UNIT 3 - THE EXPOSOME

Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev

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Unit 3 Contents

Attribution

3.1 UNIT OVERVIEW

Learning Objectives

- Explore whether the nature–nurture debate is still relevant.
- Examine the research designs that can be used to study nature–nurture questions.
- Define genetic determinism and identify how it relates to epigenetics.
- Review the developmental origins of health and disease and the impacts on long-term health outcomes.
- Establish how the exposome can influence gene expression.
- Determine the relationship between the social determinants of health and genetics and identify policy implications.
- Explore how adverse early childhood experiences or toxic stress can lead to adverse health outcomes later in life.
- Establish the significance of epigenetics to practice.

Outline

Topics covered in this chapter include:

- Nature vs nurture
- Epigenetics
- Developmental origins of health and disease
- The exposome
- Adverse early childhood experiences
- Epigenetics in practice

Competencies Nurses will Develop in this Chapter

ANA (2023):

Nursing assessment: Applying/integrating genomic knowledge:

- Collects, reviews, and updates personal and family health history to include any genomic testing and environmental and other risk factors.
- Conducts health and physical assessments that incorporate knowledge about known or potential environmental, genomic, and other risk factors (e.g., behavioral, lifestyle).

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 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; and
  relating it to the prevention and management of a genomic condition or response to treatment.

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

- being responsive to changing needs through the life-stages and during periods of uncertainty.

Key terminology

Adverse Childhood Experiences (ACEs)

ACEs are potentially traumatic events that occur in childhood (0-17 years) and can include, but are not limited to experiencing violence, abuse, or neglect, witnessing violence in the home or community, having a family member attempt of die by suicide, growing up with substance use or mental health issues in the home, parental separation or divorce, or having family members in prison. ACEs can have a lasting effect on health and well-being well into adulthood (CDC, 2024).

Adoption study

A behavior genetic research method that involves comparison of adopted children to their adoptive and biological parents (Tuckheimer, 2024).

Behavioral genetics

The empirical science of how genes and environments combine to generate behavior (Tuckheimer, 2024).

Critical Periods

Periods of development where an organism is susceptible to the influence of environmental exposures on organ development and gene expression (OTIS, 2023).

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.

Developmental Programming

The process where environmental exposures and experiences during critical developmental periods influence gene expression and shape the structure, function, and long-term health outcomes including growth, metabolism, and neurodevelopment of an individual (Padmanabhan et al., 2016).

Diagnostic Odyssey

The often long period of time it can take for a patient to receive a diagnosis for their condition (Genomics Education Programme, 2021).

Environmental Factors

Environmental factors, as related to genetics, refers to exposures to substances (such as pesticides or industrial waste) where we live or work, behaviors (such as smoking or poor diet) that can increase an individual's risk of disease or stressful situations (such as racism). Genetic studies often take environmental factors into consideration, as these exposures can increase an individual's risk of genetic damage or disease.

Epigenetics

Epigenetics (also sometimes called epigenomics) is a field of study focused on changes in DNA that do not involve alterations to the underlying sequence. The DNA letters and the proteins that interact with DNA can have chemical modifications that change the degrees to which genes are turned on and off. Certain epigenetic modifications may be passed on from parent cell to daughter cell during cell division or from one generation to the next. The collection of all epigenetic changes in a genome is called an epigenome.

Exposome

The measure of all the exposures of an individual in a lifetime and how those exposures relate to health (CDC, 2022).

Fraternal Twins

Fraternal twins (also called dizygotic twins) result from the fertilization of two separate eggs with two different sperm during the same pregnancy. Fraternal twins may not have the same sex or appearance. They share half their genomes, just like any other siblings. In contrast, identical twins (or monozygotic twins) result from the fertilization of a single egg by a single sperm, with the fertilized egg then splitting into two. As a result, identical twins share the same genomes and are always the same sex.

Gene Expression

Gene expression is the process by which the information encoded in a gene is used to either make RNA molecules that code for proteins or to make non-coding RNA molecules that serve other functions. Gene expression acts as an "on/off switch" to control when and where RNA molecules and proteins are made and as a "volume control" to determine how much of those products are made. The process of gene expression is carefully regulated, changing substantially under different conditions. The RNA and protein products of many genes serve to regulate the expression of other genes.

Gene Regulation

Gene regulation is the process used to control the timing, location and amount in which genes are expressed. The process can be complicated and is carried out by a variety of mechanisms, including through regulatory proteins and chemical modification of DNA. Gene regulation is key to the ability of an organism to respond to environmental changes.

Gene–Environment Interaction

Gene–environment interaction refers to the interplay of genes (and, more broadly, genome function) and the physical and social environment. These interactions influence the expression of phenotypes. For example, most human traits and diseases are influenced by how one or more genes interact in complex ways with environmental factors, such as chemicals in the air or water, nutrition, ultraviolet radiation from the sun and social context.

Genetic Determination

Is the belief that one's biological/genetic nature if fixed and is the sole determinant of phenotype (Harden, 2023).

Genetic Imprinting

Genomic imprinting is the process by which only one copy of a gene in an individual (either from their mother or their father) is expressed, while the other copy is suppressed. Unlike genomic mutations that can affect the ability of inherited genes to be expressed, genomic imprinting does not affect the DNA sequence itself. Instead, gene expression is silenced by the epigenetic addition of chemical tags to the DNA during egg or sperm formation. Epigenetic tags on imprinted genes usually stay in place for the life of the individual.

Heritability Coefficient

An easily misinterpreted statistical construct that purports to measure the role of genetics in the explanation of differences among individuals (Tuckheimer, 2024).

Identical Twins

Identical twins (also called monozygotic twins) result from the fertilization of a single egg by a single sperm, with the fertilized egg then splitting into two. Identical twins share the same genomes and are nearly always the same sex. In contrast, fraternal (dizygotic) twins result from the fertilization of two separate eggs with two different sperm during the same pregnancy. Like most other siblings, fraternal twins share half of their genomes. The sex of one fraternal twin has no relation to the sex of the other and they may not have similar appearances.

Neuronal (or synaptic) Pruning

Synaptic pruning is a process that occurs in the brain between early childhood and adulthood where the brain eliminates extra synapses that are not being used (Gill, 2018).

Quantitative Genetics

Scientific and mathematical methods for inferring genetic and environmental processes based on the degree of genetic and environmental similarity among organisms (Tuckheimer, 2024).

Rare Disease

A disease that affects less than 1 in 2,000 of the general population (EU definition). In the UK, approximately 3.5 million people will be affected by a rare disease at some point in their life (Rare Disease UK) (Genomics Education Programme, 2022).

Twin Studies

A behavior genetic research method that involves comparison of the similarity of identical (monozygotic; MZ) and fraternal (dizygotic; DZ) twins (Tuckheimer, 2024).

Uniparental Disomy

Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent. UPD can occur as a random event during the formation of egg or sperm cells, or it may happen during early fetal development (NIH: National Library of Medicine, n.d.).

Attribution & References

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- Definitions for Rare Disease & Diagnostic Odessey from *Genomics Glossary* by Genomics Education Programme, CC BY-NC

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3.2 NATURE VS. NURTURE

People have a deep intuition about what has been called the "nature-nurture question." Some aspects of our behaviour feel like they originate in our genetic makeup, while others feel like the result of our upbringing or our hard work. The scientific field of behaviour genetics attempts to study these differences empirically by examining similarities among family members with different degrees of genetic relatedness or, more recently, by studying differences in the DNA of people with different behavioural traits. The scientific methods that have been developed are ingenious but often inconclusive. Many of the difficulties encountered in the empirical science of behaviour genetics turn out to be conceptual, and our intuitions about nature and nurture get more complicated the harder we think about them. Ultimately, it is an oversimplification to ask how "genetic" some particular behaviour is. Genes and environments always combine to produce behaviour.

Introduction

It may seem obvious that we are born with certain characteristics while others are acquired. Yet, of the questions about humans' relationship with the natural world, only nature–nurture gets referred to as a "debate." We are concerned with nature–nurture because our very sense of moral character seems to depend on it. While we may admire the athletic skills of a great basketball player, we think of his height as simply a gift, a payoff in the "genetic lottery." For the same reason, no one blames a short person for his height or someone's congenital disability on poor decisions. But we praise the concert violinist (and perhaps her parents and teachers) for her dedication, just as we condemn cheaters, slackers, and bullies for their bad behaviour.

The problem is most human characteristics aren't usually as clear-cut as height or instrument mastery, affirming our nature-nurture expectations strongly one way or the other. Even the great violinist might have some inborn qualities—perfect pitch or long, nimble fingers—that support and reward their hard work. And the basketball player might have eaten a diet while growing up that promoted their genetic tendency to be tall. When we think about our qualities, they seem under our control in some respects yet beyond our control in others. Often, the traits that don't seem to have an apparent cause are the ones that concern us the most and are far more personally significant.

Researchers have learned a great deal about the nature-nurture dynamic by working with animals. But many of the techniques used to study animals cannot be applied to people. Separating these two influences in human subjects is a more significant research challenge. **Source:** Photo by Sebastián Dario, CC BY-NC 2.0

One major problem with answering nature-nurture questions about people is how do you set up an experiment. In nonhuman animals, there are relatively straightforward experiments for tackling nature-nurture questions. Say, for example, you are interested in aggressiveness in dogs. You want to test for the more important determinant of aggression: being born to aggressive dogs or being raised by them. You could mate two aggressive dogs—angry Chihuahuas—together and two nonaggressive dogs—happy beagles—together, then switch half the puppies from each litter between the different sets of parents to raise. You would then have puppies born to aggressive parents (the Chihuahuas) but being raised by nonaggressive parents (the Beagles), and vice versa, in litters that mirror each other in puppy distribution. The big questions are: Would the Chihuahua parents raise aggressive beagle puppies? Would the beagle parents raise nonaggressive Chihuahua puppies? Would the puppies' nature win out, regardless of who raised them? Or... would the result be a combination of nature and nurture? Much of the most significant nature-nurture research has been done this way (Scott & Fuller, 1998), and animal breeders have been doing it successfully for thousands of years. It is fairly easy to breed animals for behavioural traits.

