of the protein made from the gene. Often, gene variants that could cause a genetic disorder are repaired by certain enzymes before the gene is expressed and an altered protein is produced. Each cell has a number of pathways through which enzymes recognize and repair errors in DNA. Because DNA can be changed or damaged in many ways, DNA repair is an important process by which the body protects itself from disease.

A very small percentage of all variants actually have a positive effect (**gain-of-function variant**). These variants lead to new versions of proteins that help an individual better adapt to environmental changes. For example, a beneficial variant could result in a protein that protects an individual and future generations from a new strain of bacteria.

Gene variants can be inherited from a parent or occur during a person's lifetime:

- **Inherited (or hereditary) variants** are passed from parent to child and are present throughout a person's life in virtually every cell in the body. These variants are also called **germline variants** because they are present in the parent's egg or sperm cells, which are also called germ cells. When an egg and a sperm cell unite, the resulting fertilized egg cell contains DNA from both parents. Any variants in that DNA will be present in the child's cells that grow from the fertilized egg.
- **Non-inherited variants** occur at some time during a person's life and are present only in certain cells, not in every cell in the body. Because non-inherited variants typically occur in somatic cells (cells other than sperm and egg cells), they are often called **somatic variants**. These variants cannot be passed to the next generation. Non-inherited variants can be caused by environmental factors such as sun ultraviolet radiation or an error when DNA copies itself during cell division.

Some genetic changes are described as new **(de novo) variants**; these variants are recognized in a child but not in either parent. The variant sometimes occurs in a parent's egg or sperm cell but is absent in other cells. In other cases, the variant occurs in the fertilized egg shortly after the egg and sperm cells unite. (It is often impossible to tell exactly when a de novo variant happened.) As the fertilized egg divides, each resulting cell in the growing embryo will have the variant. De novo variants are one explanation for genetic disorders in which an affected child has a variant in every cell in the body. Still, the parents do not, and there is no family history of the disorder.

Variants acquired during development can lead to **mosaicism**, in which a set of cells in the body has a different genetic makeup than others. In mosaicism, the genetic change is not present in a parent's egg or sperm cells or the fertilized egg but happens later, anytime from embryonic development through adulthood. As cells grow and divide, cells that arise from the cell with the altered gene will have the variant, while other cells will not. It is called somatic mosaicism when a proportion of somatic cells have a gene variant and others do not. Depending on the variant and how many cells are affected, somatic mosaicism may or may not cause health problems. When a proportion of egg or sperm cells have a variant and others do not, it is called **germline mosaicism**. In this situation, an unaffected parent can pass a genetic condition to their child.

Most variants do not lead to disease development, and those that do are uncommon in the general population. Some variants occur often enough in the population to be considered common genetic variation. Several variants are responsible for differences between people, such as eye colour, hair colour, and blood type. Although many of these common variations in the DNA have no adverse effects on a person's health, some may influence the risk of developing certain disorders.

Silent Changes

After mutagen treatment, most base pair changes (especially substitutions) have no noticeable effect on the phenotype. Often, this is because the change occurs in the DNA sequence of a non-coding region of the DNA, such as in **the intergenic areas** (between genes) or within an **intron** where the sequence does not

code for protein and is not essential for proper mRNA splicing. Also, even if the change affects the coding region, it may not alter the amino acid sequence (recall that the genetic code is degenerate; for example, GCT, GCC, GCA, and GCG all encode alanine) so a change in a single nucleotide may result in a **codon** that produces the same amino acid. This is referred to as a **silent variant**. The base substitution may also change an amino acid, but this does not quantitatively or qualitatively alter the product's function so that no phenotypic change would occur.

Environment and Genetic Redundancy

In some situations, a variant can cause a complete **loss of function** of a gene yet not produce a change in the phenotype, even when the mutant allele is homozygous. The lack of a visible phenotypic change can be due to environmental effects: losing that gene product may not be apparent in that specific environment but might be in another.

Alternatively, the lack of a phenotype might be attributed to **genetic redundancy**. That is, the mutant gene's lost function is compensated by another gene at another locus, encoding a similarly functioning product. Thus, the loss of one gene is compensated by the presence of another. The concept of genetic redundancy is an essential consideration in genetic screens. A gene whose function can be compensated for by another gene cannot be easily identified in a genetic screen for loss-of-function variants.

How can gene variants affect health and development?

To function correctly, each cell depends on thousands of proteins to do their jobs in the right places at the right times. A variant can cause a protein normally expressed by a gene to malfunction or to not be produced at all. When a variant alters a protein that plays a critical role in the body, it can disrupt normal development or cause a health condition. A condition caused by variants in one or more genes is called a **genetic disorder.**

It is important to emphasize that ***genes do not cause disease—genetic disorders are caused by variants that alter or eliminate a gene's function***. For example, when people say someone has "the cystic fibrosis gene," they usually refer to a version of the *CFTR* (https://medlineplus.gov/genetics/gene/cftr/) gene that contains a variant that causes the disease. All people, including those without cystic fibrosis, have a version of the *CFTR* gene.

Essential Genes and Lethal Alleles

In some cases, gene variants are so severe that they prevent an embryo from surviving until birth (lethal variants). Sometimes, it is required to reach a particular developmental stage before the phenotype resulting from a variant can be seen or scored. For example, flower colour can only be scored in plants that are mature

enough to make flowers, and eye colour can only be scored in flies that have developed to the adult stage. However, some organisms with variants may not develop sufficiently to reach a stage that can be scored for a particular phenotype. Variants in **essential genes** create recessive lethal alleles that arrest or derail the development of an individual at an immature (embryonic, larval, or pupal) stage. Therefore, this variant type may go unnoticed in a typical variant screen because they are absent from the screened progeny. Furthermore, the progeny of a monohybrid cross involving an embryonic lethal recessive allele may all be of a single phenotypic class, giving a phenotypic ratio of 1:0 (which is the same as 3:0). In this case, the variant may not be detected. Nevertheless, studying recessive lethal variants (those in essential genes) has elucidated many important biochemical pathways.

What kinds of gene variants are possible?

The human genome's most common polymorphisms (or genetic differences) are single base-pair differences. Scientists call these differences SNPs for **single-nucleotide polymorphisms.** When two different haploid genomes are compared, SNPs occur, on average, about every 1,000 bases, other types of polymorphisms—for example, differences in copy number, insertions, deletions, duplications, and rearrangements—also occur, but much less frequently (NIH & BSCS, 2007).

Note: The images in the following section still use the term "mutation."

The DNA sequence of a gene can be altered in a number of ways. Gene variants can have varying effects on health, depending on where they occur and whether they alter the function of essential proteins. Variant types include the following:

Substitution

This variant type replaces one DNA building block (nucleotide) with another. Substitution variants can be further classified by their effect on protein production from the altered gene.

- **Missense**:A missense variant is a type of substitution in which the nucleotide change replaces one protein building block (amino acid) with another in the protein made from the gene. The amino acid change may alter the function of the protein.

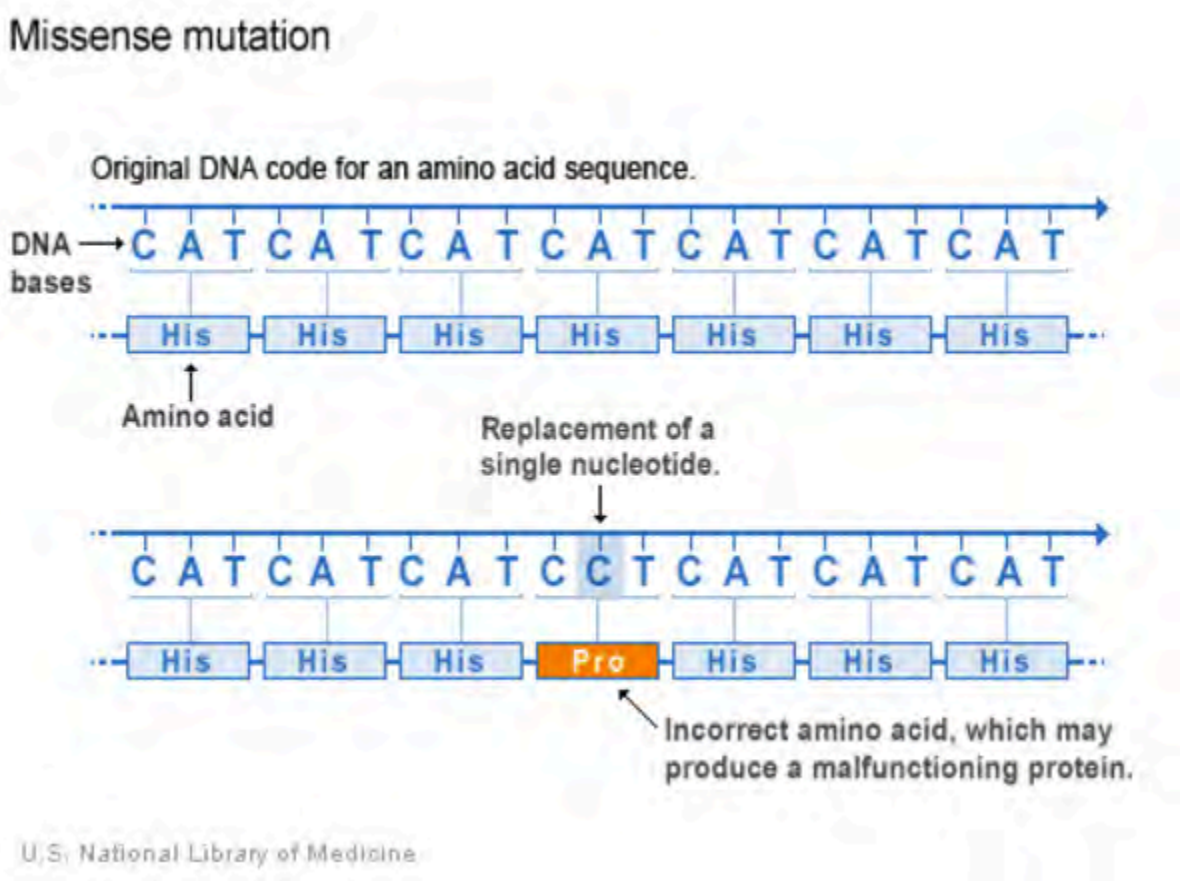

Figure 4.6 Missense mutation courtesy of U.S. National Library of Medicine, PDM with attribution

- **Nonsense**: A nonsense variant is another type of substitution. However, instead of causing a change in one amino acid, the altered DNA sequence results in a stop signal that prematurely signals the cell to stop building a protein. This type of variant results in a shortened protein that may malfunction, be nonfunctional or get broken down.

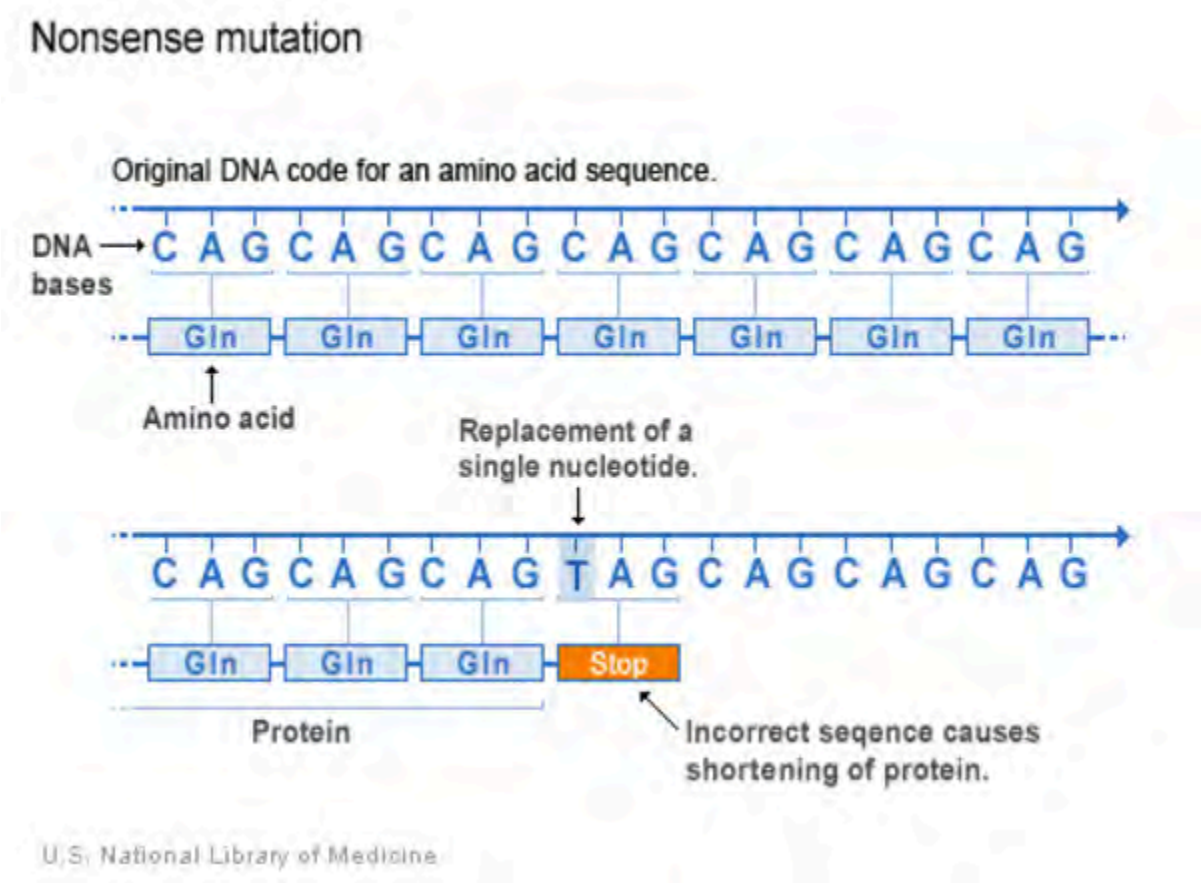

Figure 4.7 Nonsense mutation courtesy of U.S. National Library of Medicine, PDM with attribution

Insertion

An insertion changes the DNA sequence by adding one or more nucleotides to the gene. As a result, the protein made from the gene may not function properly.

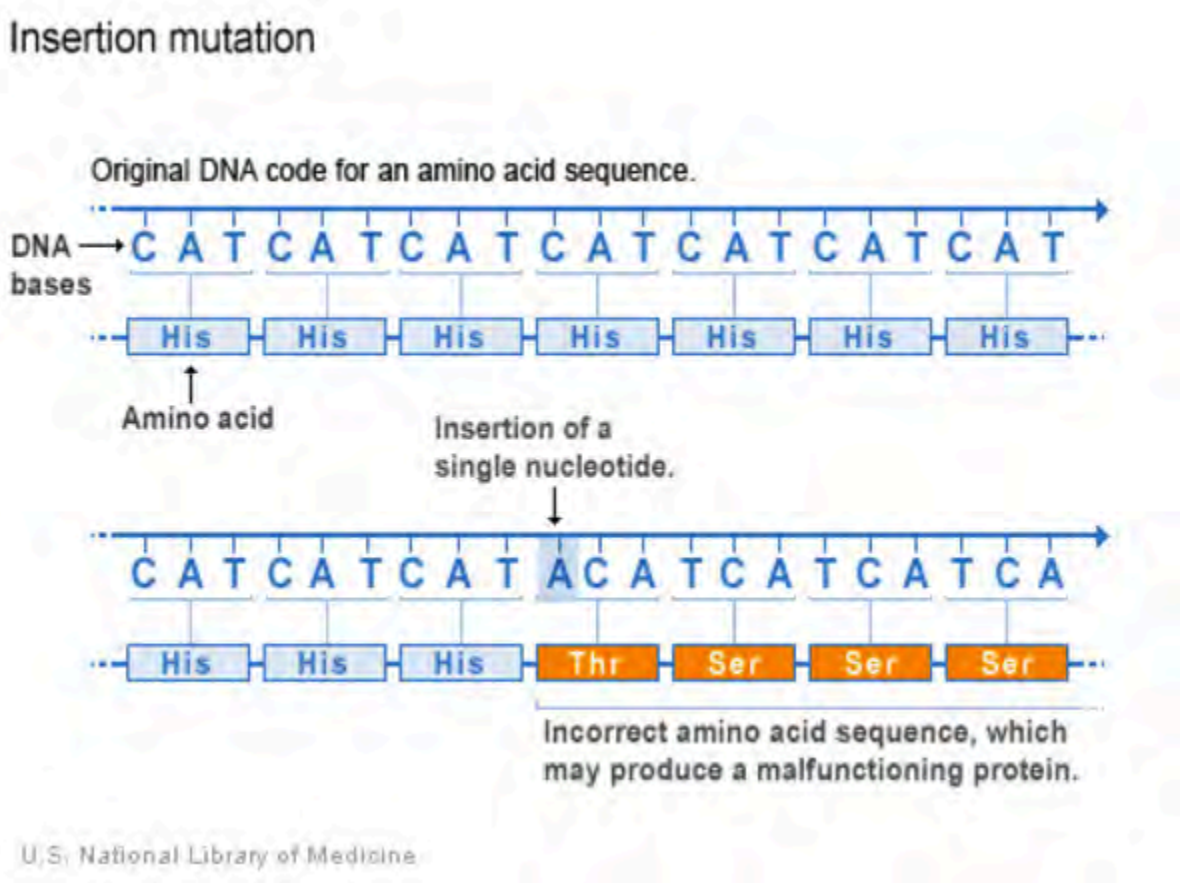

Figure 4.8 Insertion mutation courtesy of U.S. National Library of Medicine, PDM with attribution

Deletion

A deletion changes the DNA sequence by removing at least one nucleotide in a gene. Small deletions remove one or a few nucleotides within a gene, while larger deletions can remove an entire gene or several neighbouring genes. The deleted DNA may alter the function of the affected protein or proteins.

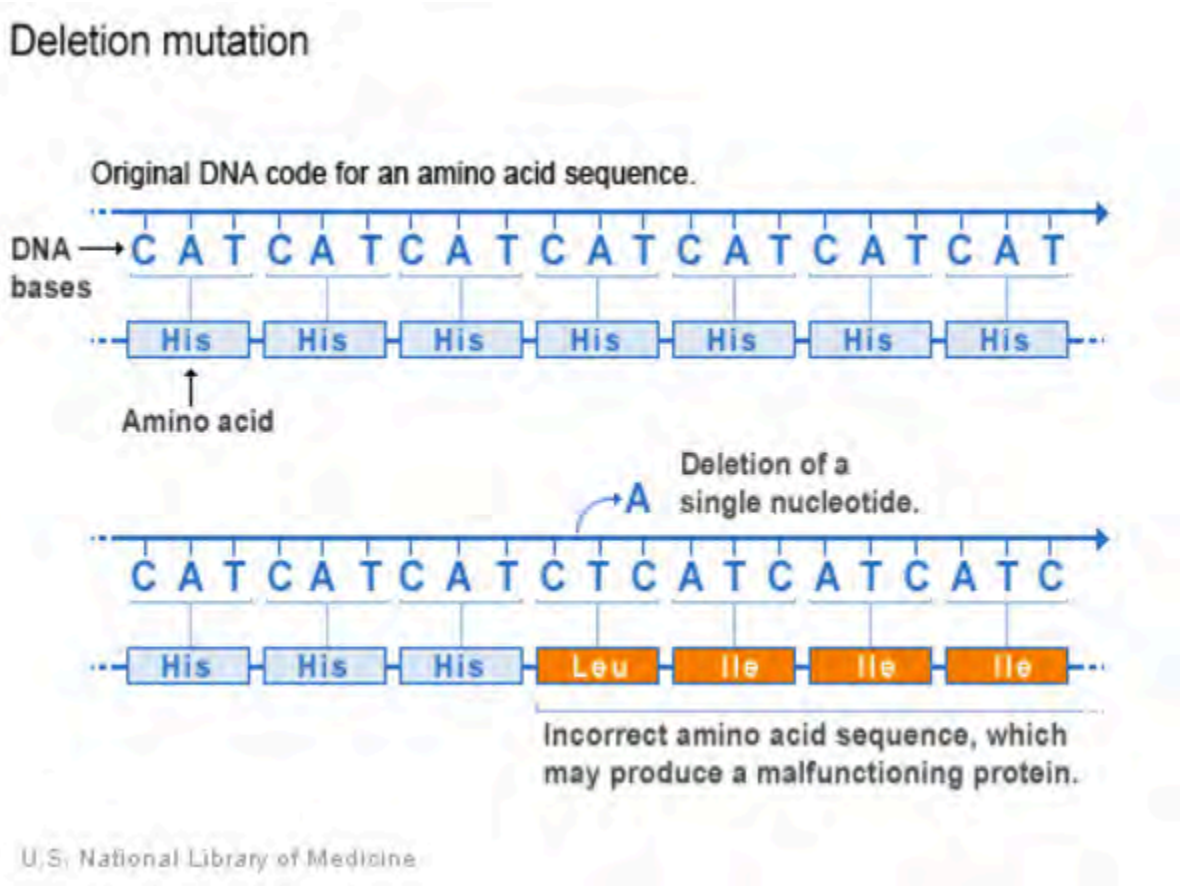

Figure 4.9 Deletion mutation courtesy of U.S. National Library of Medicine, PDM with attribution

Deletion-Insertion

This variant occurs when a deletion and insertion happen at the same time in the same location in the gene. In a deletion-insertion variant, at least one nucleotide is removed and at least one nucleotide is inserted. However, the change must be complex enough to differ from a simple substitution. The resulting protein may not function properly. A deletion-insertion (delins) variant may also be called an insertion-deletion (indel) variant.

Duplication

A duplication occurs when a stretch of one or more nucleotides in a gene is copied and repeated next to the original DNA sequence. This type of variant may alter the function of the protein made from the gene.

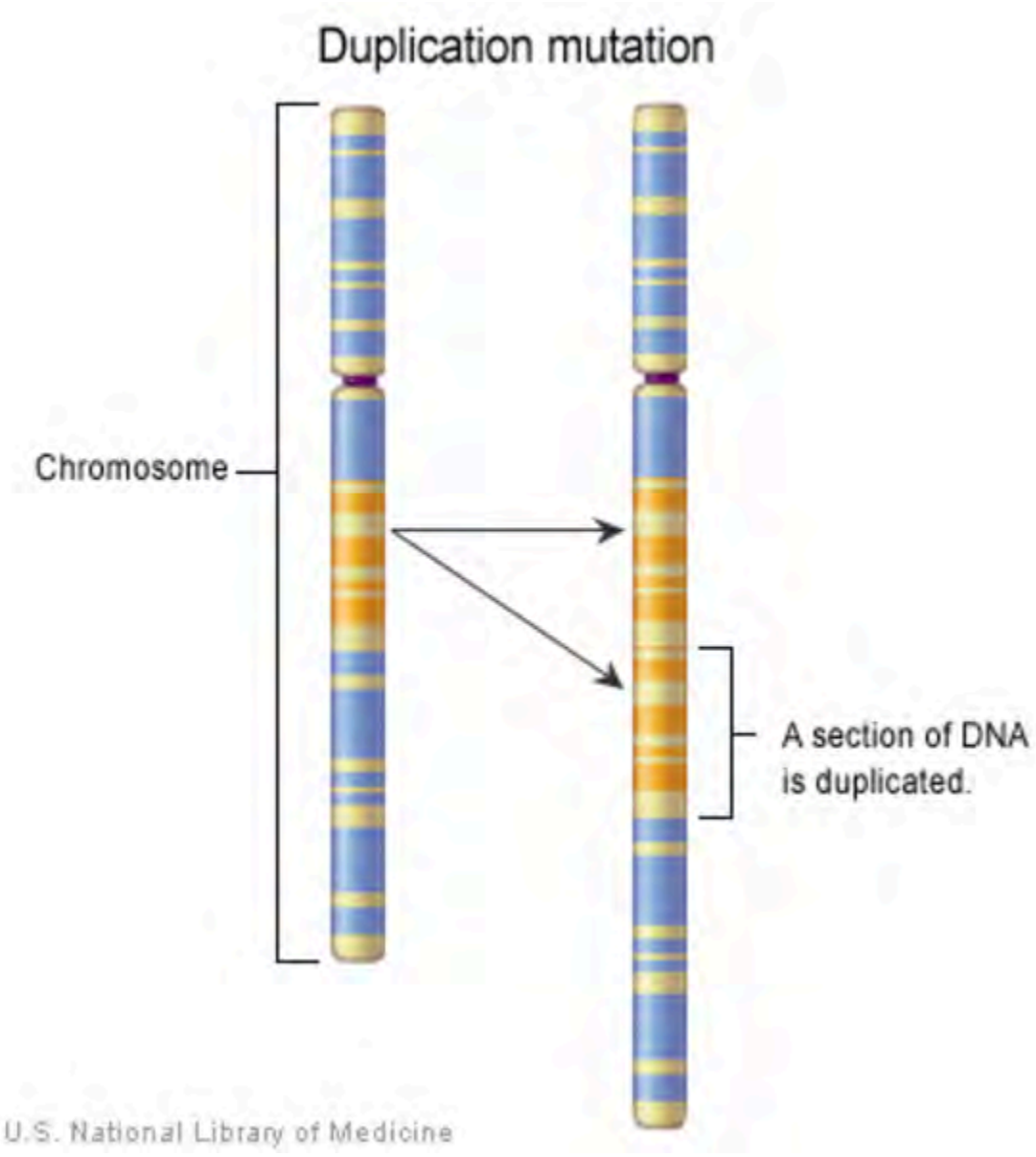

Figure 4.10 Duplication mutation courtesy of U.S. National Library of Medicine, PDM with attribution

Inversion

An inversion changes more than one nucleotide in a gene by replacing the original sequence with the same sequence in reverse order. We will discuss this further in the subsequent chapter on chromosomal disorders.

Frameshift

A reading frame consists of groups of three nucleotides that each code for one amino acid.

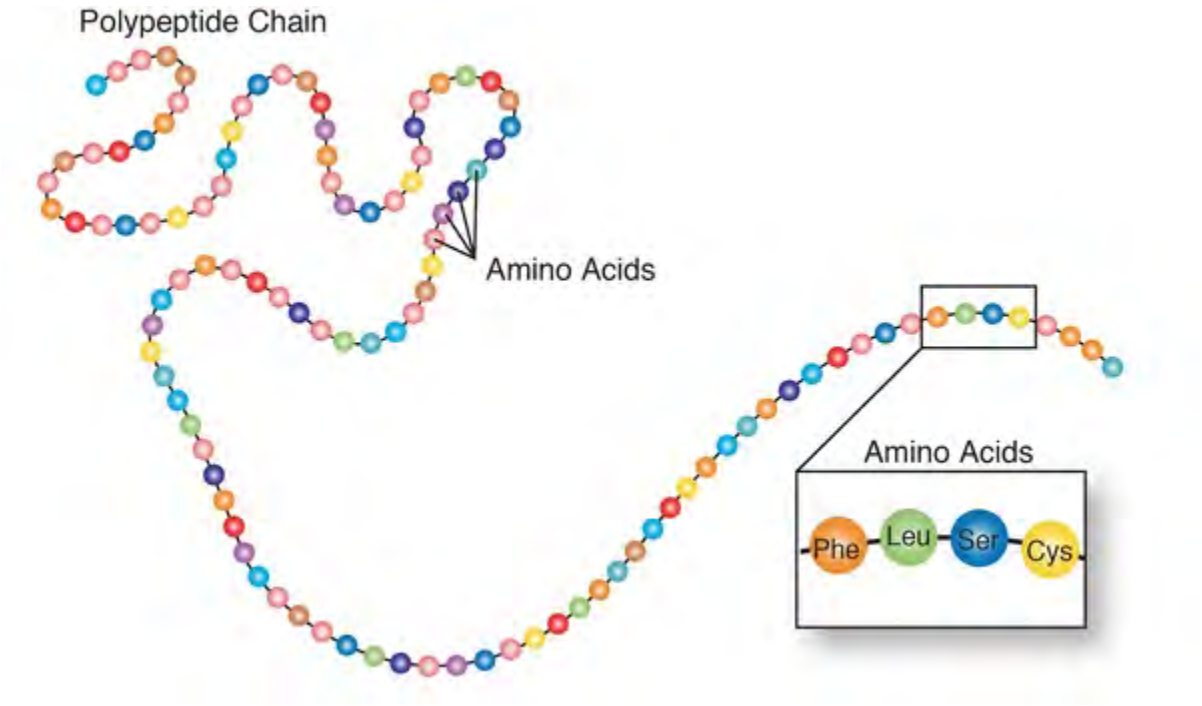

Figure 4.11 Amino acids are a set of 20 different molecules used to build proteins. Proteins consist of one or more chains of amino acids called polypeptides. The sequence of the amino acid chain causes the polypeptide to fold into a shape that is biologically active. The amino acid sequences of proteins are encoded in the genes. **Source:** Darryl Leja, NHGRI

A frameshift variant occurs when there is an addition or loss of nucleotides that shifts the grouping and changes the code for all downstream amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift variants.