With people, however, we can't assign babies to parents at random, or select parents with certain behavioural characteristics to mate, merely in the interest of science (though history does include horrific examples of such practices in misguided attempts at "eugenics," the shaping of human characteristics through intentional breeding – we will explore this more in a subsequent unit). Despite our restrictions on setting up human-based experiments, we do see real-world examples of nature-nurture at work in the human sphere—though they only provide partial answers to our many questions.

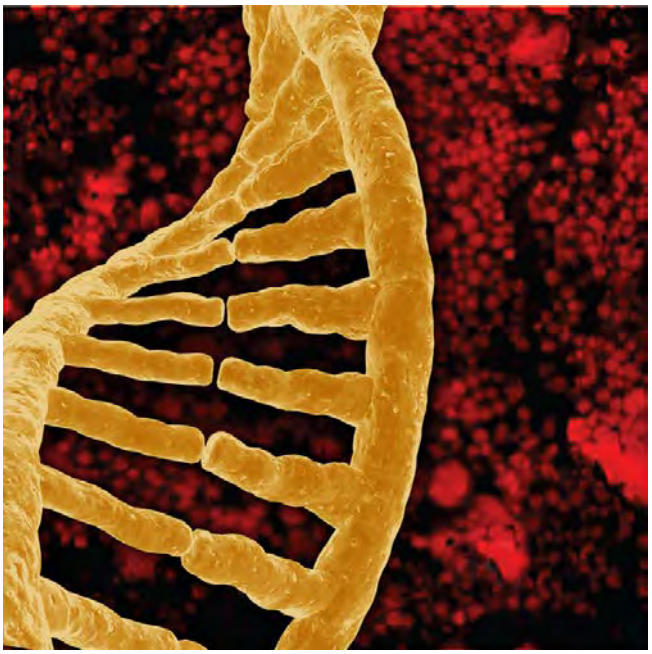
The science of how genes and environments work together to influence behaviour is called behavioural **genetics**. The easiest opportunity we have to observe this is the **adoption study**. When children are adopted, their biological parents do not raise them. If the biological child of tall parents were adopted into a family of short people, do you suppose the child's growth would be affected? What about the biological child of a Spanish-speaking family adopted at birth into an English-speaking family? What language would you expect the child to speak? And what might these outcomes tell you about the difference between height and language in terms of nature-nurture?

Studies focused on twins have led to important insights about the biological origins of many personality characteristics. **Source:** Photo by Pixabay/Pexels, CC0

Another option for observing nature-nurture in humans involves **twin studies**. Two types of twins are **monozygotic (MZ)** and **dizygotic (DZ)**. Monozygotic twins, also called "identical" twins, result from a single zygote (fertilized egg) and have the same DNA. They are essentially clones. Dizygotic twins, also known as "fraternal" twins, develop from two zygotes and share 50% of their DNA. Fraternal twins can be thought of as siblings who happen to have been born at the same time. To analyze nature–nurture using twins, we compare the similarity of MZ and DZ pairs. Sticking with the features of height and spoken language, let's take a look at how nature and nurture apply: Identical twins, unsurprisingly, are almost perfectly similar in height. The heights of fraternal twins, however, are like any other sibling pairs: more similar to each other than to people from other families, but hardly identical. This contrast between twin types gives us a clue about the role genetics plays in determining height. Now consider spoken language. If one identical twin speaks Spanish at home, the co-twin with whom she is raised almost certainly does. But the same would be valid for a pair of fraternal twins raised together. Concerning spoken language, fraternal twins are just as similar as identical twins, so it appears that the genetic match of identical twins doesn't make much difference.

Twin and adoption studies are two instances of a much broader class of methods for observing nature-nurture called **quantitative genetics,** the scientific discipline in which similarities among individuals are analyzed based on how biologically related they are. We can do these studies with siblings and half-siblings, cousins, and twins who have been separated at birth and raised separately (Bouchard, Lykken, McGue, & Segal, 1990; such twins are very rare and play a more minor role than is commonly believed in the science of nature-nurture), or with entire extended families (see Plomin, DeFries, Knopik, & Neiderhiser, 2012, for a complete introduction to research methods relevant to nature-nurture).

For better or for worse, contentions about nature-nurture have intensified because quantitative genetics produces a number called a **heritability coefficient**, varying from 0 to 1, that is meant to provide a single measure of genetics' influence on a trait. Generally, a heritability coefficient measures how strongly differences among individuals are related to differences in their genes. But beware: Heritability coefficients, although simple to compute, are deceptively challenging to interpret. Nevertheless, numbers that provide simple answers to complicated questions tend to strongly influence the human imagination, and a great deal of time has been spent discussing whether the heritability of intelligence or, personality or depression is equal to one number or another.



Source: Viral DNA by EMSL, CC BY-NC-SA 2.0

What Have We Learned About Nature–Nurture?

It would be satisfying to be able to say that nature-nurture studies have given us conclusive and complete evidence about where traits come from, with some traits clearly resulting from genetics and others almost entirely from environmental factors, such as childrearing practices and personal will, but that is not the case. Instead, *everything* has turned out to have some footing in genetics. The more genetically-related people are, the more similar they are—for *everything*: height, weight, intelligence, personality, mental illness, etc. Sure, it seems like common sense that some traits have a genetic bias. For example, adopted children resemble their biological parents even if they have never met them, and identical twins are more similar to each other than are fraternal twins. And while certain psychological traits, such as personality or mental illness (e.g., schizophrenia), seem reasonably influenced by genetics, it turns out that the same is true for political attitudes, how much television people watch (Plomin, Corley, DeFries, & Fulker, 1990), and whether or not they get divorced (McGue & Lykken, 1992).

Over the last half century, research has revealed how central genetics are to behavior. The more genetically related people are, the more similar they are not just physically but also in terms of personality and behavior. **Source:** Photo by Paul Altobelli, CC BY 2.0

It may seem surprising, but the genetic influence on behaviour is a relatively recent discovery. In the middle of the 20th century, psychology was dominated by the doctrine of behaviourism, which held that behaviour could only be explained in terms of environmental factors. Psychiatry concentrated on psychoanalysis, which probed for the roots of behaviour in individuals' early life histories. The truth is, neither behaviourism nor psychoanalysis is incompatible with genetic influences on behaviour, and neither Freud nor Skinner was naive about the importance of organic processes in behaviour. Nevertheless, in their day, it was widely thought that children's personalities were shaped entirely by imitating their parents' behaviour and that schizophrenia was caused by certain kinds of "pathological mothering." Whatever the outcome of our broader discussion of nature-nurture, the basic fact that the best predictors of an adopted child's personality or mental health are found in the biological parents they have never met, rather than in the adoptive parents who raised them, presents a significant challenge to purely environmental explanations of personality or psychopathology. The message is clear: You can't leave genes out of the equation. But remember, no behavioral traits are entirely inherited, so you can't leave the environment out altogether, either.

Trying to untangle the various ways nature-nurture influences human behavior can be messy, and often, common-sense notions can get in the way of good science. One very significant contribution of behavioural genetics that has changed psychology for good can be very helpful to keep in mind: When your subjects are biologically related, no matter how clearly a situation may seem to point to environmental influence, it is never safe to interpret behaviour as wholly the result of nurture without further evidence. For example, when presented with data showing that children whose mothers read to them often are likely to have better reading scores in third grade, it is tempting to conclude that reading to your kids out loud is important to success in school; this may well be true, but the study as described is inconclusive, because there are genetic *as well as* environmental pathways between the parenting practices of mothers and the abilities of their children. This is a case where "correlation does not imply causation," as they say. To establish that reading aloud causes success, a scientist can either study the problem in adoptive families (in which the genetic pathway is absent) or by finding a way to assign children to oral reading conditions randomly.

The outcomes of nature-nurture studies have fallen short of our expectations (of establishing clear-cut

bases for traits) in many ways. The most disappointing outcome has been the inability to organize traits from *more*– to *less*-genetic. As noted earlier, everything has turned out to be at least *somewhat* heritable (passed down), yet nothing has turned out to be *absolutely* heritable, and there hasn't been much consistency as to which traits are *more* heritable and which are *less* heritable once other considerations (such as how accurately the trait can be measured) are taken into account (Turkheimer, 2000). The problem is conceptual: The heritability coefficient, and, in fact, the whole quantitative structure that underlies it, does not match up with our nature-nurture intuitions. We want to know how "important" the roles of genes and environment are to the development of a trait, but in focusing on "important" maybe we're emphasizing the wrong thing. First of all, genes and environment are both crucial to *every* trait; without genes, the environment would have nothing to work on, and genes cannot develop in a vacuum. Even more important, because nature-nurture questions look at the differences among people, the cause of a given trait depends not only on the trait itself but also on the differences in that trait between members of the group being studied.

The classic example of the heritability coefficient defying intuition is the trait of having two arms. No one would argue against the development of arms being a biological, genetic process. But fraternal twins are just as similar to "two-armedness," as identical twins, resulting in a heritability coefficient of zero for the trait of having two arms. Usually, according to the heritability model, this result (coefficient of zero) would suggest all nurture, no nature, but we know that's not the case. This result is not a tip-off that arm development is less genetic than we imagine because people *do not vary* in the genes related to arm development—which essentially upends the heritability formula. In this instance, the opposite is likely true: the extent that people differ in arm number is likely the result of accidents and, therefore, environmental. For reasons like these, we always have to be very careful when asking nature-nurture questions, especially when we try to express the answer in terms of a single number. The heritability of a trait is not simply a property of that trait, but a property of the trait in a particular context of relevant genes and environmental factors.

Another issue with the heritability coefficient is that it divides traits' determinants into two portions—genes and environment—which are then calculated together for the total variability. This is a little like asking how much of the experience of a symphony comes from the horns and how much from the strings; the ways instruments or genes integrate is more complex than that. It turns out to be the case that, for many traits, genetic differences affect behaviour under some environmental circumstances but not others—a phenomenon called gene-environment interaction, or G x E. In one well-known example, Caspi et al. (2002) showed that among maltreated children, those who carried a particular allele of the MAOA gene showed a predisposition to violence and antisocial behaviour, while those with other alleles did not. Whereas in children who had not been maltreated, the gene had no effect. Making matters even more complicated are very recent studies of what is known as epigenetics, which we will discuss in the next chapter of this unit.