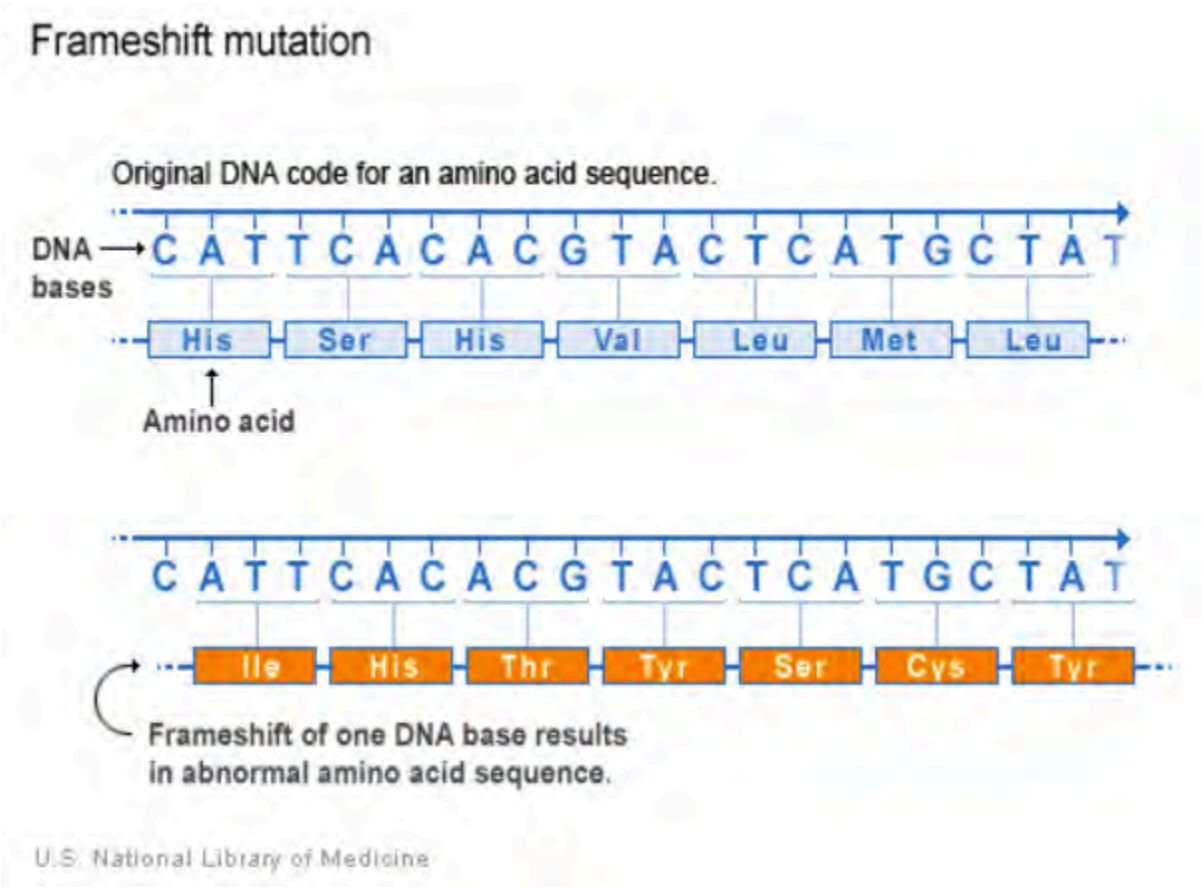

Figure 4.12 Frameshift mutation courtesy of U.S. National Library of Medicine, PDM with attribution

Repeat expansion

Some regions of DNA contain short sequences of nucleotides that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of sequences of three nucleotides, and a tetranucleotide repeat is made up of sequences of four nucleotides. A repeat expansion is a variant that increases the number of times that the short DNA sequence is repeated. This type of variant can cause the resulting protein to malfunction.

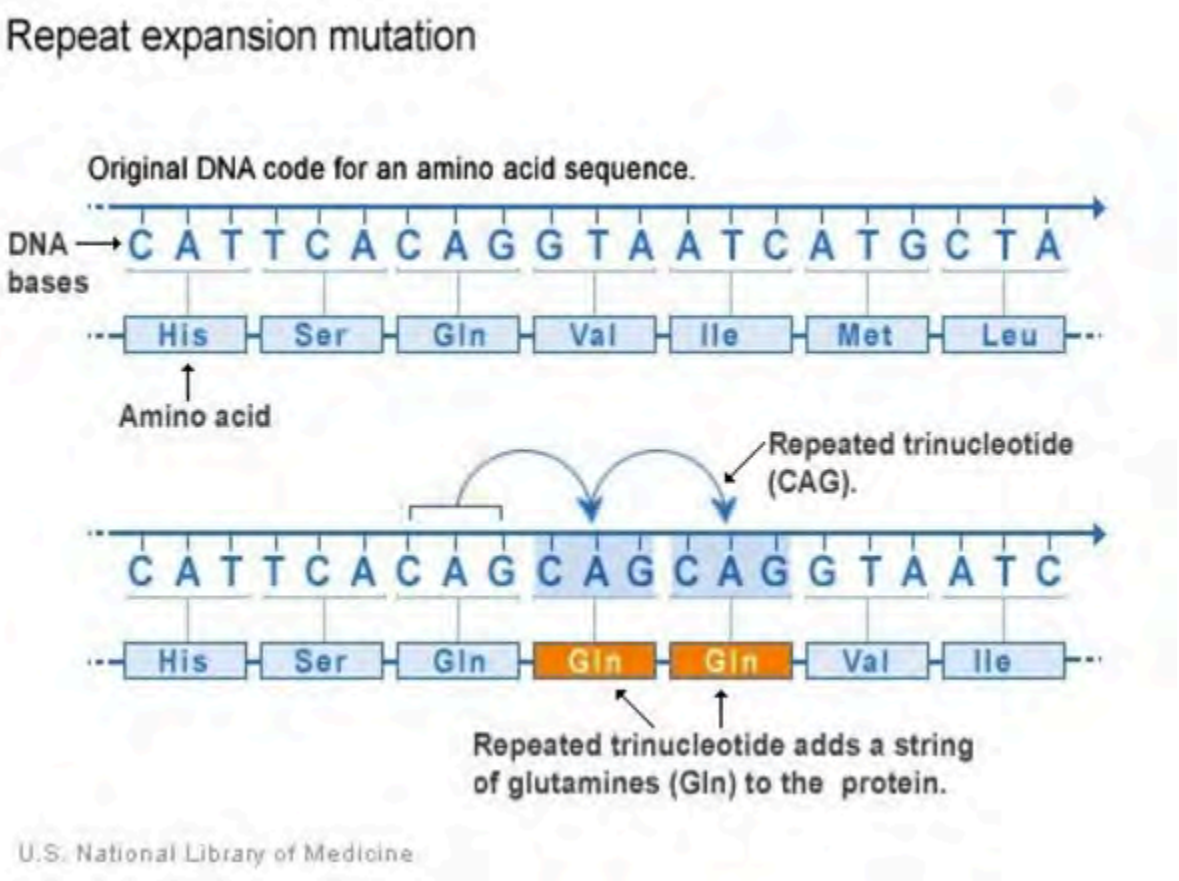

Figure 4.13 Repeat Expansion mutation courtesy of U.S. National Library of Medicine, PDM with attribution

Can a change in the number of genes affect health and development?

People have two copies of most genes, one copy inherited from each parent. In some cases, however, the number of copies varies—meaning that a person can have one, three, or more copies of particular genes. Less commonly, both copies of a gene may be missing. These genetic differences are known as **copy number variations (CNV)**.

Copy number variation results from insertions, deletions, and duplications of large segments of DNA that are at least one thousand nucleotides (also called one kilobase or 1kb) in length. These segments are often big enough to include whole genes. Variations in gene copy number can influence the activity of genes and the functioning of proteins made from them, which may affect body processes.

Copy number variation accounts for a significant amount of genetic difference between people. More than 10 percent of the human genome appears to contain differences in gene copy number. While much of this variation does not affect health or development, some differences influence a person's risk of disease, particularly some types of cancer, or response to certain drugs.

Attribution & References

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4.3 GENETIC DISORDERS

What is a genetic condition?

A genetic disorder is a disease caused in whole or in part by a change in the DNA sequence away from the normal sequence. Genetic disorders can be caused by a mutation in one gene (**monogenic disorder**), by mutations in multiple genes (**multifactorial inheritance disorder**), by a combination of gene mutations and environmental factors, or by damage to chromosomes (changes in the number or structure of entire chromosomes, the structures that carry genes).

As we unlock the secrets of the human genome (the complete set of human genes), we are learning that nearly all diseases have a genetic component. Some diseases are caused by mutations that are inherited from the parents and are present in an individual at birth, like sickle cell disease. Other diseases are caused by acquired mutations in a gene or group of genes that occur during a person's life. Such mutations are not inherited from a parent, but occur either randomly or due to some environmental exposure (such as cigarette smoke). These include many cancers, as well as some forms of neurofibromatosis.

Genetic conditions can be grouped into four main categories:

1. Single gene conditions: caused by changes to one gene, often with simple and predictable inheritance patterns.

As discussed in unit 2, different patterns of inheritance exist:

- Dominant conditions occur when a person has one unaffected copy and one mutated copy of the gene. For example, Huntington's disease.
- Recessive conditions only occur when an individual has two mutated copies of the gene. If a person has only one copy of the mutated gene, they are a carrier of the condition and may pass it to their children. For example, cystic fibrosis.
- X-linked conditions are caused by genes altered on the X chromosome – people with XY chromosomes are missing lots of genes encoded by the X, so will develop the condition if they have an altered gene on the X. For example, muscular dystrophy.

2. Chromosome conditions result from changes in the number or structure of the chromosomes.

- For example, Downs syndrome results from an extra chromosome 21. It's also called trisomy 21, referring to three copies of chromosome 21

3. Multifactorial conditions (or complex diseases) are caused by changes in multiple genes, often in a complex interaction with environmental factors.

- Many types of cancer are caused in this way. For example, certain genetic mutations can put a person at higher risk of bowel cancer. This, combined with external factors like cigarette smoke or certain foods can make a person more likely to develop the disease.

4. Mitochondrial Disorders are caused by defects in the mitochondria (NINDS, 2024).

- They can affect one part of the body or many parts, including the brain, muscles, kidneys, heart, eyes, and ears. In most cases, mitochondrial disorders affect more than one type of cell, tissue, or organ.

We will explore these four types of conditions in the following chapters.

How are genetic conditions and genes named?

Naming genetic conditions

Genetic conditions are not named in one standard way (unlike genes, which are given an official name and symbol by a formal committee). Doctors who treat families with a new, previously unknown disorder are often the first to propose a name for the condition. Later, healthcare professionals, researchers, people affected by the condition, and other interested individuals may come together to revise the name to improve its usefulness. Naming is important because it allows accurate and effective communication about particular conditions, which will ultimately improve care and help researchers find new approaches to treatment.

Condition names are often derived from one or a combination of sources:

- The basic genetic or biochemical defect that causes the condition (for example, alpha-1 antitrypsin deficiency (https://medlineplus.gov/genetics/condition/alpha-1-antitrypsin-deficiency/));

- The gene in which the variant (or mutation) that causes the condition occurs (for example, *TUBB4A*-related leukodystrophy (https://medlineplus.gov/genetics/condition/tubb4a-related-leukodystrophy/));
- One or more major signs or symptoms of the disorder (for example, hypermanganesemia with dystonia (https://medlineplus.gov/genetics/condition/hypermanganesemia-with-dystonia/), polycythemia vera (https://medlineplus.gov/genetics/condition/polycythemia-vera/), and cryptogenic cirrhosis (https://medlineplus.gov/genetics/condition/cryptogenic-cirrhosis/));
- The parts of the body affected by the condition (for example, brain-lung-thyroid syndrome (https://medlineplus.gov/genetics/condition/brain-lung-thyroid-syndrome/));
- The name of a physician or researcher, often the first person to describe the disorder (for example, Marfan syndrome (https://medlineplus.gov/genetics/condition/marfan-syndrome/), which was named after Dr. Antoine Bernard-Jean Marfan);
- A geographic area (for example, familial Mediterranean fever (https://medlineplus.gov/genetics/condition/familial-mediterranean-fever/), which occurs mainly in populations bordering the Mediterranean Sea); or
- The name of a patient or family with the condition (for example, amyotrophic lateral sclerosis (https://medlineplus.gov/genetics/condition/amyotrophic-lateral-sclerosis/) is often called Lou Gehrig disease after the famous baseball player who was diagnosed with the condition).

Conditions named after a specific person are called eponyms. They can be in the possessive form (e.g., Alzheimer's disease (https://medlineplus.gov/genetics/condition/alzheimers-disease/)) or in the nonpossessive form (e.g., Down syndrome (https://medlineplus.gov/genetics/condition/down-syndrome/)).

Naming genes

The HUGO Gene Nomenclature Committee (https://www.genenames.org/) (HGNC) designates an official name and symbol (an abbreviation of the name) for each known human gene. The HGNC is a nonprofit organization funded by the U.S. National Human Genome Research Institute and the UK's Wellcome Trust. The Committee has named more than 19,000 of the estimated 20,000 to 25,000 protein-coding genes in the human genome.

During the research process, genes often acquire several alternate names and symbols from researchers investigating the same gene. To resolve this confusion, the HGNC assigns a unique name and symbol to each human gene, which allows effective organization of genes in large databanks, aiding the advancement of research. For specific information about how genes are named, refer to the HGNC's Guidelines for Human Gene Nomenclature (https://www.genenames.org/about/guidelines).

A note on genetic nomenclature in relation to variants

Many genes are first identified in variant screens and, so, they tend to be named after their variant phenotypes — not the normal function or phenotype. This can cause some confusion for students of genetics. For example, there is an X-linked gene named *white* in fruit flies. Null variants of the *white* gene have white eyes, but the normal *white+* allele has red eyes. This tells us that the wild type (normal) function of this gene is required to make red eyes. We now know its product is a protein that imports a colourless pigment precursor into developing cells of the eye. Why don't we call it the "red" gene, since that is what its product does? Because there are more than one-dozen genes that, when mutant, alter the eye colour: *violet, cinnabar, brown, scarlet*, etc. For all of these genes, their function is also needed to make the eye wild-type red, and not the mutant colour. If we used the name "red" for all these genes, it would be confusing. So we use the distinctive mutant phenotype as the gene name. However, this can be problematic, as with the "lethal" variants described above. This problem is usually handled by giving numbers or locations to the gene name, or making up names that describe how they die (e.g., *even-skipped, hunchback, hairy, runt*, etc.).

What does it mean to have a genetic predisposition to a disease?

A genetic predisposition (sometimes also called genetic susceptibility) is an increased likelihood of developing a particular disease based on a person's genetic makeup. A genetic predisposition results from specific genetic variations that are often inherited from a parent. These genetic changes contribute to the development of a disease but do not directly cause it. Some people with a predisposing genetic variation will never get the disease while others will, even within the same family.

Genetic variations can have large or small effects on the likelihood of developing a particular disease. For example, certain variants (also called mutations) in the *BRCA1* (https://medlineplus.gov/genetics/gene/brca1/) or *BRCA2* (https://medlineplus.gov/genetics/gene/brca2/) genes greatly increase a person's risk of developing breast cancer (https://medlineplus.gov/genetics/condition/breast-cancer/) and ovarian cancer (https://medlineplus.gov/genetics/condition/ovarian-cancer/). Particular variations in other genes, such as *BARD1* and *BRIP1,* appear to have a much smaller impact on a person's breast cancer risk.

Current research is focused on identifying genetic changes that have a small effect on disease risk but are common in the general population. Although each of these variations only slightly increases a person's risk, having changes in several different genes may combine to increase disease risk significantly. Changes in many genes, each with a small effect, may underlie susceptibility to many common diseases, including cancer, obesity, diabetes, heart disease, and mental illness. Researchers are working to calculate an individual's estimated risk for developing a common disease based on the combination of variants in many genes across their genome. This measure, known as the polygenic risk score, is expected to help guide healthcare decisions in the future.

In people with a genetic predisposition, the risk of disease can depend on multiple factors in addition to an identified genetic change. These include other genetic factors (sometimes called modifiers) as well as lifestyle and environmental factors. Diseases that are caused by a combination of factors are described as multifactorial (https://medlineplus.gov/genetics/understanding/mutationsanddisorders/complexdisorders/). Although a person's genetic makeup cannot be altered, some lifestyle and environmental modifications (such as having more frequent disease screenings and maintaining a healthy weight) may be able to reduce disease risk in people with a genetic predisposition.

Modifiable and non-modifiable risk factors

Traditional risk factors for health outcomes, such as age, sex, and genetic inheritance (non-modifiable) and diet, physical activity, and smoking (modifiable), are paralleled by social and environmental factors that impact the epigenome, such as experiencing racism or living near industrial pollution. This illustrates how gene expression and, consequently, disease risk can be altered throughout an individual's life.

Family health history is a non-modifiable risk factor—or is it?

"I met three different women who had been tested [genetic testing for mutations in the BReast CAncer susceptibility (BRCA) genes] early on, in 1996, when the BRCA *test first came out. They told me their family history story of mothers, aunts, uncles, and a dad who suffered from breast or ovarian or related cancers, and it was heartbreaking. But then the story changed with them. They were diagnosed with cancer, they got testing, and they shared this information with their family members. So they had stories of children and grandchildren—one woman even had great grandchildren—who were old enough to decide whether or not they wanted to be counseled and some decided to get testing. Many did not carry any of the mutations in the family, and others did. And those who found out that they were a mutation carrier, they had actual things to do. And none of them—none of those family members as we cascade down—have died of cancer." Summer Lee Cox, Oregon Public Health Division* (as cited in Green, 2014).

Read

CDC. (2024, September 25). *Family health history and adults*. Family Health History. https://www.cdc.gov/family-health-history/family-health-history-and-you/family-health-history-and-adults.html

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4.4 SINGLE GENE DISORDERS

Single-Gene Disorders

Single gene disorders are among the most well-understood genetic disorders, given their straightforward inheritance patterns (recessive or dominant) and relatively simple genetic etiology. Although the majority of these diseases are rare, in total, they affect millions of Americans. Some of the more common single-gene disorders include cystic fibrosis (https://www.genomicseducation.hee.nhs.uk/documents/cystic-fibrosis/), hemochromatosis (https://www.genome.gov/Genetic-Disorders/Hereditary-Hemochromatosis), Tay-Sachs (https://www.genome.gov/Genetic-Disorders/Tay-Sachs-Disease), and sickle cell disease (https://www.genomicseducation.hee.nhs.uk/documents/sickle-cell-disease/).

Even though a single gene primarily causes these diseases, several different mutations can result in the same disease but with varying degrees of severity and phenotype. However, even the same mutation can result in slightly different phenotypes. This may be caused by differences in the patient's environment and other genetic variations that may influence the disease phenotype or outcome. For example, other genes have been shown to modify the cystic fibrosis phenotype in children who carry the same CFTR mutation. In addition, mutations in different genes can result in similar phenotypes for some disorders, such as galactosemia.

Genetic testing is available for many single-gene disorders. However, the clinical examination is extremely important in the differential diagnosis, particularly in patients with no family history. For some genetic conditions, patients can often be treated for their symptoms or modify their diets to prevent the onset of symptoms if diagnosed at an early age (newborn screening). However, despite advancements in the understanding of genetic etiology and improved diagnostic capabilities, no treatments are available to prevent disease onset or slow disease progression for a number of these disorders.

Some useful resources to bookmark include GeneTests (http://www.genetests.org) and OMIM (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM). GeneTests is an online genetic testing laboratory database providing information about conditions and laboratory testing services. The Online Mendelian Inheritance in Man database is a comprehensive resource that includes information about the genetic etiology, clinical symptoms, and a bibliography. Of over 5,000 known genetic conditions, the molecular basis is known in almost 2,000.

Table 1: Conditions, Genes & Inheritance Patterns

Condition	Gene (Chr. Location)	Inheritance Pattern
Congenital Deafness (nonsyndromic)	Connexin 26 (13q11)	Recessive
Tay-Sachs	hexosaminidase A (15q23)	Recessive
Familial hypercholesterolemia	LDL receptor (19p13)	Dominant
Sickle cell anemia	Beta-globin (11p15)	Recessive
Duchenne muscular dystrophy	Dystrophin (Xq21)	X-linked Recessive
Cystic Fibrosis	CFTR (7q31)	Recessive
Hemochromatosis	HFE (6p21)	Recessive
Huntington disease	Huntington (4p16)	Dominant

Cystic Fibrosis (CF) — Autosomal Recessive

Cystic fibrosis (CF) is one of many diseases that geneticists have shown to be primarily caused by mutation in a single, well-characterized gene. Cystic fibrosis is the most common ($\frac{1}{2,500}$) life-limiting autosomal recessive disease among people of European heritage, with ~ 1 in 25 people being carriers. The frequency varies in different populations. Most of the deaths caused by CF are the result of lung disease, but many CF patients also suffer from other disorders, including infertility and gastrointestinal disease. The disease is due to a mutation in the *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) gene, first identified by Lap-chee Tsui's group at the University of Toronto (Tsui, 1995). Lap-Chee Tsui was inducted into the Canadian Medical Hall of Fame in March 2012 and is still a leader in CF research (Canadian Medical Association, n.d.).

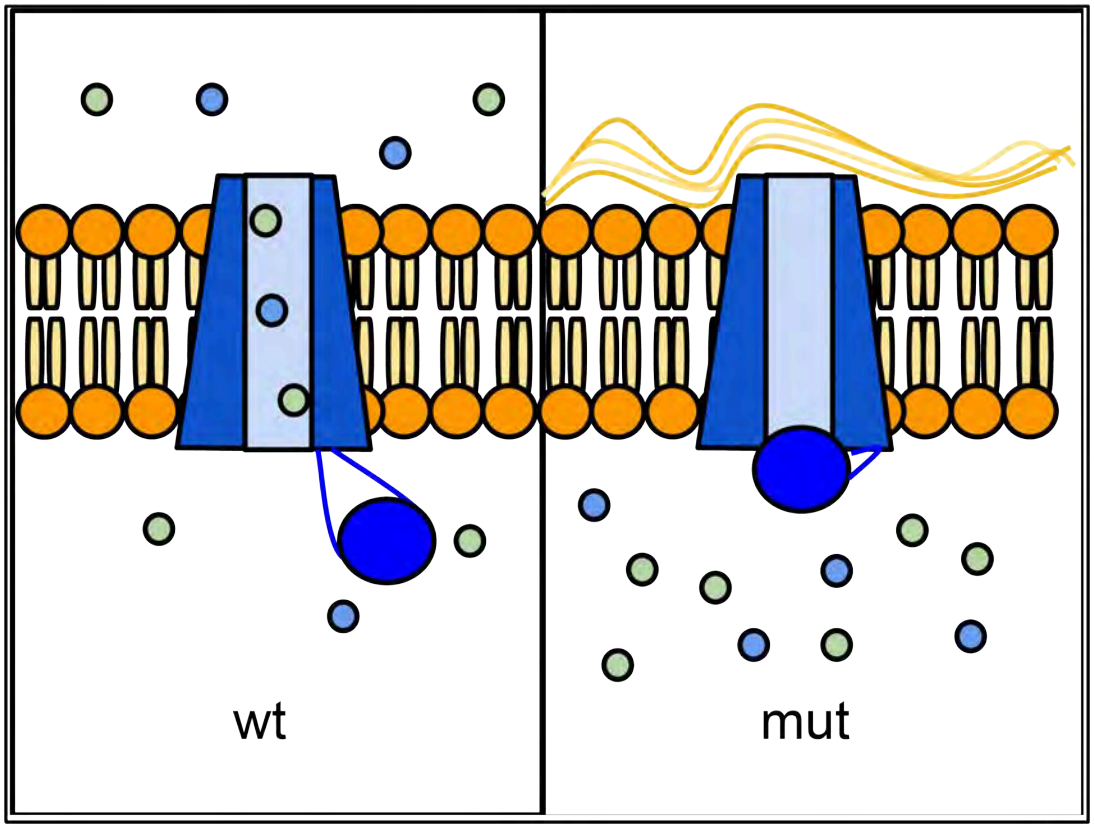

Figure 4.14 Wild-Type and Mutant Forms of CFTR in the Cell Membrane. In wild-type, the CFTR ion channel is gated. When activated by ATP, the channel opens and allows ions to move across the membrane. In some CFTR mutants, the channel does not open. This prevents ions and water movement, allowing mucus to build up on the lung epithelium. **Source:** CFTR Protein by Lbudd14, CC BY-SA 3.0.

Epithelial tissues in some organs rely on the CFTR protein to transport ions (especially Cl-) across their cell membranes. The passage of ions through a six-sided channel is gated by another part of the CFTR protein, which binds to ATP. If there is insufficient activity of CFTR, an imbalance in ion concentration results, which disrupts the properties of the liquid layer that normally forms on the epithelial surface. In the lungs, this causes mucus to accumulate and can lead to infection. Defects in CFTR also affect the pancreas, liver, intestines, and sweat glands — all of which need this ion transport. CFTR is also expressed at high levels in the salivary gland and bladder. Still, defects in CFTR function do not cause problems in these organs, probably because other ion transporters can compensate.

Concept in Action

Watch The video Cystic Fibrosis | Molecular Mechanism & Genetics (4 mins) by Hussain

Biology (2018) on YouTube (https://youtu.be/QfjIGXNey3g) which discusses the genetic basis and mechanism by which cystic fibrosis occurs.

Over one thousand different mutant alleles of *CFTR* have been described. Any mutation that prevents CFTR from sufficiently transporting ions can lead to cystic fibrosis (CF). Worldwide, the most common *CFTR* allele among CF patients is called *ΔF508* (delta-F508; or PHE508DEL), which is a deletion of three nucleotides that eliminates phenylalanine from position 508 of the 1480 aa wild-type protein. Mutation *ΔF508* causes CFTR to be folded improperly in the endoplasmic reticulum (ER), preventing CFTR from reaching the cell membrane. *ΔF508* accounts for approximately 70% of CF cases in North America, with ~1/25 people of European descent being carriers. The high frequency of the *ΔF508* allele has led to speculation that it may confer some selective advantage to heterozygotes, perhaps by reducing dehydration during cholera epidemics or by reducing susceptibility to certain pathogens that bind to epithelial membranes.

CFTR is also notable because it is one of the well-characterized genetic diseases for which a drug has been developed that compensates for the effects of a specific mutation. The drug, **Kalydeco (Ivacaftor)** (https://www.cysticfibrosis.ca/our-programs/advocacy/access-to-medicines/kalydeco), was approved by the FDA and Health Canada in 2012, decades after the *CFTR* gene was first mapped to DNA markers (in 1985) and cloned (in 1989). Kalydeco is effective on only some *CFTR* mutations, most notably *G551D* (i.e., where glycine is substituted by aspartic acid at position 551 of the protein *GLY551ASP*). This mutation is found in less than 5% of CF patients. The *G551D* mutation affects the ability of ATP to bind to CFTR and open the channel for transport. Kalydeco compensates for this mutation by binding to CFTR and holding it in an open conformation. Kalydeco is expected to cost approximately $250,000 per patient per year.

Exercises

Explore the National Human Genome Research Institute website or the Genomics Education Programme (https://www.genomicseducation.hee.nhs.uk/doc-type/genetic-conditions/page/3/) website for the following genetic disorders:

- Beta-thalassemia
- Down syndrome
- Duchenne muscular dystrophy

- Familial adenomatous polyposis
- Familial hypercholesterolemia
- Fragile X syndrome
- Hemophilia
- Huntington's disease
- Klinefelter syndrome
- Lynch syndrome
- Marfan syndrome
- Parkinson's disease
- Phenylketonuria
- Sickle cell disease

Consider the following:

1. Are these disorders caused by a single gene? If so, what is the pattern of inheritance?
2. Is it a chromosomal or mitochondrial condition?
3. Is it a multifactorial condition?
4. What is the gene and chromosome that is affected?
5. How do penetrance and expressivity affect the phenotype in these disorders?
6. What is anticipation, and which disorders does it apply to?