Some common questions about nature–nurture are: how susceptible is a trait to change, how malleable is it, and do we "have a choice" about it? These questions are much more complex than they may seem at first glance. For example, phenylketonuria is an inborn error of metabolism caused by a single gene; it prevents the body from metabolizing phenylalanine. Untreated, it causes intellectual disability and death. However, it can be treated effectively by a straightforward environmental intervention: avoiding foods containing phenylalanine. Height seems like a trait firmly rooted in our nature and unchangeable. Still, the average height of many populations in Asia and Europe has increased significantly in the past 100 years due to changes in diet and the alleviation of poverty. Even the most modern genetics has not answered nature–nurture questions definitively. When it was first becoming possible to measure the DNA sequences of individual people, it was widely thought that we would quickly progress to finding the specific genes that account for behavioural characteristics, but that hasn't happened. A few rare genes have been found to have significant (almost always adverse) effects, such as the single gene that causes Huntington's disease, or the Apolipoprotein gene that causes early onset dementia in a small percentage of Alzheimer's cases. Aside from these rare genes of significant effect, the genetic impact on behavior is broken up over many genes, each with minimal effects. For most behavioural traits, the effects are so minor and distributed across so many genes that we have not been able to catalogue them in a meaningful way. The same is true of environmental effects. We know that extreme environmental hardship causes catastrophic effects for many behavioral outcomes, but fortunately, extreme environmental hardship is very rare. Within the usual range of environmental events, those responsible for differences (e.g., why some children in a suburban third-grade classroom perform better than others) are much more challenging to grasp.

The answer to the nature–nurture question has not turned out to be as straightforward as we would like. The many questions we can ask about the relationships among genes, environments, and human traits may have many different answers, and the answer to one tells us little about the answers to the others. **Source:** Photo by Sundaram Ramaswamy, CC BY 2.0

The difficulties with finding clear-cut solutions to nature-nurture problems bring us back to the other great questions about our relationship with the natural world: the mind-body problem and free will. Investigations into what we mean, when we say we are aware of something, reveal that consciousness is not simply the product of a particular area of the brain, nor does choice turn out to be an orderly activity that we can apply to some behaviours but not others. So it is with nature and nurture: What at first may seem a

straightforward matter, able to be indexed with a single number, becomes more and more complicated the closer we look. The many questions we can ask about the intersection among genes, environments, and human traits—how sensitive are traits to environmental change, and how common are those influential environments; are parents or culture more relevant; how sensitive are traits to differences in genes, and how much do the relevant genes vary in a particular population; does the trait involve a single gene or a great many genes; is the trait more easily described in genetic or more-complex behavioural terms?—may have different answers, and the answer to one tells us little about the answers to the others. It is tempting to predict that the more we understand the wide-ranging effects of genetic differences on all human characteristics—especially behavioural ones—our cultural, ethical, legal, and personal ways of thinking about ourselves will have to undergo profound changes in response. One of the most important things modern genetics has taught us is that almost all human behaviour is too complex to be nailed down. The science of nature and nurture has demonstrated that genetic differences among people are vital to human moral equality, freedom, and self-determination, not opposed to them. We should indulge our fascination with nature-nurture while resisting the temptation to oversimplify it.

Questions for Reflection

1. Is your personality more like one of your parents than the other? If you have a sibling, is their personality like yours? In your family, how did these similarities and differences develop? What do you think caused them?
2. Can you think of a human characteristic for which genetic differences would play almost no role?
3. Do you think the time will come when we can predict almost everything about someone by examining their DNA on the day they are born?
4. Identical twins are more similar than fraternal twins for the trait of aggressiveness, and for criminal behavior. Do these facts have implications for the courtroom? If it can be shown that a violent criminal had violent parents, should it make a difference in culpability or sentencing?

Outside Resources

- Web: Institute for Behavioral Genetics (http://www.colorado.edu/ibg/)

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3.3 EPIGENETICS

Genetic Determinism

The belief that our biological nature, or genotype, is entirely responsible for an individual's phenotype is also known as "**genetic determinism**." There is no longer a debate over whether nature or nurture exerts the most significant influence on phenotype. We now know it is a combination of the two because our experiences and exposures can influence the expression of genes. The article by Harden (2023) in the optional reading list of 3.8 explores the differences between genetic determinism, essentialism, and reductionism.

Key points from Harden (2023)

Genetic determinism, essentialism, and reductionism influence how people discuss human genetics, but they are often misunderstood or misused and can lead to everyday discrimination.

- **Genetic determinism** is the belief that a person's traits are entirely determined by their genes, regardless of the environment. In other words, this belief implies that knowing someone's genes would allow you to predict their traits with certainty. Genetic determinism is not the same as heritability. Genetic determinism suggests a causal relationship between genotype and phenotype. Heritability is a statistical measure of the variance due to genetic differences in a population.
    - Example: Having five fingers is often considered genetically determined. However, most traits, like how much education someone completes, are influenced by many factors.
    - Implications of misunderstanding and misuse: This can lead to the false idea that social inequalities are unchangeable.
- **Genetic essentialism** is the idea that DNA gives things an unchanging "essence" that defines what they are. Essentialism views group membership as based on biology, as opposed to social constructs, with distinct boundaries, stability, and exclusivity.
    - Example: It assumes that people with certain traits, like skin colour, also have a more profound genetic similarity.
    - Implications of misunderstanding and misuse can lead to prejudice and stereotypes.
- **Genetic reductionism** is the belief that understanding genes alone can fully explain complex traits or behaviours.
    - Example: It suggests that studying genes is enough to explain conditions like depression. Most scientists support looking at multiple factors, including social and environmental influences.

- Implications of misunderstanding and misuse: It can overemphasize genetic research while ignoring other important factors.

Epigenetics

Epigenetics (sometimes called epigenomics) focuses on changes in DNA that do not involve alterations to the underlying sequence. The term "epigenetics" means above (epi) the gene. The DNA letters and the proteins that interact with DNA can have chemical modifications that change the degrees to which genes are expressed (referred to as **gene expression**) causing alterations to the normal production of proteins from these genes. Certain epigenetic modifications may be passed on from parent to daughter cell during cell division or from generation to generation. Others are acquired throughout life. The collection of all epigenetic changes in a genome is called an epigenome.

Read

Fessele, K. L., & Wright, F. (2018). Primer in genetics and genomics, article 6: Basics of epigenetic control. *Biological Research for Nursing*, *20*(1), 103–110. https://doi.org/10.1177/1099800417742967 (https://doi.org/10.1177/1099800417742967) .

Same Genome, Different Cell

To understand epigenetics, we must first consider our genome – our DNA. Nearly all the cells in our body contain an identical copy of our genome, which includes the instructions to build and repair us. Yet, despite having the same set of instructions, cells from different tissues and organs can be very diverse. They may look completely different and have very different functions.

Look at the images below to see how four different types of cells can be different despite having an identical genome.

So, if the genome is the same in all these cells, why are they different? The answer is in how the genes are regulated (how they are used in other cells). This process differs between cells and is partly controlled by something called epigenetics.

This image has four sections. From the top left, moving clockwise, the first image shows an immune cell, the second a nerve cell, the third, an epithelial cell, and the fourth a muscle cell. These are illustrations to show that there can be differences in cell types with the same genome.

Differences in cell types despite the same genome. **Source:** Genomics Education Programme, CC BY-NC 4.0

Types of epigenetic modifications

Many different forms of epigenetic modification take place in, or 'tag,' an organism's genome. – see the gallery below.

The most researched epigenetic modification is DNA methylation, which acts like a dimmer switch, altering gene expression. A chemical called a methyl group attaches to a region near the start of a gene and prevents it from being expressed or reduces expression. For example, methylation of one of the two X chromosomes in every female cell is inactivated during embryonic development. X-chromosome inactivation stops female cells from having twice as many X chromosome gene products as male cells. Hypermethylation often occurs, inhibiting gene expression, but hypomethylation can also occur, resulting in the opposite effect.

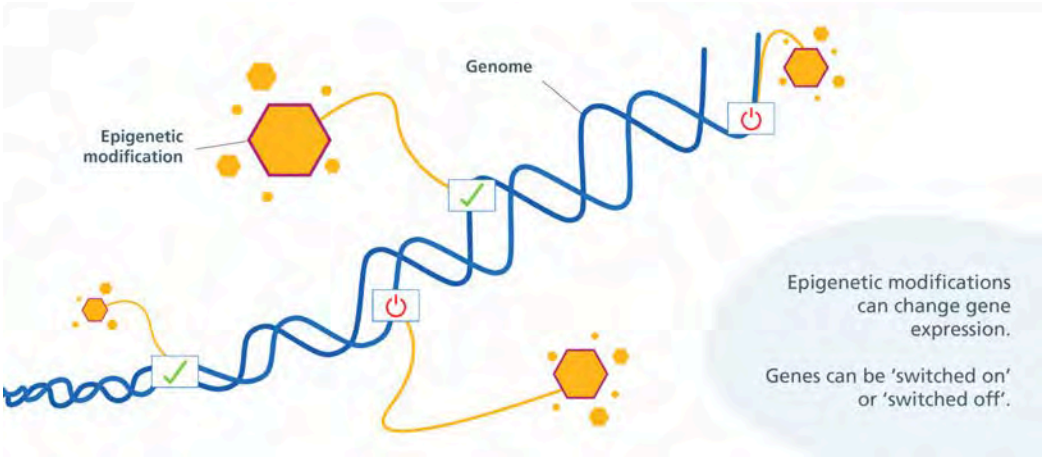
Another modification known as chromatin remodelling can alter how tightly the DNA is packaged in the chromosomes, relaxing the tightly packed chromosomes to allow the transcription factors which control gene expression access to the genes within.