Assignment tip: the Scholarly Poster Presentation assignment asks you to select an actionable gene variant. Reviewing these disorders may lead you to choose a variant that can cause a disorder you would be interested in doing the project on.

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4.5 POLYGENIC DISORDERS

Phenotype Variability

The phenotypes described thus far correlate nearly perfectly with their associated genotypes. In other words, an individual with a particular genotype always has the expected phenotype. However, most phenotypes are not determined entirely by genotype alone. Instead, they are determined by an interaction between genotype and environmental factors and can be conceptualized in the following relationship:

Genotype + Environment

$\Rightarrow$ Phenotype (G + E $\Rightarrow$ P)

Or:

Genotype + Environment + InteractionGE

$\Rightarrow$ Phenotype (G + E + IGE $\Rightarrow$ P)

***GE = Genetics and Environment**

This interaction is especially relevant in studying economically important phenotypes, such as human diseases or agricultural productivity. For example, a particular genotype may predispose an individual to cancer, but cancer may only develop if the individual is exposed to certain DNA-damaging chemicals or carcinogens. Therefore, not all individuals with a particular genotype will develop the cancer phenotype; only those who experience a particular environment will. The terms penetrance and expressivity are also helpful to describe the relationship between certain genotypes and their phenotypes.

Penetrance

Penetrance is the proportion of individuals with a particular genotype that display a corresponding phenotype (see figure below). It is usually expressed as a percentage of the population. Because all pea plants are homozygous for the allele for white flowers, this genotype is entirely (100%) penetrant. In contrast, many human genetic diseases are incompletely penetrant since not all individuals with the disease genotype develop symptoms associated with the disease (less than 100%).

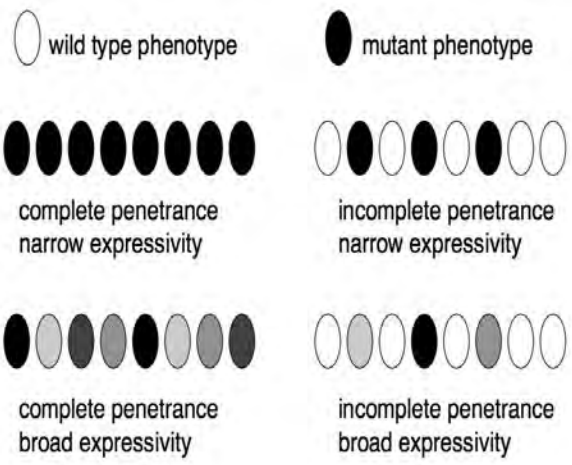

Figure 4.15 Relationship Between Penetrance and Expressivity in Eight Individuals With a Mutant Genotype. Penetrance can be complete (all eight have the mutant phenotype) or incomplete (only some have the mutant phenotype). Among those individuals with the mutant phenotype, the expressivity can be narrow (minimal variation) to broad (lots of variation). **Source:** Original by Locke (2017), CC BY-NC 3.0, Open Genetics Lectures.

Expressivity

Expressivity describes the variability in mutant phenotypes observed in individuals with a particular phenotype (see figure below). Many human genetic diseases provide examples of broad expressivity since individuals with identical genotypes may vary significantly in the severity of their symptoms. Incomplete penetrance and broad expressivity are due to random chance, non-genetic (environmental), and genetic factors (mutations in other genes).

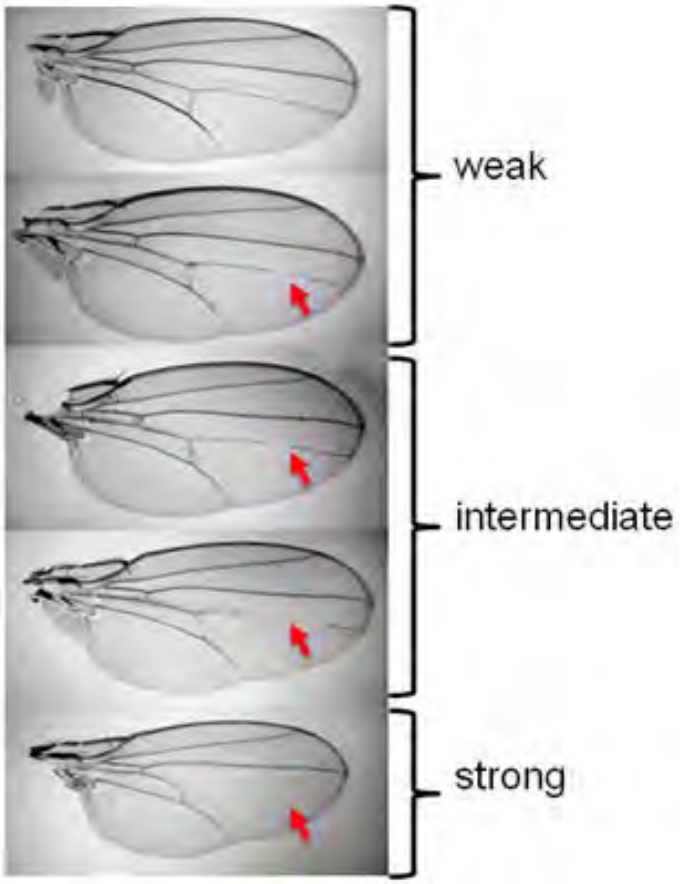

Figure 4.16 Five different mutations demonstrated in the wings of Drosophila show weak to strong expressivity, which describes the variability in mutant phenotypes observed in individuals with a particular phenotype, which can be due to random chance, environment and/or other genetic factors. **Source:** Original by Locke (2017), CC BY-NC 3.0, Open Genetics Lectures

Concept in Action

Watch the video Penetrance vs. Expressivity (3 mins) by The Excel Cycle (2020) on YouTube (https://youtu.be/nurrFUIDBHc) which discusses the difference between expressivity and penetrance.

Read

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Genotype as a predictor for the development of disease

This unit taught us that our genotype can predispose us to disease development, but multiple factors influence it, including polygenic contributions and epigenetic mechanisms. While some individuals may inherit genetic variants that increase susceptibility, the expression of these genes can be significantly modified by epigenetic changes, which are often influenced by environmental and lifestyle factors.

Usually, no one-to-one correspondence between a gene and a physical characteristic exists. Often, a gene is responsible for several phenotypic traits and is said to be **pleiotropic**. Pleiotropy occurs when one gene influences two or more seemingly unrelated phenotypic traits. Such a gene that exhibits multiple phenotypic expression is called a pleiotropic gene. For example, mutations in Drosophila's vestigial gene (vg) result in an easily visible short-wing phenotype. However, mutations in this gene also affect the number of egg strings, the position of the bristles on the scutellum, and the lifespan of Drosophila. Therefore, the *vg* gene is said to be pleiotropic in that it affects many different phenotypic characteristics. During his study of inheritance in pea plants, Mendel made several interesting observations regarding the colour of various plant components. Specifically, Mendel noticed that plants with coloured seed coats always had coloured flowers and coloured leaf axils — axils are the parts of the plant that attach leaves to stems. Mendel also observed that pea plants with colourless seed coats always had white flowers and no pigmentation on their axils. In other words, in Mendel's pea plants, seed coat colour was always associated with specific flower and axil colours. We know that Mendel's observations resulted from pleiotropy, or the phenomenon in which a single gene contributes to multiple phenotypic traits. In this case, the seed coat colour gene, denoted *a*, was responsible for seed coat colour and flower and axil pigmentation.

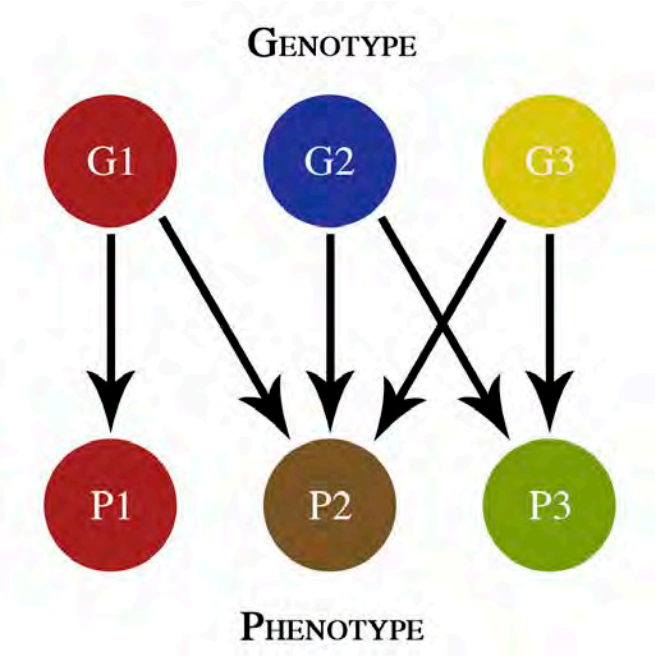

Figure 4.17 Image result for pleiotropy. Pleiotropy occurs when one gene influences two or more seemingly unrelated phenotypic traits. This relationship between genes and phenotypes is demonstrated by mapping one genotype; e.g., G1 to multiple phenotypes; e.g.; P1 and P2. **Source:** Simple Genotype Phenotype Map by Alphillips6, CC BY-SA 4.0

On the other hand, single characteristics can be affected by mutations in multiple, different genes. This implies that many genes are needed to make each characteristic. For example, if we return to the Drosophila wing, there are dozens of genes that, when mutant, alter the normal shape of the wing, not just the *vg* locus. Thus, many genes are needed to make a normal wing; the mutation of any one causes an abnormal, mutant phenotype. This type of arrangement is called **polygenic inheritance**.

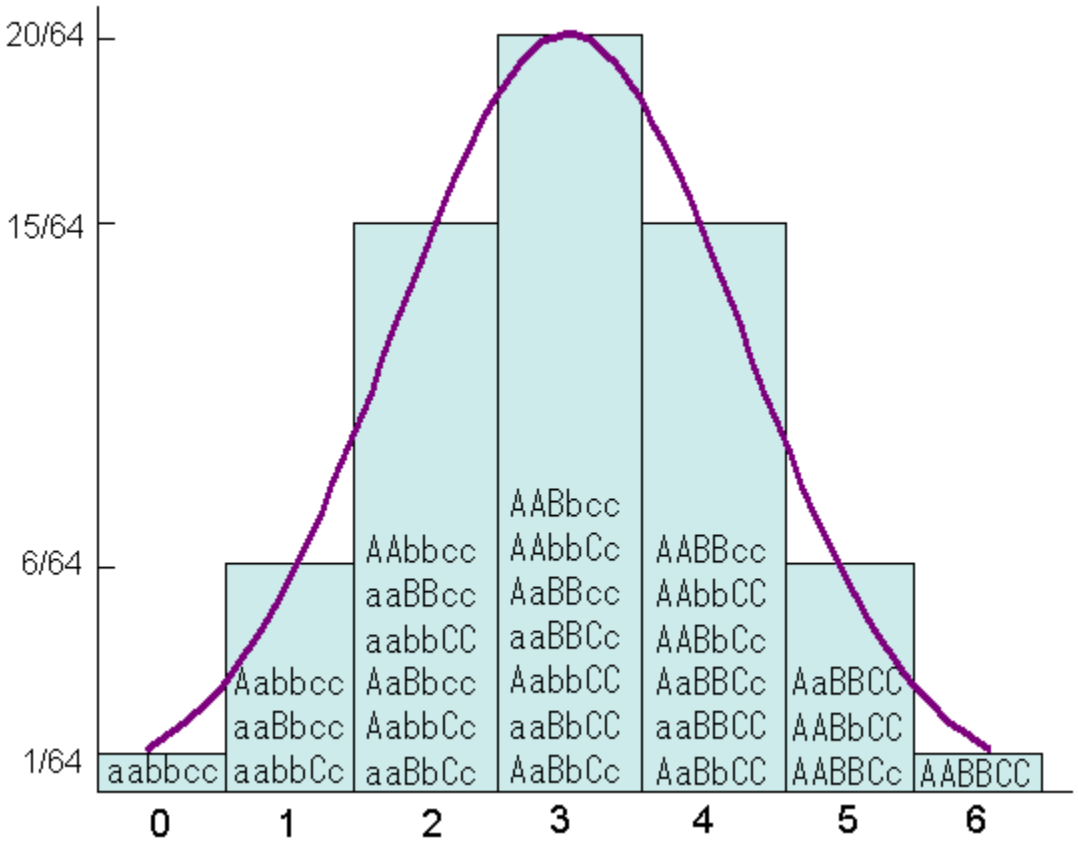

Figure 4.18 Typical Distribution of Phenotypes in Polygenic Inheritance. Traits that display a continuous distribution, such as height or skin colour, are polygenic. A bell curve showing the typical distribution of phenotypes in Polygenic Inheritance. On the extreme left and the extreme right of the curve, a small frequency of outlier genotypes are represented. As the curve approaches the middle, the frequency of more common genotypes increases. At the very centre of the curve, a maxima is achieved, producing the typical bell shaped graph. **Source:** Polygene00 by Maulits, CC BY-SA 4.0

What are complex or multifactorial disorders?

Researchers are learning that nearly all conditions and diseases have a genetic component. Some disorders, such as sickle cell disease (https://medlineplus.gov/genetics/condition/sickle-cell-disease/) and cystic fibrosis (https://medlineplus.gov/genetics/condition/cystic-fibrosis/), are caused by variants (also known as mutations) in single genes. The causes of many other disorders, however, are much more complex. Common health problems such as heart disease, type 2 diabetes (https://medlineplus.gov/genetics/condition/type-2-diabetes/), and obesity do not have a single genetic cause—they are influenced by multiple genes (polygenic) in combination with lifestyle and environmental factors, such as exercise, diet, or pollutant exposures. Conditions caused by many contributing factors are called complex or multifactorial disorders.

Although complex disorders often cluster in families, they do not have a clear-cut inheritance pattern. Identifying the role of genetics in these disorders may be challenging, mainly because families often share

environments and have similar lifestyles. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified. Researchers continue to look for major contributing genes for many common, complex disorders.

Continuous Variation

Most of the phenotypic traits commonly used in introductory genetics are qualitative. This means the phenotype exists in only two (or possibly a few more) discrete, alternative forms, such as purple or white flowers, or red or white eyes. These qualitative traits are, therefore, said to exhibit **discrete variation**. On the other hand, many interesting and important traits exhibit **continuous variation**, meaning they exhibit a continuous range of phenotypes that are usually measured quantitatively, such as intelligence, body mass, blood pressure in animals (including humans), and yield, water use, or vitamin content in crops. Traits with continuous variation are often complex, and do not show the simple Mendelian segregation ratios (e.g., 3:1) observed with some qualitative traits. The environment heavily influences many complex traits; nevertheless, complex traits can often have a heritable component, which must involve one or more genes.

How can genes, which are inherited (in the case of a diploid) as, at most, two variants each, explain the wide range of continuous variation observed for many traits? The lack of an immediately obvious explanation to this question was one of the early objections to Mendel's explanation of the mechanisms of heredity. However, upon further consideration, it becomes clear that the more loci that contribute to the trait, the more phenotypic classes may be observed for that trait (see figure below).

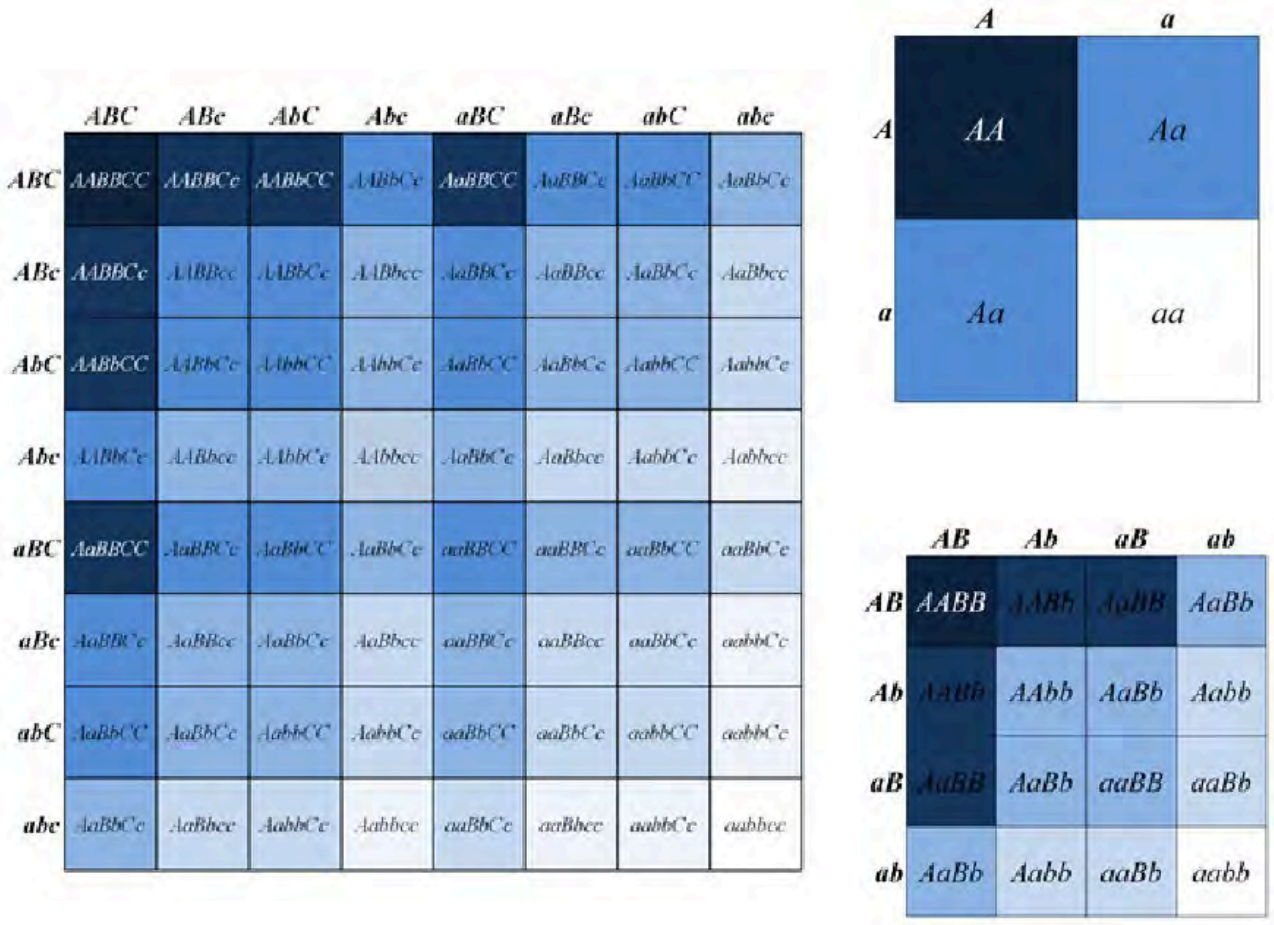

Figure 4.19 Punnett Squares for One, Two, or Three Loci. This is a simplified example of up to three semi-dominant genes, and in each case, the effect on the phenotype is additive, meaning the more "upper case" alleles present, the stronger the phenotype. A comparison of the Punnett squares and the associated phenotypes shows that the larger the number of genes that affect a trait, the more intermediate phenotypic classes will be expected under these conditions. **Source:** Original by Deyholos (2017), CC BY-NC 3.0, Open Genetics Lectures

If the number of phenotypic classes is sufficiently large (as with three or more loci), individual classes may become indistinguishable (particularly when environmental effects are included), and the phenotype appears as a continuous variation (see figure below). Thus, quantitative traits are sometimes called **polygenic traits**, because it is assumed that the combined activity of many genes controls their phenotypes. Note that this does not imply that each of the individual genes has an equal influence on a polygenic trait — some may have a major effect, while others are only minor. Furthermore, any single gene may influence more than one trait, whether these traits are quantitative or qualitative traits.

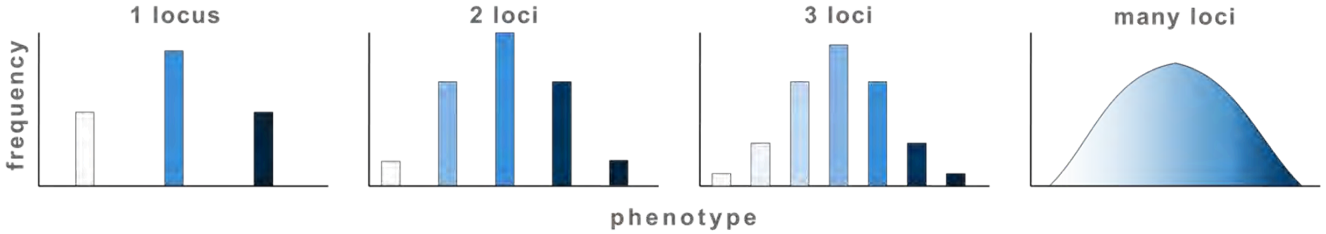

Figure 4.20 The More Loci that Affect a Trait, the Larger the Number of Phenotypic Classes Can Be Expected. The number of contributing loci is so large that the phenotypic classes blend in apparently continuous variation for some traits. Bar charts and bell curves demonstrate that the more loci that are affecting a trait, the larger the number of phenotypic classes can be expected. For some traits, the number of contributing loci is so large that the phenotypic classes blend together in apparently continuous variation. **Source:** Original by Deyholos (2017), CC BY-NC 3.0, Open Genetics Lectures

Concept in Action

Watch the video, *Polygenic Inheritance* (13 mins) by AK Lectures (2015) on YouTube (https://youtu.be/tKnOvPtwZL4), which discusses the genetic basis of Polygenic Inheritance.

Attribution & References

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- What are complex or multifactorial disorders? In *Help Me Understand Genetics* by MedlinePlus, National Library of Medicine, Public Domain with attribution

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4.6 CHROMOSOMAL DISORDERS

Inherited disorders can arise when chromosomes behave abnormally during meiosis. Chromosome disorders can be divided into two categories: chromosome number abnormalities and structural rearrangements. Because even small segments of chromosomes can span many genes, chromosomal disorders are characteristically dramatic and often fatal.

Disorders in Chromosome Number

The isolation and microscopic observation of chromosomes form the basis of cytogenetics and is the primary method by which clinicians detect chromosomal abnormalities in humans. A **karyotype** is the number and appearance of chromosomes, including their length, banding pattern, and centromere position. To obtain a view of an individual's karyotype, cytologists photograph the chromosomes and then cut and paste each chromosome into a chart or karyogram (see figure below).

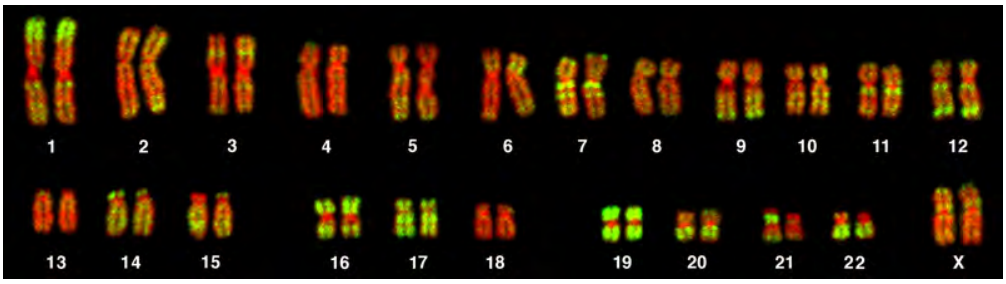

Figure 4.21 This karyogram shows the chromosomes of a female human immune cell during mitosis. **Source**: Image by Andreas Bolzer, et al, CC BY 2.5

Geneticists Use Karyograms to Identify Chromosomal Aberrations

The karyotype is a method by which traits characterized by chromosomal abnormalities can be identified from a single cell. A person's cells (like white blood cells) are first collected from a blood sample or other tissue to observe an individual's karyotype. In the laboratory, the isolated cells are stimulated to begin actively dividing. A chemical is then applied to the cells to arrest mitosis during metaphase. The cells are then fixed to a slide.

The geneticist then stains chromosomes with one of several dyes to better visualize each pair's distinct and reproducible banding patterns. Following staining, chromosomes are viewed using bright-field microscopy.

An experienced cytogeneticist can identify each band. In addition to the banding patterns, chromosomes are further determined based on size and centromere location. The geneticist obtains a digital image, identifies each chromosome, and manually arranges the chromosomes into this pattern to get the classic depiction of the karyotype in which homologous pairs of chromosomes are aligned in numerical order from longest to shortest.

At its most basic, the karyogram may reveal genetic abnormalities in which an individual has too many or too few chromosomes per cell. Examples of this are **Down syndrome**, identified by a third copy of chromosome 21, and Turner syndrome, characterized by the presence of only one X chromosome in women instead of two. Geneticists can also identify large deletions or insertions of DNA. For instance, Jacobsen syndrome, which involves distinctive facial features as well as heart and bleeding defects, is determined by a deletion on chromosome 11. Finally, the karyotype can pinpoint translocations, which occur when a segment of genetic material breaks from one chromosome and reattaches to another or a different part of the same chromosome. Translocations are implicated in certain cancers, including chronic myelogenous leukemia.

By observing a karyogram, geneticists can visualize an individual's chromosomal composition to confirm or predict genetic abnormalities in offspring even before birth.

Nondisjunctions, Duplications, and Deletions

Of all the chromosomal disorders, abnormalities in chromosome number are the most easily identifiable from a karyogram. Disorders of chromosome number include the duplication or loss of entire chromosomes and changes in the number of complete sets of chromosomes. They are caused by **nondisjunction**, which occurs when pairs of homologous chromosomes or sister chromatids fail to separate during meiosis. The risk of nondisjunction increases with the age of the parents.

Nondisjunction can occur during either meiosis I or II, with different results (see figure below). If homologous chromosomes fail to separate during meiosis I, the result is two gametes that lack that chromosome and two gametes with two copies of the chromosome. If sister chromatids fail to separate during meiosis II, the result is one gamete that lacks that chromosome, two normal gametes with one copy of the chromosome, and one gamete with two copies.

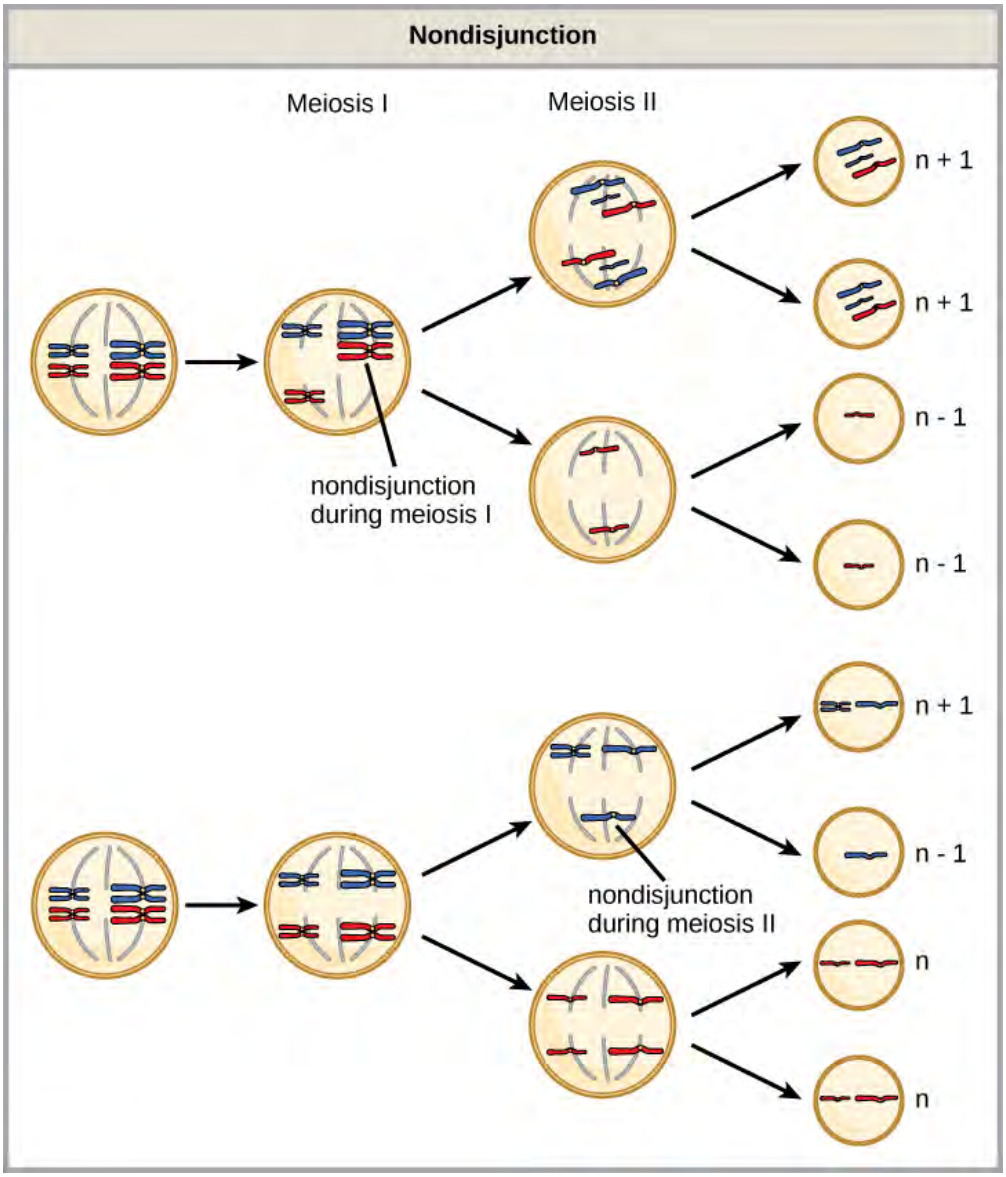

Figure 4.22 Figure 7.8 Following meiosis, each gamete has one copy of each chromosome. Nondisjunction occurs when homologous chromosomes (meiosis I) or sister chromatids (meiosis II) fail to separate during meiosis. **Source:** *Concepts of Biology (OpenStax)*, CC BY 4.0