Another type of epigenetic modification degrades (breaks down) the messenger RNA (mRNA) created when DNA is copied by the cell – a process called transcription. Here, non-coding RNA (a type of RNA that does not code for proteins) attaches to the mRNA and marks it for degradation.

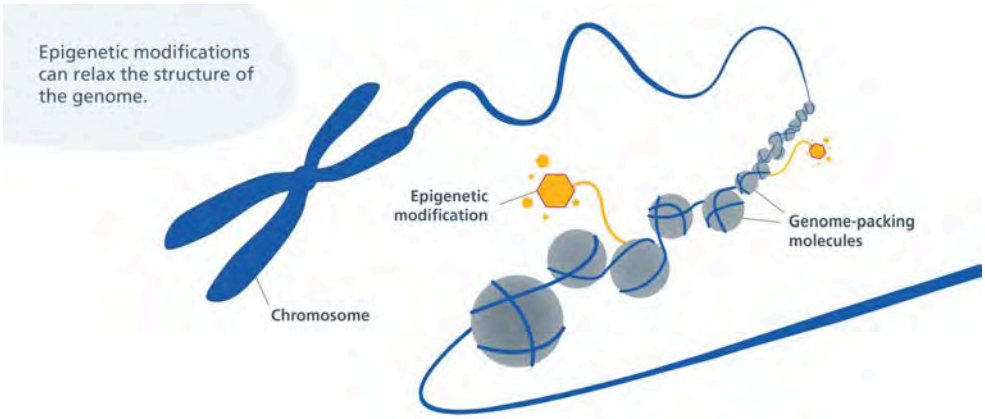
Most epigenetic modifications are transient and reversible, allowing our cells to respond and adapt to changes in environment and behaviour. Although they happen on a molecular level, they can have a considerable impact on us and can also be influenced by external factors, such as diet and lifestyle.

Without epigenetics, you wouldn't have developed from a fertilized egg to the multicellular organism you are today – and epigenetics will continue to impact on you, regulating specific genes in specific cells, in specific places and at specific times during your growth and development.

Image slider – text version



The image displays methyl groups being added to the genome resulting in changes to gene expresson. Epigenetic modifications can change gene expression. Genes can be 'switched on' or 'switched off'. **Source:** Genomics Education Programme, CC BY-NC 4.0



Epigenetic modifications can also relax the structure of the genome making it more accessible. **Source: Genomics Education Programme, CC BY-NC 4.0**

Concept in Action

Watch Epigenetics (3 mins) on YouTube (https://youtu.be/ga4n-rGfdVY) for a short video that gives a succinct overview of Epigenetics and some of the factors that influence epigenetic modifications.

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3.4 DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

The Developmental Origins of Health and Disease

Epigenetic changes begin before you are born. All your cells have the same genes but look and act differently. As you grow and develop, epigenetics helps determine which function a cell will have. For example, it may become a heart cell, nerve cell, muscle cell, or skin cell.

EXAMPLE: Nerve cell and muscle cell. Your nerve cells and muscle cells have the same DNA, but they work differently. A nerve cell transports information to other cells in your body. A muscle cell has a structure that aids in your body's ability to move. Epigenetics allows the muscle cell to turn on genes to make proteins important for its job and turn off genes important for a nerve cell's job.

The developmental origins of health and disease (DOHaD) paradigm, rooted in the 1980s work of Barker, underscores the critical role of the intrauterine environment in shaping fetal development and influencing health outcomes across generations. The concept of "programming" was initially proposed by Dörner in 1974, who explored how early life exposures, including hormones and neurotransmitters, affect neurodevelopment and adult disease (Koletzko, 2005). Although Dörner suggested **gene-environment interactions** early on, empirical support emerged only with advances in epigenetics. In 1991, Lucas coined the term "developmental programming" (Lucas, 1991).

Read

Padmanabhan, V., Cardoso, R. C., Puttabyatappa, M. (2016). Developmental programming, a pathway to disease. *Endocrinology*, *157*(4), 1328–1340. https://doi.org/10.1210/en.2016-1003

Concept in Action

Watch Developmental origins of health and diseases (DOHaD) (3 mins) on YouTube (https://youtu.be/MDjBNlPyqvs).

What are critical periods of development?

In pregnancy, each part of the fetus' body forms during a specific time. This specific time is called the "critical period of development" for that body part. During this critical time of development, the body can be very sensitive to exposures. Examples of exposures may include medications, alcohol, infections, health conditions, or other substances.

Critical Periods of Development – Fact Sheet

An interactive H5P element has been excluded from this version of the text. You can view it online here: https://ecampusontario.pressbooks.pub/personalizedhealthnursing/?p=1330#h5p-32

Access an HTML version of this fact sheet on the NIH Bookself (https://pubmed.ncbi.nlm.nih.gov/35951922).

Source: Critical Periods of Development – Mother to Baby Fact Sheet by Organization of Teratology Information Specialists (OTIS), CC BY-NC-ND 3.0.

Does the chance for different types of birth defects change during pregnancy?

Every pregnancy starts out with a 3-5% chance of having a birth defect. This is called the background risk. If an exposure can increase the chance for birth defects, the chance depends on what body part is developing at the time of exposure. Once a body part has formed, it is no longer at risk to develop major birth defects. Some exposures could still affect a body part's growth and/or function even after that body part has formed.

The chart in the Critical Periods of Development – Fact Sheet (https://www.ncbi.nlm.nih.gov/books/NBK582659/) (above) shows the critical periods of development for different parts of the body. The chart starts from the time of conception when the egg and sperm join. The weeks listed on the chart are the "embryonic age" or "fetal age" of a pregnancy. This is different from a common way of dating a pregnancy called "gestational age." Gestational age begins with the first day of a person's last menstrual period. This day is usually about two weeks before a pregnancy is conceived. For example, 12 gestational weeks (since the first day of your last period) is the same as 10 fetal weeks (since the first day of conception).

Birth defects are physical or structural differences that may change how a body part looks and/or works. Birth defects are typically classified as "major" if they cause significant medical problems and may need surgery or other treatment. Heart defects, spina bifida, and clubfeet are examples of major birth defects. The solid bars on the chart show when each body part is most sensitive to harmful exposures and at risk for major birth defects.

"Minor" birth defects by themselves do not cause significant medical problems and usually do not require treatment or surgery. Minor birth defects can also be variations of typical development. Wide-set eyes and large ears are examples of minor birth defects. The striped bars show periods when the body parts are still at risk of developing minor birth defects and functional defects. "Functional defects" change how a part of the body works without changing how it looks. Intellectual disability and hearing loss are both examples of functional defects.

The chart also shows the location of the most common birth defects that can occur during each week. In general, major birth defects of the body and internal organs are more likely to happen between 3 to 12 embryonic/fetal weeks. This is the same as 5 to 14 gestational weeks (weeks since the first day of your last period). This is also referred to as the first trimester. Minor defects and functional defects, including those affecting how the brain works, can also occur later in pregnancy.

There are certain exposures that are known to contribute to fetal abnormalities, called teratogens, which include certain medications, illegal and legal substances, chemicals, and certain maternal infections. It is also known that environmental exposures can cause epigenetic changes and there is a greater likelihood of an impact on the epigenome during critical periods.

The First 1000 days

Researchers have learned that the first 1000 days of a child's life are critical to a child's optimal growth and development. How did they come up with the number 1000?

Concept in Action – the First 1000 Days

The First 1000 Days (text version)

- **Watch First 1,000 days Introduction (1 min) on YouTube (https://youtu.be/cLVZUDo41MA)**

Activity source: created by Andrea Gretchev, CC BY-NC 4.0 except where otherwise noted.

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- Critical Periods of Development – Mother to Baby Fact Sheet by Organization of Teratology Information Specialists (OTIS), CC BY-NC-ND 3.0.

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Organization of Teratology Information Specialists (OTIS). (2023, February). Critical periods of development, mother to baby | Fact sheets. https://www.ncbi.nlm.nih.gov/books/NBK582659/ CC BY-NC-ND 3.0.

3.5 THE EXPOSOME

Epigenetics and the Influence of the Environment on Gene Expression – The Exposome

Ontogeny

Ontogeny refers to an organism's development across its entire lifecycle, from fertilization to adulthood. During this process, the genetic blueprint of the organism is expressed under the influence of external factors. In cases of nutrient deficiency, essential organs like the brain receive the majority of the scarce nutrients, prioritizing them over less critical organs, such as the pancreas or kidneys. Research has indicated that if such nutrient allocation happens during a critical developmental period, changes in cellular structure and function may become permanent.

Epigenetics and age

Your epigenetics change throughout your life. Your epigenetics at birth are not the same as your epigenetics during childhood or adulthood.

EXAMPLE: A newborn, 26-year-old, and 103-year-old. Scientists measured DNA methylation at millions of sites in a newborn, 26-year-old, and 103-year-old. The level of DNA methylation decreased with age. The newborn had the highest level of DNA methylation, the 103-year-old had the lowest level of DNA methylation, and the 26-year-old had a DNA methylation level that was between that of the newborn and the 103-year-old (Heyn et al., 2012).

The Exposome

Success in mapping the human genome has fostered the complementary concept of the "exposome". The exposome can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health. An individual's exposure begins before birth and includes insults from **environmental factors** and occupational sources. Understanding how exposures from our environment, diet, lifestyle, etc. interact with our own unique characteristics such as genetics, physiology, and epigenetics impact our health is how the exposome will be articulated.

Epigenetics and exposures

Your epigenetics can change in response to your behaviors and environment.

Factors that influence the epigenome

Most epigenetic modifications are transient and reversible, allowing our cells to respond and adapt to changes in environment and behaviour. Although they happen on a molecular level, they can have a considerable impact on us. External factors, such as diet and lifestyle can also influence them.

Internal and external factors that influence the epigenome include medications, pollution, family history, toxins, diet/nutrition, alcohol, smoking, infection and exercise. **Source:** Genomics Education Programme (GEP), CC BY-NC 4.0

Nutrition during pregnancy

A pregnant person's environment and behavior during pregnancy, such as whether they eat healthy food, can change the baby's epigenetics. Some of these changes can remain for decades and might make the child more likely to get certain diseases.