An individual with the appropriate number of chromosomes for their species is called **euploid**; in humans, euploidy corresponds to 22 pairs of autosomes and one pair of sex chromosomes. An individual with an error in chromosome number is described as **aneuploid**, a term that includes **monosomy** (loss of one chromosome) or **trisomy** (gain of an extraneous chromosome). Monosomic human zygotes missing any one copy of an autosome invariably fail to develop to birth because they have only one copy of essential genes. Most autosomal trisomies also fail to develop to birth; however, duplications of some smaller chromosomes

(13, 15, 18, 21, or 22) can result in offspring that survive for several weeks to many years. Trisomic individuals suffer from a different genetic imbalance: an excess gene dose. Cell functions are calibrated to the amount of gene product produced by two copies (doses) of each gene; adding a third copy (dose) disrupts this balance. The most common trisomy is that of chromosome 21, which leads to **Down syndrome**. Individuals with this inherited disorder have characteristic physical features and developmental delays in growth and cognition. The incidence of Down syndrome is correlated with maternal age, such that childbearing people over the age of 35 experience an increased probability of giving birth to children with Down syndrome (see figure below). It should be noted that the majority of children with Down syndrome are born to mothers under 35, likely because pre-natal screening for those over 35 is common. The probability related to age and the actual incidence are separate and distinct.

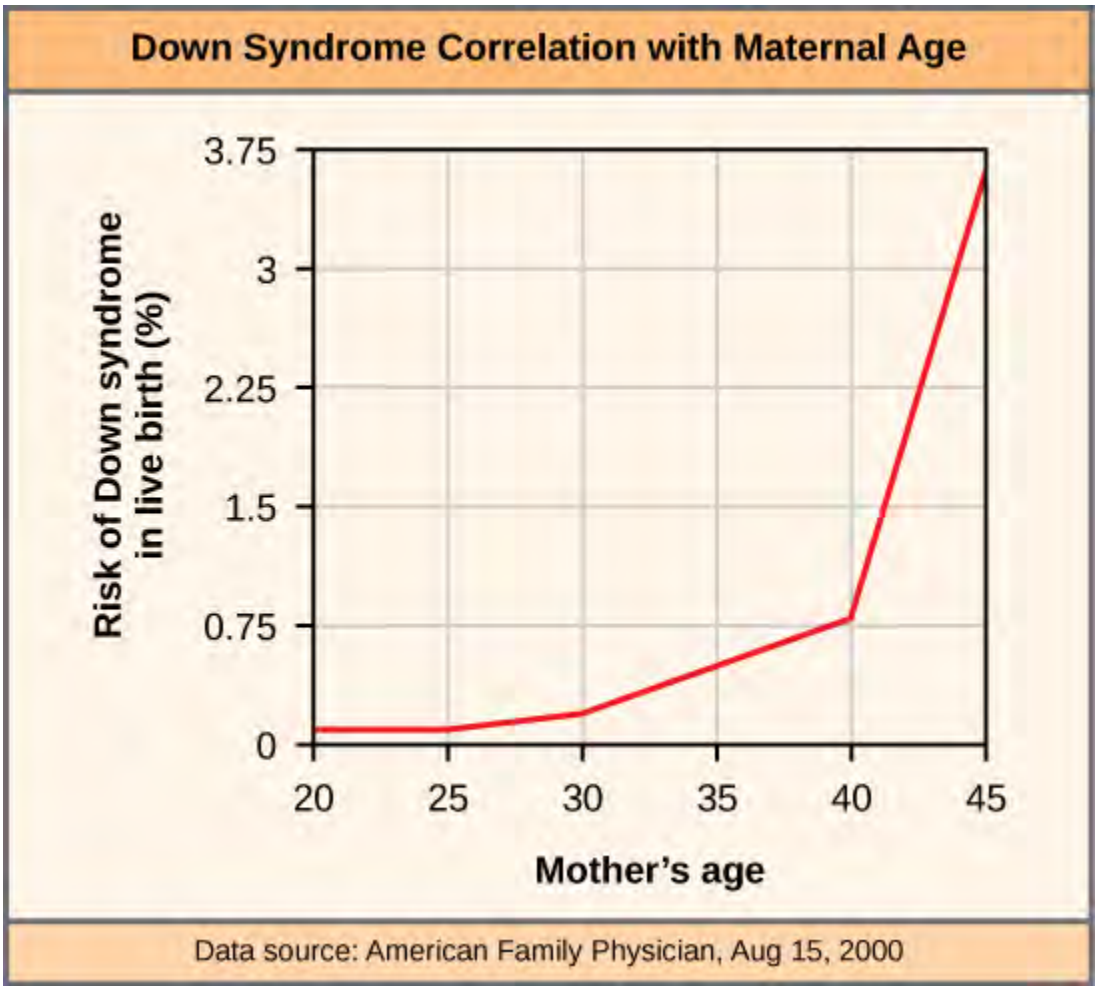

Figure 4.23 The incidence of having a fetus with trisomy 21 increases dramatically with maternal age. **Source:** *Concepts of Biology (OpenStax)*, CC BY 4.0

Concept in Action

Visualize the various outcomes of nondisjunction in this animation.

Watch Chromosome Nondisjunction Animation (5 mins) on YouTube (https://youtu.be/4bzY9e-YQqI)

Humans display dramatic deleterious effects with autosomal trisomies and monosomies. Therefore, it may seem counterintuitive that human females and males can function normally despite carrying different numbers of the X chromosome. In part, this occurs because of a process called X inactivation. Early in development, when female mammalian embryos consist of just a few thousand cells, one X chromosome in each cell inactivates by condensing into a Barr body structure. The genes on the inactive X chromosome are not expressed. The particular X chromosome (maternally or paternally derived) that is inactivated in each cell is random, but once the inactivation occurs, all cells descended from that cell will have the same inactive X chromosome. By this process, females compensate for their double genetic dose of X chromosome.

In so-called "tortoiseshell" cats, X inactivation is observed as coat-colour variegation (see figure below). Females heterozygous for an X-linked coat colour gene will express one of two different coat colours over other regions of their body, corresponding to whichever X chromosome is inactivated in the embryonic cell progenitor of that region. When you see a tortoiseshell cat, you will know it must be a female.

Embryonic inactivation of one of two different X chromosomes encoding different coat colours gives rise to the tortoiseshell phenotype in cats. (credit:) Photo of a tortoiseshell cat. **Source:** Michael Bodega – Concepts of Biology (OpenStax), CC BY 4.0

In an individual carrying an abnormal number of X chromosomes, cellular mechanisms will inactivate all but one X in each cell. As a result, X-chromosomal abnormalities are typically associated with mild mental and physical defects and sterility. If the X chromosome is absent altogether, the individual will not develop.

Several errors in sex chromosome numbers have been characterized. Individuals with three X chromosomes, called triple-X, appear female but express developmental delays and reduced fertility. The XXY chromosome complement, corresponding to one type of **Klinefelter syndrome**, corresponds to male individuals with small testes, enlarged breasts, and reduced body hair. The extra X chromosome undergoes inactivation to compensate for the excess genetic dosage. Turner syndrome, characterized as an X0 chromosome complement (i.e., only a single sex chromosome), corresponds to a female individual with short stature, webbed skin in the neck region, hearing and cardiac impairments, and sterility.

An individual with more than the correct number of chromosome sets (two for diploid species) is called **polyploid**. For instance, fertilizing an abnormal diploid egg with a normal haploid sperm would yield a triploid zygote. Polyploid animals are scarce, with only a few examples among the flatworms, crustaceans, amphibians, fish, and lizards. Triploid animals are sterile because meiosis cannot proceed normally with an odd number of chromosome sets. In contrast, polyploidy is very common in the plant kingdom, and polyploid plants tend to be larger and more robust than euploids of their species.

Chromosome Structural Rearrangements

Cytologists have characterized numerous structural rearrangements in chromosomes, including partial duplications, deletions, inversions, and translocations. Duplications and deletions often produce offspring that survive but exhibit physical and mental abnormalities. **Cri-du-chat** (from the French for “cry of the cat”) is a syndrome associated with nervous system abnormalities and identifiable physical features that result from a deletion of most of the small arm of chromosome 5 (see figure below). Infants with this genotype emit a characteristic high-pitched cry upon which the disorder’s name is based.

Figure 4.24 This individual with cri-du-chat syndrome is shown at various ages: (A) age two, (B) age four, (C) age nine, and (D) age 12. **Source:** Paola Cerruti Mainardi – *Concepts of Biology (OpenStax)*, CC BY 4.0.

Chromosome inversions and translocations can be identified by observing cells during meiosis because homologous chromosomes with a rearrangement in one of the pairs must contort to maintain appropriate gene alignment and pair effectively during prophase I.

A chromosome inversion is the detachment, 180° rotation, and reinsertion of part of a chromosome. Unless they disrupt a gene sequence, inversions only change the orientation of genes and are likely to have milder effects than aneuploid errors.

A **translocation** occurs when a chromosome segment dissociates and reattaches to a different, nonhomologous chromosome. Translocations can be benign or have devastating effects, depending on how the positions of genes are altered concerning regulatory sequences. Notably, specific translocations have been

associated with several cancers and with schizophrenia. **Reciprocal translocations** result from the exchange of chromosome segments between two nonhomologous chromosomes such that there is no gain or loss of genetic information (see figure below).

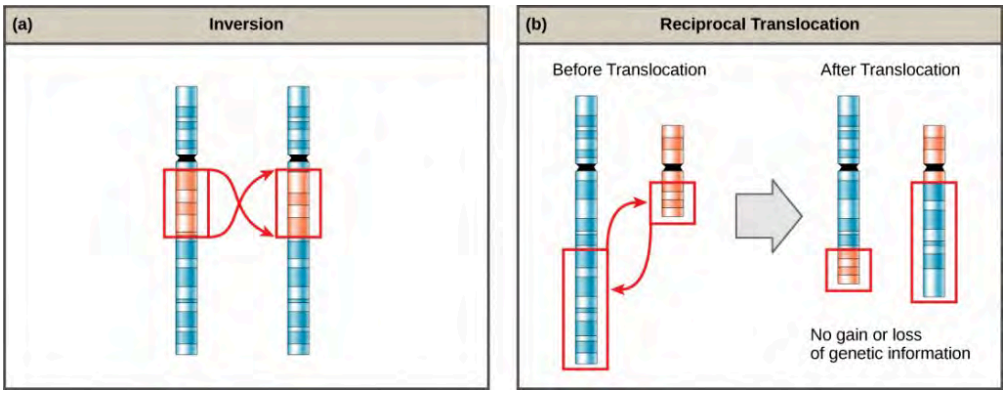

Figure 4.25 An (a) inversion occurs when a chromosome segment breaks from the chromosome, reverses its orientation, and then reattaches to the original position. A (b) reciprocal translocation occurs between two nonhomologous chromosomes and does not cause any genetic information to be lost or duplicated. **Source:** modification of work by National Human Genome Research Institute (USA) – *Concepts of Biology (OpenStax)*, CC BY 4.0

When an individual's cells differ in their chromosomal makeup, it is known as chromosomal mosaicism.

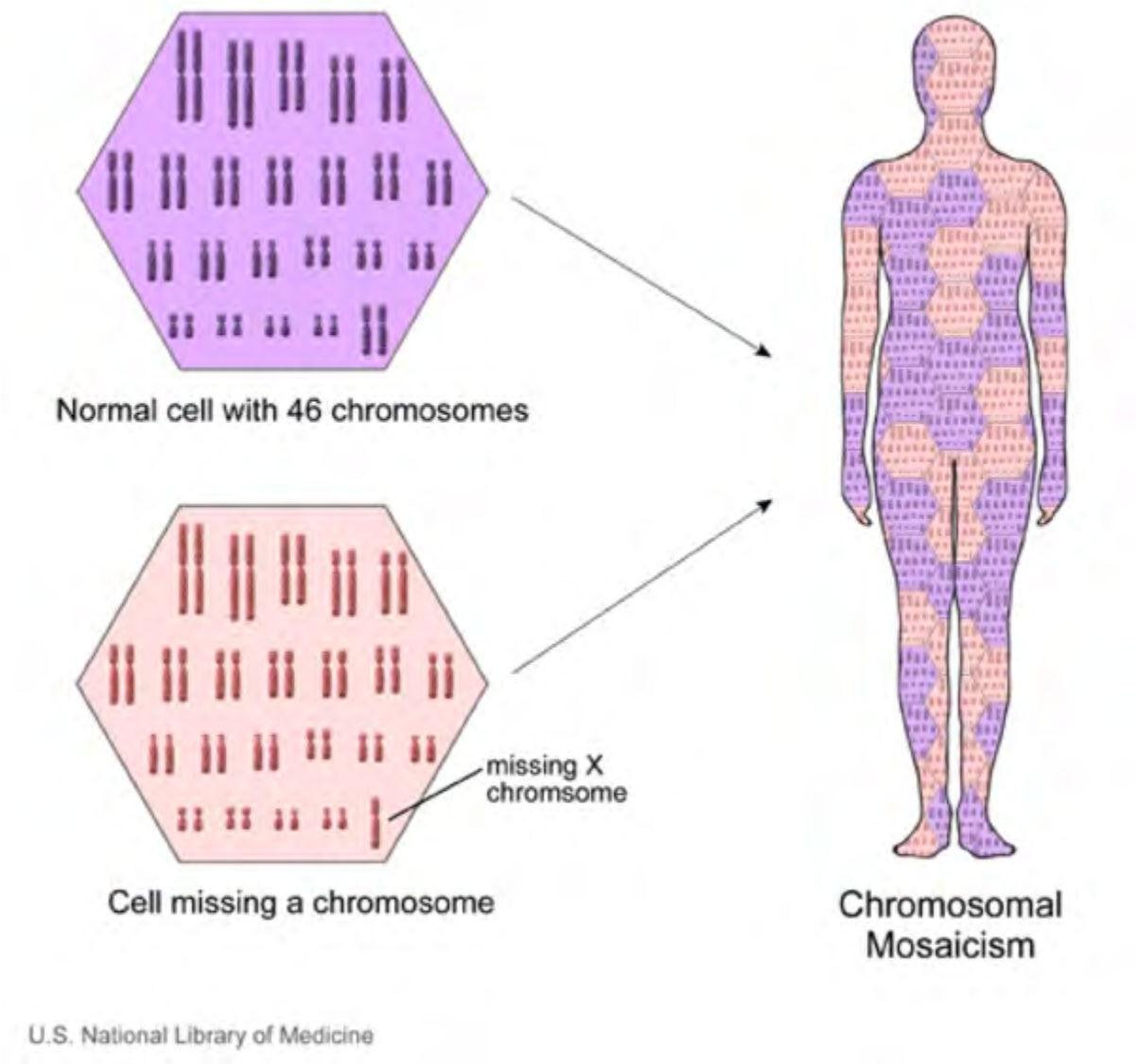

Figure 4.26 U.S. National Library of Medicine, PDM with attribution

Chromosomal mosaicism occurs from an error in cell division in cells other than eggs and sperm. Most commonly, some cells end up with one extra or missing chromosome (for a total of 45 or 47 chromosomes per cell), while other cells have 46 chromosomes. Mosaic Turner syndrome is one example of chromosomal mosaicism. In females with this condition, some cells have 45 chromosomes because they are missing one copy of the X chromosome, while other cells have the usual number of chromosomes.

Many cancer cells also have changes in their number of chromosomes. These changes are not inherited; they occur in somatic cells (cells other than eggs or sperm) during the formation or progression of a cancerous tumour.

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4.7 MITOCHONDRIAL DISORDERS

Can changes in mitochondrial DNA affect health and development?

Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, *mitochondria also have a small amount of their own DNA* (known as **mitochondrial DNA** or mtDNA). In some cases, inherited changes in mitochondrial DNA can cause problems with growth, development, and function of the body's systems. These variants disrupt the mitochondria's ability to generate energy efficiently for cells.

Conditions caused by variants in mitochondrial DNA often involve multiple organ systems. The effects of these conditions are most pronounced in organs and tissues that require a lot of energy (such as the heart, brain, and muscles). Although the health consequences of inherited mitochondrial DNA alterations vary widely, frequently observed features include muscle weakness and wasting, problems with movement, diabetes, kidney failure, heart disease, loss of intellectual functions (dementia), hearing loss, and problems involving the eyes and vision.

Genetic changes that are not inherited (somatic variants) may also occur in mitochondrial DNA. Recall that somatic variants occur in the DNA of certain cells (not sperm or egg cells) during a person's lifetime and are not passed to future generations. Because mitochondrial DNA cannot repair errors, these variants tend to build up over time. A buildup of somatic variants in mitochondrial DNA has been associated with some forms of cancer and an increased risk of certain age-related disorders such as heart disease, Alzheimer's disease (https://medlineplus.gov/genetics/condition/alzheimer-disease/), and Parkinson's disease (https://medlineplus.gov/genetics/condition/parkinson-disease/). Additionally, research suggests that the progressive accumulation of these variants over a person's lifetime may play a role in the normal aging process.

Symptoms of mitochondrial disorders vary because a person can have a unique mixture of healthy and defective mitochondria, with a unique distribution of each within the body.

Mitochondrial disorders that mainly cause muscular problems are called **mitochondrial myopathies** ("myo" means muscle and "pathos "means disease), while mitochondrial disorders that cause both muscular and neurological problems are called **mitochondrial encephalomyopathies** (encephalo refers to the brain).

Mitochondrial myopathy

The main symptoms of mitochondrial myopathy are:

- Muscle fatigue
- Weakness
- Exercise intolerance

The severity of any of these symptoms varies greatly from one person to the next, even within the same family.

In some individuals, the weakness is most prominent in the muscles that control eye and eyelid movements. This can lead to these muscles eventually becoming paralyzed, called progressive external ophthalmoplegia (PEO). People with PEO may also experience a drooping of the upper eyelids, called ptosis. They also have difficulty moving their eyes up and down and side to side. Often, people automatically compensate for PEO by moving using their necks to look in different directions and might not notice any visual problems. Ptosis can impair vision and cause a listless expression. Surgery can help correct this.

Mitochondrial myopathies can cause weakness and wasting in other muscles of the face and neck, which can lead to difficulty with swallowing and, more rarely, slurred speech. People with mitochondrial myopathies also may experience muscle weakness in their arms and legs.

Exercise intolerance, also called exertional fatigue, refers to unusual feelings of exhaustion brought on by physical exertion. The degree of exercise intolerance varies significantly among individuals. Some people might need help with athletic activities like jogging, while others might experience problems with everyday activities such as walking to the mailbox or lifting a milk carton. In rare instances, this exercise intolerance can lead to muscle breakdown after exercise. This breakdown causes a protein called myoglobin to leak from a person's muscles into their urine. The leakage, sometimes accompanied by muscle cramps, usually occurs when a person with exercise intolerance "overdoes it" and can happen during physical activity or several hours afterward.

While people with mitochondrial myopathy should avoid overdoing it, moderate exercise can help them maintain strength.

Mitochondrial encephalomyopathy

Mitochondrial encephalomyopathy often includes some symptoms of myopathy plus one or more neurological symptoms.

In addition to affecting the muscles around the eye, mitochondrial encephalomyopathy can affect the eye and parts of the brain involved in vision. For instance, vision loss is a common symptom of mitochondrial encephalomyopathy. This can be caused by shrinkage of the optic nerve or a breakdown of the cells that line the back of the eye.

Other common symptoms of mitochondrial encephalomyopathy include migraine headaches and seizures. There are many effective medications for treating and helping to prevent migraines and seizures, including anticonvulsants and other drugs developed to treat epilepsy.

Hearing loss is another common symptom of mitochondrial disorders. It is caused by damage to the inner

ear or the auditory nerve, which connects the inner ear to the brain. This kind of hearing loss is permanent, but it can be managed. Alternative forms of communication (like sign language), hearing aids, or cochlear implants can help.

Mitochondrial disorders can cause ataxia, which is trouble with balance and coordination. People with ataxia are prone to falls and may need to use supportive aids such as railings, a walker, or a wheelchair. Physical and occupational therapy also may help.

In some cases, mitochondrial disorders can lead to issues with breathing, heart health, kidney issues, diabetes, or digestive problems. People with mitochondrial disorders should get regular health check-ups to identify and monitor these potential problems.

Mitochondrial disorders in children

Although PEO and ptosis typically cause only mild visual impairment in adults, they can be much more harmful in children. During childhood, these conditions can cause permanent damage to the brain's visual system. Children with signs of PEO or ptosis need to have their vision checked by a specialist.

Children with mitochondrial disorders may have difficulty developing specific skills due to either muscle weakness, neurological problems, or both. For example, they might take longer than usual to learn to sit, crawl, or walk. As they get older, they may be unable to get around as easily as other children their age or may have problems with speech or learning. Children affected by these problems may benefit from early intervention and services such as physical and speech therapy or an individualized education program at school.

To read about different types of mitochondrial disorders, visit this NIH web resource (https://www.ninds.nih.gov/health-information/disorders/mitochondrial-disorders#toc-types-of-mitochondrial-disorders)or this mitochondrial myopathies fact sheet (https://www.mda.org/disease/mitochondrial-myopathies) from the Muscular Dystrophy Association.

How are mitochondrial disorders diagnosed and treated?

Diagnosing mitochondrial disorders

A diagnosis generally includes:

- An evaluation of medical and family history.
- Physical and neurological exams. The physical exam typically includes tests of strength and endurance, such as an exercise test (which can involve repeatedly making a fist). The neurological exam can consist of tests of reflexes, vision, speech, and basic cognitive (thinking) skills.
- Laboratory tests to look for diabetes, liver and kidney problems, and elevated lactic acid in the blood and

urine. Lactic acid in the cerebral spinal fluid may be measured using a spinal tap or estimated via less invasive MRI imaging.

- EKG (electrocardiogram) to check the heart for signs of arrhythmia and cardiomyopathy.
- Diagnostic imaging, such as CT (computed tomography) or MRI, to inspect the brain for developmental abnormalities or signs of damage. In an individual with seizures, the doctor might order an EEG (electroencephalogram), which involves placing electrodes on the scalp to record brain activity.
- Genetic testing can determine whether someone has a genetic mutation. Although a positive test result can confirm the diagnosis of a mitochondrial disorder, a negative test result can be more complex to interpret and does not definitively rule out the presence of a genetic mutation. It could mean a person has a mutation that the test could not detect.
- Muscle biopsy involves removing and examining a small sample of muscle tissue. When treated with a dye that stains mitochondria red, muscles affected by mitochondrial disorders often show ragged red fibres—muscle cells (fibres) with excessive mitochondria. Other stains can detect the absence of essential mitochondrial enzymes in the muscle. It also is possible to extract mitochondrial proteins from the muscle and measure their activity. Genetic testing for mutations in mitochondrial DNA is more sensitive than testing for mutations in blood in certain mitochondrial disorders. Noninvasive techniques like MR spectroscopy can examine muscle without taking a tissue sample.

Treating mitochondrial disorders

There are currently no cures or specific treatments for mitochondrial disorders. Generally, treatment is focused on managing symptoms and may include physical and occupational therapy, moderate, physician-led exercise programs, anti-seizure medications, heart medications, vitamins and supplements, or special diets. People with eye and vision symptoms may benefit from assistive devices and surgery, as can individuals with hearing loss. People with any unique issues mentioned below should be monitored by their healthcare provider to track their symptoms and identify appropriate treatments.

People with mild respiratory problems might require occasional respiratory support, such as pressurized air. Someone with more severe problems might require permanent support from a ventilator.

Some mitochondrial disorders may cause cardiomyopathy (heart muscle weakness) or arrhythmia (irregular heartbeat). Although dangerous, cardiac arrhythmia is treatable with a pacemaker, which stimulates a normal heartbeat.

People with mitochondrial disease may experience gastrointestinal problems, diabetes, and kidney problems. These associated conditions and disorders should be managed with appropriate treatments for each. While some of these problems are directly related to mitochondrial disorders, others may be indirectly affected by the disorder. For example, having myoglobin in a person's urine causes the kidneys to work harder to filter it out, which can lead to kidney damage.

Attribution & References

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4.8 UNIT SUMMARY AND REVIEW

Key Takeaways

Gene variants are slight differences in DNA sequences that occur at specific locations in the genome, contributing to individual uniqueness. While many variants do not impact health, some may increase or reduce disease risk. Variants can be inherited (germline) or occur during a person's lifetime (somatic). Variants can be classified by their effects, such as morphological, lethal, or conditional, depending on their influence on traits, development, or survival. Some variants are "silent," meaning they do not alter protein function or phenotype.

Genetic disorders are categorized into four main types: single gene disorders, chromosomal conditions, multifactorial conditions, and mitochondrial disorders. Naming genetic conditions varies based on factors such as the genetic mutation involved or affected body parts, while a formal committee standardizes gene nomenclature. Genetic predisposition is an increased likelihood of developing certain diseases based on inherited genetic variations, although lifestyle and environmental factors can also play a significant role.

Mutations in a single gene cause single-gene disorders and can follow dominant, recessive, or X-linked inheritance patterns. Despite their rarity, these diseases affect millions globally, including conditions like cystic fibrosis (CF), sickle cell anemia, and Tay-Sachs disease. Advances in genetic testing have improved diagnostics, but treatments for many single-gene disorders remain limited.

The concepts of penetrance and expressivity explain the extent to which a genotype results in the expected phenotype and the variability of phenotypes among individuals with the same genotype. Pleiotropy, where one gene affects multiple traits, and polygenic inheritance, where multiple genes influence a single trait, further illustrate the complexity of genotype-phenotype relationships. Complex traits and diseases often result from multifactorial influences, combining genetic, environmental, and epigenetic components, leading to continuous phenotypic variation.

Inherited disorders can result from abnormal chromosomal behaviour during meiosis, leading to numerical or structural chromosome abnormalities. Chromosomal disorders, such as Down

syndrome (trisomy 21) and Turner syndrome (monosomy X), can be identified using karyograms, revealing chromosome number or structure abnormalities. Nondisjunction, a failure in chromosome separation during meiosis, can cause aneuploidy, leading to trisomy or monosomy. Structural rearrangements, including inversions and translocations, may cause genetic disorders or contribute to cancer. X inactivation helps mitigate the effects of extra X chromosomes, as seen in conditions like Klinefelter syndrome. Chromosomal mosaicism occurs when some cells have differing chromosomal compositions, as observed in conditions like mosaic Turner syndrome.

Mitochondrial disorders result from mutations in mitochondrial DNA, which impair energy production in cells and can affect multiple organ systems, particularly those with high energy demands, such as the heart, brain, and muscles. Symptoms range from muscle weakness, exercise intolerance, and vision problems to neurological issues like seizures, hearing loss, and ataxia. In children, developmental delays may occur. Diagnosis typically involves medical history, physical exams, genetic testing, and muscle biopsies. While no cure exists, treatment focuses on managing symptoms through therapies, medications, and supportive care.

Additional Optional Readings

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Attribution & References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

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