EXAMPLE: Dutch Hunger Winter famine (1944–1945). People whose mothers were pregnant with them during the famine were more likely to develop certain diseases, such as heart disease, schizophrenia, and type 2 diabetes (Roseboom, 2019). Around 60 years after the famine, researchers looked at DNA methylation levels in people whose mothers were pregnant with them during the famine. These people had increased DNA

methylation at some genes and decreased DNA methylation at other genes, compared with their siblings who were not exposed to famine before birth (Tobi et al., 2018). These differences in DNA methylation could help explain why these people had an increased likelihood for certain diseases later in life (Roseboom, 2019; Tobi et al., 2018; Dayeh et al., 2016).

Concept in Action – Maternal Nutrition

Watch this short video to see how animals models contributed to this theory of maternal nutrition. How can two genetically identical mice look completely different?

Watch Why do Two Genetically Identical Mice Look Vastly Different? (3 mins) on YouTube (https://youtu.be/IYJ_nd9glvw)

Smoking

Exposures such as smoking can cause epigenetic changes. However, these epigenetic changes can be reversible in some cases.

EXAMPLE: Smokers, nonsmokers, and former smokers. Smoking can result in epigenetic changes. For example, at certain parts of the *AHRR* gene, smokers tend to have less DNA methylation than nonsmokers. The difference is greater for heavy smokers and long-term smokers. After quitting smoking, former smokers can begin to have increased DNA methylation at this gene. Eventually, they can reach levels similar to those of nonsmokers. In some cases, this can happen in less than a year, but the length of time depends on how long and how much someone smoked before quitting (McCartney et al., 2018).

Concept in Action – Foundational Studies

This video provides a good overview of some of the foundational studies that form the basis of what we know about epigenetics today. It also illustrates the many ways in which the exposome can impact the epigenome.

Watch Epigenetics with Dr. Moshe Szyf (Part 1) (18 mins) on YouTube (https://youtu.be/OEAJmDPJz_I)

Food for thought: Consider the legacy of generational trauma resulting from colonialism. What connections can you make between intergenerational trauma and some of the epidemiological

patterns you may be familiar with regarding non-communicable diseases in some of the populations affected by colonialization? What role does epigenetics play in these health outcomes?

Exposomics

Exposomics is the study of the exposome and relies on the application of internal and external exposure assessment methods. Internal exposure relies on fields of study such as genomics, metabonomics, lipidomics, transcriptomics and proteomics. Commonalities of these fields include 1) use of biomarkers to determine exposure, effect of exposure, disease progression, and susceptibility factors, 2) use of technologies that result in large amounts of data and 3) use of data mining techniques to find statistical associations between exposures, effect of exposures, and other factors such as genetics with disease. External exposure assessment relies on measuring environmental stressors. Common approaches include using direct reading instruments, laboratory-based analysis, and survey instruments. The extent to which internal and external exposure assessment will contribute to our understanding of the exposome is being debated as each approach has certain merits.

A key factor in describing the exposome is the ability to accurately measure exposures and effect of exposures. Many of the "omics" technologies have the potential to further our understanding of disease causation and progression. Metabonomics and adductomics (DNA and protein adduct measurement) have been used in the past to establish exposure-disease relationships. Research is needed to determine the utility of the "omics" technologies in defining the exposome.

Why should we study the exposome?

One of the promises of the human genome project was that it could revolutionize our understanding of the underlying causes of disease and aid in the development of preventions and cures for more diseases. However, genetics has been found to account for only about 10% of diseases, and the remaining causes appear to be from environmental causes. So to understand the causes and eventually the prevention of disease, environmental causes need to be studied.

What are the challenges of advancing exposomics?

Some challenges that may limit the progress in this field of study are evident. An individual's exposome is highly variable and dynamic throughout their lifetime. The impact of exposures can also vary with the individual's stage of life. For examples, exposure to the drugs thalidomide or valproic acid during specific developmental periods in utero causes malformation of limbs; exposure to lead in infants and early childhood

can lead to cognitive deficiencies. Exposures during early years may also predispose an individual to certain chronic diseases later in life.

The impact of environmental or occupational exposures can be different for each individual because of differences in genetic and other personal factors. Some people will develop a disease while another person with the same or greater exposure will not. The exposome may help to determine the underlying causes for this difference. Mapping an entire exposome for an individual will be difficult, if not impossible because of the complexity of a life-time of exposure. Specific exposures can be difficult to measure due to lack of sensitive methods or not knowing that an exposure has even occurred. Even when the exposure is known, measuring that exposure can be difficult since the indicators of exposure may be transient, such as for most chemicals, which are rapidly excreted and only a short time frame exists to directly measure them. In other cases, past exposure can be defined using legacy biomarkers. A common example of a legacy biomarker is antibodies produced by exposures to environmental or occupational insults.

The experience in studying genetic involvement in diseases serves as a model for studying the relationship between exposures and disease. In the past, hypotheses of the role of specific genes in disease were tested. Currently, genome-wide association studies are performed with the aid of new technologies which produce cheaper and faster analyses to generate hypotheses about the relationship between genes and disease. These studies identify gene pathways associated with disease, and, when an association has been identified specific hypotheses about the role of specific genes in disease can be generated and tested. An approach to the exposome is to use internal biological media and measure multiple endpoints. The data would be analyzed to identify associations between health outcomes and biomarkers of exposures, biomarkers of response, or patterns of biomarkers (exposure-wide association studies).

One important aspect of the exposome will be adherence to strict ethical principles as the exposome is deciphered. This will be paramount to ensure that the rights of individuals are not compromised when determining exposures and the relationship to their health.

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3.6 ADVERSE EARLY CHILDHOOD EXPERIENCES

Trigger Warning

This chapter contains material that may be upsetting or distressing. Contents may include discussion of traumatic experiences such as abuse, violence, suicide, mental illness, and racism.

Overview

As you review this material, reflect on how you think the social determinants of health align with the DOHaD paradigm and the influence of the exposome on phenotype development?

- Life history, sociology, and biology combine to create lifelong prospects for health and social success at the earliest stages of life.
- The branch of social epigenetics examines the impacts of health disparities on genetics or how inequities literally "get under our skin."
- Focusing on improving environments can change our biology and disease trajectory for future generations.

Adverse Childhood Experiences

Adverse childhood experiences (ACEs) are common and can have lasting, negative effects on health and well-being. They can also negatively impact education and job opportunities.

Children and families thrive when they have access to safe, stable, nurturing relationships and environments. These relationships and environments are essential to creating positive childhood experiences and preventing adverse childhood experiences. The harmful effects of ACEs can affect everyone in our communities, and everyone can help prevent and reduce their impact.

What are adverse childhood experiences?

Adverse childhood experiences, or ACEs, are potentially traumatic events that occur in childhood (0-17 years). Examples include (Merrick et al., 2019):

- Experiencing violence, abuse, or neglect.
- Witnessing violence in the home or community.

- Having a family member attempt or die by suicide.

Also included are aspects of the child's environment that can undermine their sense of safety, stability, and bonding. Examples can include growing up in a household with (Merrick et al., 2019):

- Substance use problems.
- Mental health problems.
- Instability due to parental separation.
- Instability due to household members being in jail or prison.

The examples above are not a complete list of adverse experiences. Many other traumatic experiences could impact health and well-being. This can include not having enough food to eat, experiencing homelessness or unstable housing, or experiencing discrimination (Cain et al, 2022; *Experiencing discrimination*, 2021; Font et al, 2016; Smith-Grant et al., 2022).

Quick facts and stats

ACEs are common. About 64% of adults in the United States reported they had experienced at least one type of ACE before age 18. Nearly one in six (17.3%) adults reported they had experienced four or more types of ACEs (Swedo et al., 2023).

Three in four high school students reported experiencing one or more ACEs, and one in five experienced four or more ACEs. ACEs that were most common among high school students were emotional abuse, physical abuse, and living in a household affected by poor mental health or substance abuse (Swedo, et al. 2024).

Preventing ACEs could potentially reduce many health conditions. Estimates show up to 1.9 million heart disease cases and 21 million depression cases potentially could have been avoided by preventing ACEs.1 Preventing ACEs could reduce suicide attempts among high school students by as much as 89%, prescription pain medication misuse by as much as 84%, and persistent feelings of sadness or hopelessness by as much as 66% (Swedo, et al. 2024).

Some people are at greater risk of experiencing one or more ACEs than others. While all children are at risk of ACEs, numerous studies show inequities in such experiences. These inequalities are linked to the historical, social, and economic environments in which some families live (Sedlak et al., 2010; Font et al., 2016). ACEs were highest among females, non-Hispanic American Indian or Alaska Native adults, and adults who are unemployed or unable to work (Swedo et al., 2023).

ACEs are costly. ACEs-related health consequences cost an estimated economic burden of $748 billion annually in Bermuda, Canada, and the United States (Bellis et al., 2019).

Outcomes

ACEs can have lasting effects on health and well-being in childhood and life opportunities well into adulthood. Life opportunities include things like education and job potential. These experiences can increase the risks of injury, sexually transmitted infections, and involvement in sex trafficking. They can also increase risks for maternal and child health problems including teen pregnancy, pregnancy complications, and fetal death. Also included are a range of chronic diseases and leading causes of death, such as cancer, diabetes, heart disease, and suicide (Ciciolla et al, 2021; Diamond-Welch et al., 2020; Merrick et al., 2020; Mersky et al., 2019; Miller et al., 2021; Read et al., 2019; Sulaiman et al., 2021).

ACEs and associated social determinants of health, such as living in under-resourced or racially segregated neighborhoods, can cause toxic stress (Jones et al., 2020). Toxic stress, or extended or prolonged stress, from ACEs can negatively affect children's brain development, immune system, and stress-response systems (Clements et al., 2024; Ross et al., 2021; Yu et al., 2022).

Children growing up with toxic stress may have difficulty forming healthy and stable relationships. They may also have unstable work histories as adults and struggle with finances, job stability, and depression throughout life (Clements et al., 2024). These effects can also be passed on to their own children (Narayan et al., 2017; Schofield et al., 2018). Some children may face further exposure to toxic stress from historical and ongoing traumas, including experiences of racial discrimination.

Concept in Action

Watch Dr. Nadine Burke Harris discuss how childhood trauma can affect health across a lifetime (16 mins) on Ted.com (https://www.ted.com/talks/nadine_burke_harris_how_childhood_trauma_affects_health_across_a_lifetime?language=en)

Prevention

Adverse childhood experiences can be prevented. Certain factors may increase or decrease the risk of experiencing adverse childhood experiences. Preventing adverse childhood experiences requires understanding and addressing the factors that put people at risk for or protect them from violence. Creating safe, stable, nurturing relationships and environments for all children prevent ACEs and help all children reach their full potential. These relationships and environments are essential to creating positive childhood experiences.

Risk factors

Individual and family risk factors

- Families experiencing caregiving challenges related to children with special needs (for example, disabilities, mental health issues, chronic physical illnesses) (Crouch et al., 2019a).
- Children and youth who don't feel close to their parents/caregivers and feel like they can't talk to them about their feelings (Priyam, P., & Nath, 2021).
- Children and youth with few or no friends or with friends who engage in aggressive or delinquent behavior (Biglan et al., 2017).
- Families with caregivers who were abused or neglected as children (Schickedanz et al., 2018).
- Families with young caregivers or single parents (Crouch et al., 2019b).
- Families with low income (Giovanelli & Reynolds, 2021).
- Families with adults with low levels of education (Hughes et al., 2017).
- Families experiencing high levels of parenting stress or economic stress (Crouch et al., 2019b)
- Families with caregivers who use spanking and other forms of corporal punishment for discipline (Afifi et al., 2017).
- Families that are isolated from and not connected to other people (extended family, friends, neighbors) (Calvano et al., 2021).
- Families with high conflict and negative communication styles (Lackova Rebicova et al., 2020).

Community risk factors

- Communities with high rates of violence and crime (Lopez-Tomayo et al., 2022).
- Communities with high unemployment rates (Manyema et al., 2019).
- Communities where neighbors don't know or look out for each other and there is low community involvement among residents (Khanijahani & Sualp., 2022).
- Communities with few community activities for young people (Bledsoe et al., 2021).
- Communities with unstable housing and where residents move frequently (Barnes et al., 2021).
- Communities where families frequently experience low socioeconomic status and food insecurity (Manyema et al., 2019).
- Communities with high levels of social and environmental disorder (Gentner & Leppert, 2019).

Protective factors

Individual and family protective factors

- Families who create safe, stable, and nurturing relationships, meaning children have a consistent family life where they are safe, taken care of, and supported (Asmundson, 2019; Luther, 2019)
- Children who have positive friendships and peer networks (Guo et al., 2021; Luther, 2019; Narayan et al., 2018)
- Children who do well in school (Bethell et al., 2022; Goetschius et al., 2021; Liu et al., 2020; Narayan et al., 2018)
- Children who have caring adults outside the family who serve as mentors or role models (Bellis et al., 2022; Narayan et al., 2018).
- Families where caregivers can meet basic needs of food, shelter, and health services for children (Narayan et al., 2018; Liu et al., 2020).
- Families where caregivers have college degrees or higher (Merrick et al., 2018; Nabors et al., 2021)
- Families where caregivers have steady employment (Liu et al., 2020; Merrick et al., 2018).
- Families with strong social support networks and positive relationships with the people around them (Bethell et al., 2019; Bethell et al., 2022; Guo et al., 2021; Letourneau et al., 2020; Luther, 2019; Narayan et al., 2018).
- Families where caregivers engage in parental monitoring, supervision, and consistent enforcement of rules (Bethell et al., 2022; Bethell et al., 2019; Guo et al., 2021; Liu et al., 2020).
- Families where caregivers/adults work through conflicts peacefully (Bethell et al., 2022; Bethell et al., 2019; Nabors et al., 2021).
- Families where caregivers help children work through problems (Bethell et al., 2022; Bethell et al., 2019; Nabors et al., 2021).
- Families that engage in fun, positive activities together (Bethell et al., 2019; Nabors et al., 2021).
- Families that encourage the importance of school for children (Liu et al., 2020).

Community protective factors

- Communities where families have access to economic and financial help (Dietz, 2017; Sege et al., 2017).
- Communities where families have access to medical care and mental health services (Dietz, 2017; Sege et al., 2017)
- Communities with access to safe, stable housing (Sege et al., 2017)
- Communities where families have access to nurturing and safe childcare (Sege et al., 2017).
- Communities where families have access to safe, engaging after school programs and activities (Dietz, 2017)
- Communities where adults have work opportunities with family-friendly policies (Dietz, 2017).
- Communities with strong partnerships between the community and business, health care, government, and other sectors (Dietz, 2017).
- Communities where residents feel connected to each other and are involved in the community (Narayan

et al., 2018; Dietz, 2017).

Concept in Action

Watch Moving Forward (3 mins) on YouTube

Why prevention is important (CDC, 2024)

Every child possesses incredible potential for health, well-being, and making a positive impact. When we prevent ACEs, we also prevent potential later involvement in violence, substance use, depression, and suicidal behavior. We also reduce the risk of other health challenges like cancer, diabetes, and heart disease.

All children deserve the best chance at lifelong health and well-being. Preventing, identifying, and responding to ACEs is the most powerful way to achieve this. Working together, we can help create neighborhoods, communities, and a world in which every child can thrive.

Neurodevelopment

Neurodevelopment is the process by which the brain and nervous system grow and mature, particularly during early life. The growing brain is extremely susceptible to inputs from the environment, particularly during critical periods. During these times, factors such as attachment and environmental influences play a crucial role in shaping brain architecture and function. Secure attachment and a nurturing environment promote optimal cognitive, emotional, and social development, while adverse conditions, such as neglect or stress, can disrupt neurodevelopmental pathways, leading to long-term implications for behavior and mental health.

Neurodevelopment and the importance of strong parental attachments

Review the four videos by using the interactive slide show, or click to watch on YouTube in the text version.

Neurodevelopment and the importance of strong parental attachments (text version)

1. Watch Experiences Build Brain Architecture (2 mins) on YouTube (https://youtu.be/VNNsN9IJkws)
2. Watch Serve & Return Interaction Shapes Brain Circuitry (2 mins) on YouTube (https://youtu.be/m_5u8-QSh6A)
3. Watch Toxic Stress Derails Healthy Development (2 mins) on YouTube (https://youtu.be/rVwFkcOZHJw)
4. Watch InBrief: The Science of Neglect (6 mins) on YouTube (https://youtu.be/bF3j5UVCSCA)

The first 1000 days is not the only critical period. Adolescence is also a period of vulnerability. Learn how early experiences and genetic predispositions can impact the develop of psychiatric disorders later in life.

Watch Dr. Dan Siegel – Brainstorm: Adolescence, opportunity, vulnerability, and pruning (2 mins) on YouTube

Resilience

What does resilience have to do with genetics? Resilience is a protective factor.

Watch InBrief: The Science of Resilience (2 mins) on YouTube

Attribution & References

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- Risk and Protective Factors

Adaptation & use notes: Updated references have been added to original source material to enhance student learning. Use of CDC material does not imply endorsement by CDC. Material is otherwise available on the CDC website free of charge.

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3.7 EPIGENETICS IN PRACTICE

The Impact on Health and Clinical Practice

Certain diseases can change your epigenetics. In addition, some epigenetic changes can make you more likely to develop certain diseases, such as cancer.

Infections (CDC, n.d.)

Germs can change your epigenetics to weaken your immune system. This helps the germ survive.

EXAMPLE: *Mycobacterium tuberculosis* causes tuberculosis. Infections with these germs can cause epigenetic changes in some of your immune cells that result in turning off the *IL-12B* gene. Turning off the *IL-12B* gene weakens your immune system and improves the survival of *Mycobacterium tuberculosis* (Chandran et al., 2015).

Cancer (CDC, n.d.)

Certain gene variants make you more likely to develop cancer. Likewise, some epigenetic changes increase your cancer risk. Most cancers display different epigenetic patterns than those of healthy cells, and these patterns can be important for the development of the disease. For example, some genes produce proteins that stop cell growth and division. If expression is suppressed in these genes when it shouldn't be, this could cause cells to divide uncontrollably, leading to cancer development. Additionally, having a mutation in the *BRCA1* gene that prevents it from working properly makes you more likely to get breast and other cancers. Similarly, increased DNA methylation that results in decreased *BRCA1* gene expression raises your risk for breast and other cancers (Tang et al., 2016). While cancer cells have increased DNA methylation at certain genes, overall DNA methylation levels are lower in cancer cells compared with normal cells. These differences can help us to understand, manage and treat cancers more effectively. However, epigenetics alone cannot diagnose cancer. Cancers would need to be confirmed with further screening tests. An example of the use of epigenetics in cancer diagnostics is the methylation profile of tumours can help to grade the current stage of a cancer or to track the disease as it progresses over time. Further, many drugs have been discovered that target specific epigenetic modifications, either by removing them or preventing their removal – depending on the desired effect. These drugs are mostly used to treat different types of cancer, but there is ongoing work to establish their effectiveness for other conditions.

EXAMPLE: Colorectal cancers have abnormal DNA methylation near certain genes, which affects

expression of these genes. Some commercial colorectal cancer screening tests (for example, Cologuard®) use stool samples to look for this abnormal DNA methylation. It is important to know that if the result of one of these tests is positive or abnormal, further screening is required with a colonoscopy (Chan & Liang, 2022).

Epigenomic studies spotlight new level of cancer evolution (NHS, 2023 (https://www.genomicseducation.hee.nhs.uk/blog/epigenomic-studies-spotlight-new-level-of-cancer-evolution/))

Two studies cast a light on the role of epigenomics in oncology. A multi-omic level of cancer evolution has been characterized by researchers from the Institute of Cancer Research. In a pair of *Nature* publications, they highlighted the importance of epigenomic changes to a cancer's resilience, and how genome-only testing methods may be missing important cancer markers. Every cancer is different, yet even within one mass, its cells are not identical: the cells can differ by which genes they express and their susceptibility to treatment. Both studies examined the evolution of colorectal cancers and tried to understand why cells within a cancer differ in terms of what drives cancer growth and cancer cell survival.

Epigenomic changes are common

In the first of the two studies (https://www.nature.com/articles/s41586-022-05202-1), researchers looked at 30 patients with bowel cancer. They examined each cancer's genome and its epigenome. Using this multi-omic approach, they found that changes to the epigenome were common around a cancer's driver genes. Cancer driver genes are genes that are normally involved in a cell's division and growth but gene variants alter their normal functioning. Additionally, the epigenomic changes were found to be passed on to the next generation of cells; they were present in cancer cells that had survival advantages over other cells.

Tumours persist due to variation across its cells

Cells within a cancer mass can often be different from each other. The second study took a deep dive into the differences found within tumours (https://www.nature.com/articles/s41586-022-05311-x). The researchers did this by sampling many different sections of individual tumours to understand how and why the cells of a single cancer can be so diverse. They found that, while there is variation in the expression of genes within tumours, in most cases this doesn't alter the ability of cells to survive or grow. However, if the cancer's environment changes (such as during anti-cancer treatment), then this variation becomes important for its future survival as it may mean that some of its cells survive while others do not. Ultimately, it's the cancer's surviving cells that pass on their resistance to treatment to their daughter cells, meaning the cancer, in some form, persists.

"For years our understanding of cancer has focused on gene variants which permanently change the DNA code," said Institute of Cancer Research director and lead author Professor Trevor Graham, "But our research

has shown that the way the DNA folds up can change which genes are read without altering the DNA code, and this can be very important in determining how cancers behave."

How is this being used in practice?

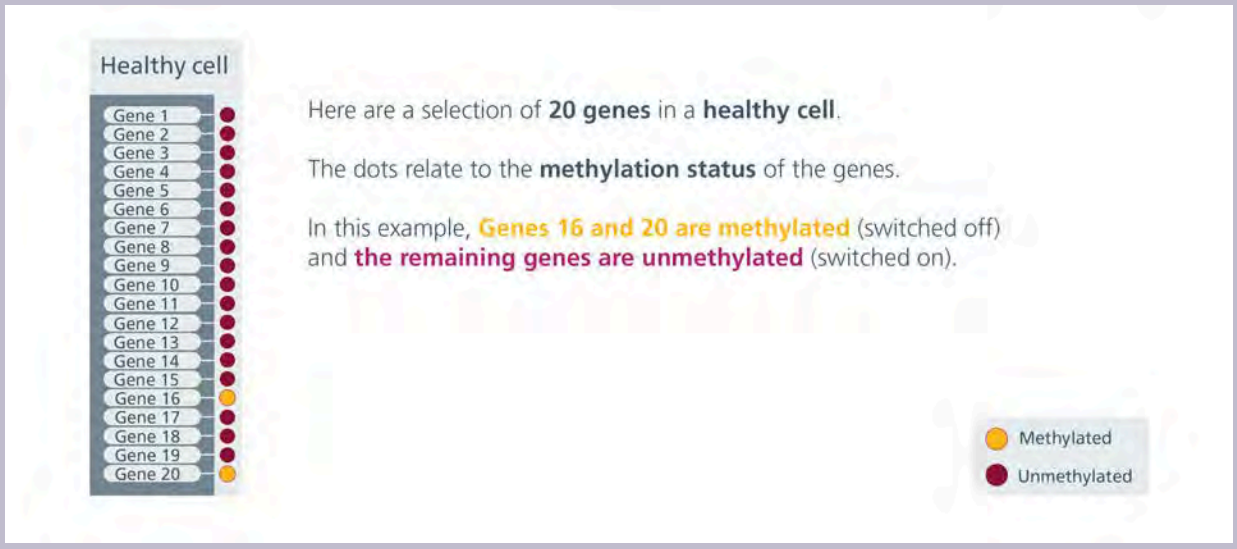
Knowledge around cancer epigenomics and how it fuels cancer growth is already being used in cancer detection. For example, the Galleri multi-cancer test (https://www.genomicseducation.hee.nhs.uk/blog/nhs-to-trial-new-multi-cancer-blood-test/), uses epigenomic markers to detect non-symptomatic cancers. Yet the epigenome is not widely being used in precision cancer treatment. If it was, Professor Graham noted that, "we could, potentially, much more accurately predict which treatments will work best for a particular person's cancer." Tools are available that could make personalized cancer treatment a reality, such as long-read sequencing approaches, like nanopore, which allow real-time 'reading' of DNA to understand the genome, and parts of the epigenome too.

To learn more about the latest advances in epigenetics and its real-world impact on healthcare, visit the dedicated epigenomics topic on the NHS Genomics Education Programme's blog (https://www.genomicseducation.hee.nhs.uk/blog/tag/epigenomics/).

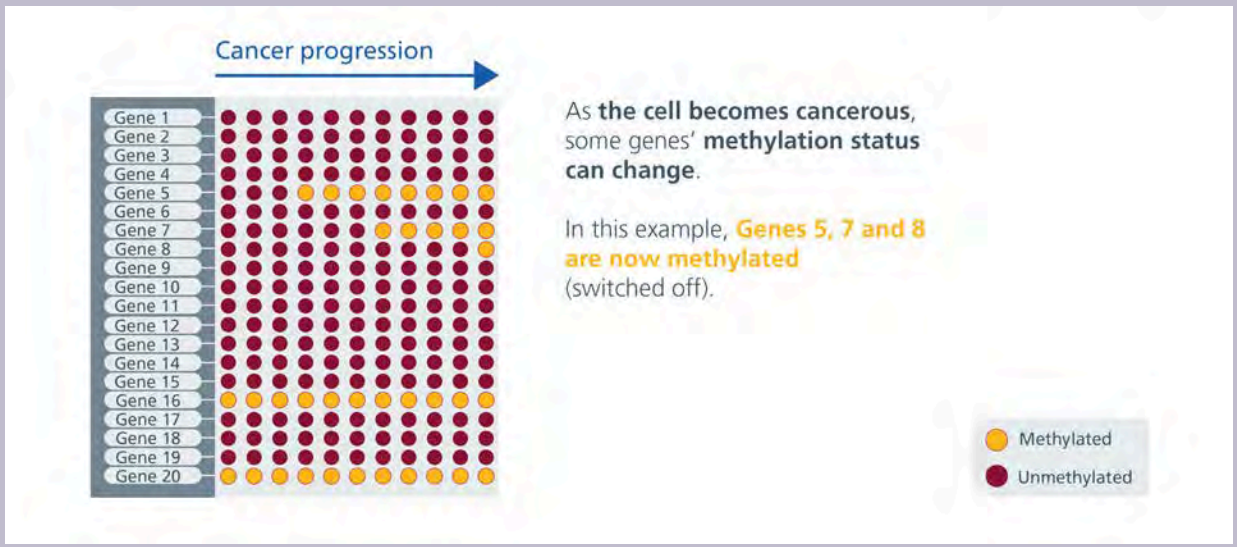
Check out the gallery below to see how epigenetic patterns can change between healthy cells and cancer cells.

Epigenetic Patterns in Health and Cancerous Cells – Gallery

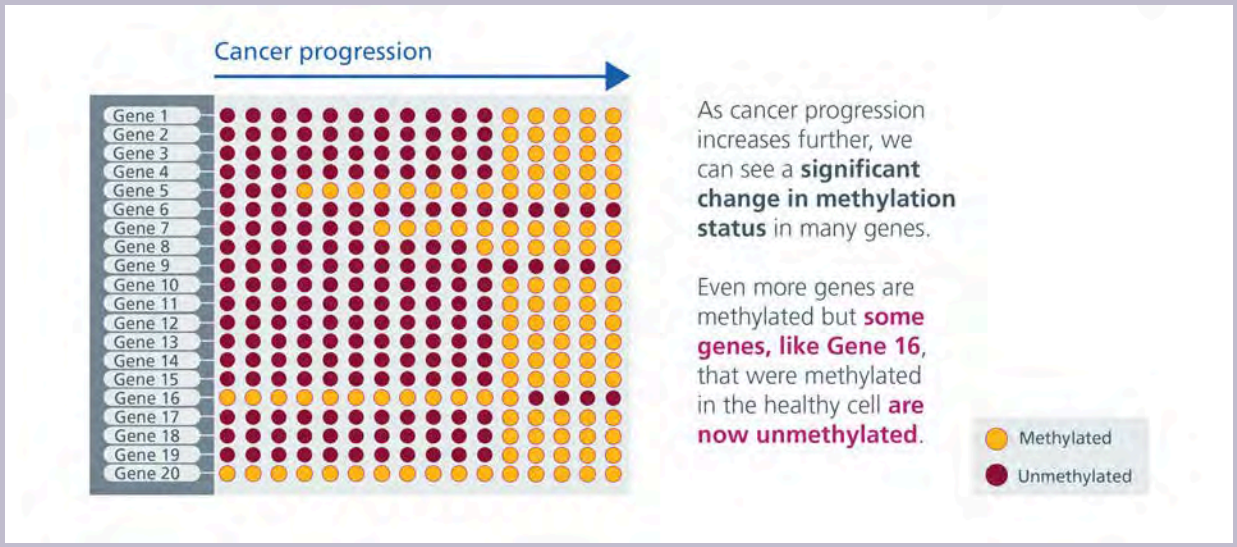
Epigenetic Patterns in Health and Cancerous Cells – Gallery (text version)



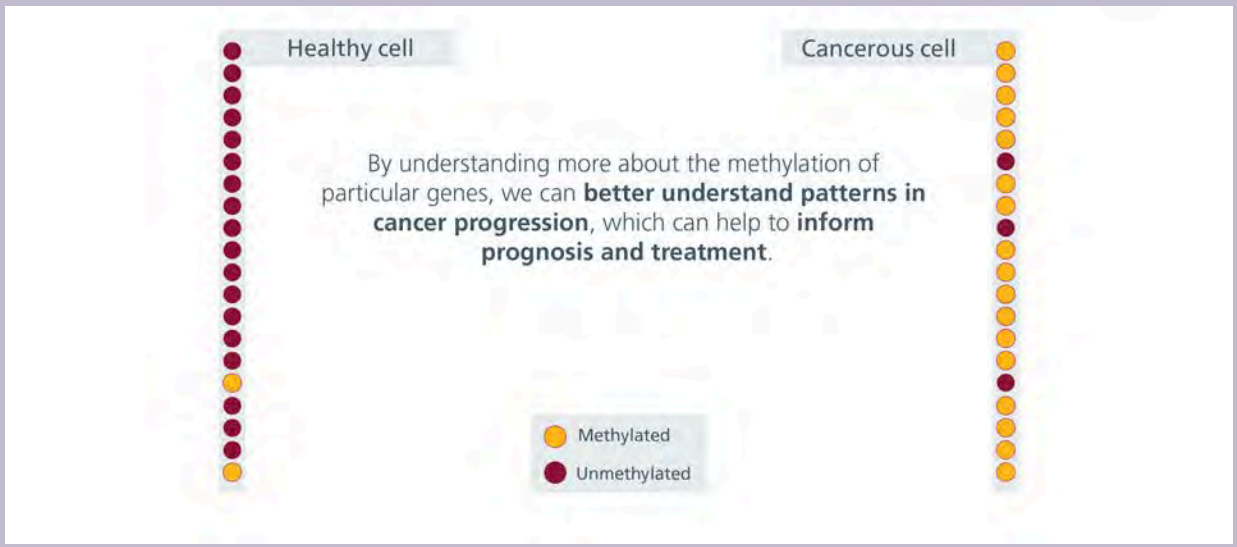
Healthy Cell Methylation Status: A healthy cell is shown with 20 genes. Dots represent methylation status of genes. Genes 16 and 20 are methylated (switched off) and the remaining genes are unmethylated (switched on). **Source:** Genomics Education Programme, CC BY-NC 4.0.



Cancer Progression: As the cell becomes cancerous some genes' methylation status changes. Now genes 5, 7, and 8 appear methylated (switched off). **Source:** Genomics Education Programme, CC BY-NC 4.0.



Further cancer progression: As cancer progresses further there is a significant change in methylation status in many genes. Even more genes are methylated but some genes, like Gene 16 that were methylated in the healthy cell are now unmethylated. **Source:** Genomics Education Programme, CC BY-NC 4.0.



Cancer and Healthy Cell Comparison: The image shows methylation in a healthy cell vs cancerous cell. Understanding methylation of genes helps us understand patterns in cancer progression, which can help to inform prognosis and treatment. **Source:** Genomics Education Programme, CC BY-NC 4.0.

Source: Genomics Education Programme, CC BY-NC 4.0

Imprinting disorders

Individually a **rare disease** is rare, but collectively they are common. Many people with rare diseases often go through a **diagnostic odyssey** with many tests that do not necessarily lead to an explanation or treatment for their disease. It is thought that the majority of rare diseases have a genetic cause. Finding this cause can lead to a diagnosis and possibly treatment options. Increasingly, more people with undiagnosed rare diseases are undergoing genomic testing which is providing a diagnosis for some. Not everyone who has a genomic test will receive a diagnosis initially, but those without a diagnosis may receive one as more is discovered about the function of the genome.

A variety of factors can cause rare diseases. Many occur because of alterations to the DNA sequence itself, but some can be caused by epigenetic modifications: in other words, changes in gene expression. **Genomic imprinting** is one such modification that affects the regulation of certain genes, but how can it cause disease?

As we have learned, epigenetic changes happen because our gene expression is altered by various mechanisms. This suppression or amplification of gene expression is very common, and indeed is an important part of normal, healthy gene regulation. However, if this regulation is disrupted, it can lead to certain genes being over or under expressed, or silenced completely.

Although many of our genes are affected by epigenetic modifications, only a very small percentage are known to undergo genomic imprinting. These genes are mostly found in two clusters – one on the short arm of chromosome 11 and the other on the long arm of chromosome 15.

How genomic imprinting works

Genomic imprinting refers to the process by which certain genes are 'branded' with the parent of origin. When gametes (sperm and eggs) are made, epigenetic markers that were inherited from our parents or accumulated in life are removed, but in genes that undergo genomic imprinting, new markers are added that identify the gene as coming from either the mother or the father.

These new markers change gene expression, resulting in the imprinted copy of the gene being turned off and the other copy being turned on. For example, if the allele inherited from the father is imprinted, it is silenced and only the allele from the mother is expressed; if the allele from the mother is imprinted, then only the allele from the father is expressed.

Uniparental disomy

Genomic imprinting can cause disease when there are errors in gamete production, or during early embryonic development. One common complication is **uniparental disomy (UPD)**, which is when a person inherits two copies of a chromosome from one parent, and none from the other.

When the chromosome in question does not contain imprinted regions, UPD may have no deleterious effects, but when chromosomes 11 or 15 are involved, the situation can be more complex. Because some genes in these regions are inactivated by maternal or paternal imprinting, an individual who inherits two copies from one parent can lack an active copy of some essential genes – even though they are present in the genome.

Which conditions can it cause?

The first conditions that were identified as being caused by imprinting were Angelman Syndrome and Prader-Willi Syndrome. Both conditions are caused by missing genetic information on chromosome 15 – one of the chromosomes where genomic imprinting is common.

Angelman syndrome (https://www.nhs.uk/conditions/angelman-syndrome/) occurs when the *UBE3A* gene is not working properly or is missing entirely. The paternal copy of the gene is imprinted, or silenced, meaning that only the copy inherited from the person's mother is active. Problems with or **deletion** of the maternal copy of the gene, or the section of chromosome 15 where it resides, can lead to Angelman syndrome.

In Prader-Willi syndrome (PWS) (https://www.nhs.uk/conditions/prader-willi-syndrome/), the same region of chromosome 15 is involved. In this case, though, the condition is linked to problems with the paternal copy of the chromosome rather than the maternal copy. Certain genes in the region, such as *SNRPN*, are imprinted, with the maternal copy being silenced and the paternal copy being active. Problems with the paternal copies of these genes can lead to PWS.

Watch the video on Prader-Willi syndrome (https://www.nhs.uk/conditions/prader-willi-syndrome/) (bottom of the page) from the NHS to learn about the features of PWS.

Comparison between two chromosomes: Chromosome 15 (normal function) has genes turned off through normal imprinting on the maternal copy. The same genes are active in the paternal copy and are being used. In a Chromosome 15 with Prader-Willi Syndrome, genes are naturally turned off through imprinting on the maternal copy, but genes are deleted by anomaly (no working copies available) in the paternal copy. **Source:** *Genomics Education Programme*, CC BY-NC

Most cases of Angelman syndrome and PWS are caused by deletions, although a significant minority are due to UPD.

Another condition linked to genomic imprinting is Beckwith-Wiedemann syndrome (BWS) (https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/beckwith-wiedemann-syndrome-bws/). It is caused by changes to imprinted genes in the chromosome 11 cluster, with a number of genes being implicated thus far, including *H19* and *IGF2*. It is associated with abnormal growth and an increased chance of childhood cancers, especially in the liver and kidneys.

Scientists hope that continued research into the genetic pathways involved in BWS will help to improve treatment methods and outcomes for those with the condition.

Implications for Policy: Social and Environmental Epigenetics

DNA methylation serves as a biological record of early social or environmental conditions, offering valuable insights for policy and interventions aimed at improving the social and structural determinants of health. Policy implications include (Schmidt, 2019):

- **Guiding Policy Directions:** Epigenetic research highlights the long-term health impact of early-life environments, similar to how evidence of second-hand smoke risks led to public smoking bans. Raising awareness about these biological effects could support child-focused interventions and policies that regulate environmental (e.g. air pollution) and social exposures (e.g. food security). For example, stricter regulations on industrial emissions or agricultural chemicals may be justified by findings demonstrating their long-term health impacts through epigenetic mechanisms.
- **Biomarkers for Early Screening:** Epigenetics may offer biomarkers for identifying children at risk of health conditions, like fetal alcohol spectrum disorder (FASD), allowing for screening and early interventions that maximize health outcomes as well as targeted health campaigns.
- **Evaluating Intervention Effectiveness:** Epigenetic markers may contribute to the assessment of the biological impact of interventions long before physical health outcomes manifest, enabling quicker and more cost-effective policy evaluations.
- **Shaping Global Environmental and Health Strategies:** As epigenetic research works toward finding evidence of how environmental factors affect health across generations, it has the potential to shape global agreements and policies. Collaborative efforts could focus on reducing environmental health disparities, addressing climate change, and prioritizing sustainable practices that protect vulnerable populations.

Quiz – Units 1-3

See the Blackboard course shell for the syllabus which provides details about the quiz content and due dates.

Attribution & References

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3.8 UNIT SUMMARY AND REVIEW

Key Takeaways

This chapter highlighted the shift away from the nature versus nurture debate and explored the pitfalls of genetic determinism. It emphasized the importance of the developmental origins of health and disease, developmental programming, and ontogeny, particularly during critical periods of growth and development. Epigenetics can regulate gene expression without altering the DNA sequence by altering gene expression. Most of these changes are reversible, allowing for adaptability to environmental stimuli. The exposome—encompassing social and environmental exposures—significantly influences health outcomes through its impact on the epigenome, and is closely tied to the social determinants of health. This chapter also examined the link between epigenetic changes and diseases such as cancer and imprinting disorders and illustrated the use of epigenetics in tumour profiling and personalized treatment approaches. As epigenetic research progresses, it holds the potential for considerable policy implications.

Brain story certification

Interested in learning more about this topic? The University of Oxford, in partnership with the Alberta Family Wellness Initiative, is working to share knowledge about the science of brain development for families and professionals. This is important information for everybody to understand how our earliest experiences can affect our long-term mental and physical health.

They offer a free, in-depth course (https://www.albertafamilywellness.org/training/) for anyone who wants to learn more about the science of brain development.

Additional Optional Readings:

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Attribution