7 When One Gene Is Enough: The Enzyme Missing in an Inherited Disease

The particular genetic endowment we receive from our parents or bequeath to our children can be a powerful motivator in our lives. For those confronted with a devastating inherited disease, the deep-seated questions—why did this disease occur? how did it occur?—can be a potent force driving the motivation to do something about it. That force sometimes leads to undreamed-of accomplishments. It led one woman to worldwide renown.

In 1914, an American woman who had been raised in China by her missionary parents returned to Chinkiang after attending college in Virginia, to care for her ill mother. There she fell in love with and married an agricultural economist from Cornell University who had come to China to teach farming methods. In 1920, at the age of twenty-seven, she gave birth to a beautiful daughter, whom she named Carol. "Mine was a pretty baby, unusually so," she would write much later. "Her features were clear, her eyes, even then, it seemed to me, were wise and calm."

But while Carol's body began to grow, her mind failed to develop. "I think I was the last to perceive that something was wrong," her mother wrote. When the child still was not speaking by the age of three, the woman was comforted by Chinese friends who told her that speech comes at different ages, even though they themselves suspected a deeper problem.

When Carol was nearly four, her mother heard a lecture about retarded mental development in preschool children given by a pediatrician visiting from the United States, and learned the danger signs to watch for: slowness to walk, slowness to talk, and incessant restlessness. The doctor examined Carol and added other concerns: a short attention span, blank eyes, and lack of responsiveness. The woman resolved to take her daughter back to the United States to find out what was wrong with her. She later wrote:

> Then began that long journey which parents of such children know so well. I have talked with many of them since and it is always the same. Driven by the conviction that there must be someone who can cure, we take our children over the surface of the whole earth, seeking the one who can heal. We spend all the money we have and we borrow until there is no one else to lend. We go to doctors good and bad, to anyone, for only a wisp of hope. . . . We crossed the sea and we went everywhere, to child clinics, to gland specialists, to psychologists. I know now that it was all no use. There was no hope from the first—there never had been any.

The end of the journey came at the Mayo Clinic in Rochester, Minnesota. A German doctor, blunt and honest, not meaning to be cruel but unwilling to delude her, delivered the grim news: "'I tell you, madame, the child can never be normal. Do not deceive yourself. You will wear out your life and beggar your family unless you give up hope and face the truth. . . . This child will be a burden on you all your life. . . . Find a place where she can be happy and leave her there and live your own life.'"

With no hope left, the woman endured unbearable sorrow. Her lone consolation was the realization that Carol herself had no knowledge of her deficiencies and was destined to spend her whole life as if in childhood. The mother's sense of hopelessness was intense, and she often thought how much better it would be if Carol died. But she also came to perceive how coping with her daughter was sapping her own life. "For the despair into which I had sunk when I realized that nothing could be done for the child and that she would live on and on had become a morass into which I could easily have sunk into uselessness. Despair so profound and absorbing poisons the whole system and destroys thought and energy."

The woman became aware that she must find an institution for Carol in the United States, one with appropriate companions and future security. She and her husband had become estranged, for he wanted nothing to do with spending money on private care for their daughter, and she realized that financing long-term care would be difficult. "I had found out enough to know that the sort of place I wanted my child to live in would cost money that I did not have. There was no one to pay for this except myself. I must devise means to do what I wanted to do for my child." She became a writer.

Why do you resemble your parents more than you resemble any of the other six and a half billion people on this planet? Why do siblings bear an uncanny resemblance to each other? Why is a woman whose mother

and aunt get breast cancer before they are fifty concerned that she may be at high risk to get this disease? Why was Carol born with a metabolic disorder that leads to profound mental retardation? It's simple: our personal DNA code is made up of specific versions of the roughly twenty thousand genes we get from our parents.

Genes specify proteins, which build the intricate apparatuses that constitute our cells, which make up our tissues and organs, our blood, nerves, skin, and hair. You resemble your parents and your siblings because your personal DNA code is composed of pieces of their personal DNA codes: you share with them particular versions of each gene, causing you and them to be composed of very similar proteins. Since those versions of proteins compose and operate you and your parents and your brothers and sisters, you all have similar traits. But you are certainly not identical to your parents or to your brothers and sisters, because your cells possess a unique combination of their personal DNA codes and thus a unique combination of the varieties of their proteins.

How do we explain the patterns of inheritance we observe? What were the chances that you inherited Uncle Bert's large nose, or your mother's sunny disposition, or the colon cancer that has struck so many people in your family? What were the chances that Carol would inherit a metabolic disorder from her parents?

The principles of heredity were worked out in the 1860s by Gregor Mendel, a monk living in Brno, Moravia, which is now part of the Czech Republic. Mendel deduced these principles by examining the characteristics of pea plants—their height, the color of their pods and seeds, and several other such easily observed features—noting what happened to these characteristics in the offspring of pea plants that he planted in his monastery's garden. The principles that Mendel discovered in his work on peas—there are basically only two of them—are straightforward and easy to understand and apply to all organisms, including humans. Because these principles are universal, with nearly all organisms transmitting their genes to their offspring in the same way, we'll discuss them in terms of human traits.

The first principle is that our genes come in pairs because our chromosomes come in pairs. We have two copies of each of 22 chromosomes, plus two copies of the sex chromosomes (two X chromosomes for females, one X chromosome and one Y chromosome for males), for a total of 46

chromosomes. Our chromosomes came from our mother and father, each of whom likewise has 46 chromosomes, but we didn't end up with 92, and our children won't have 184, because we get just half of each parent's chromosomes: sperm and egg cells have only half the number of chromosomes as the rest of the cells of our bodies.

This reduction in chromosome number that occurs when sperm and egg cells are formed is not a random selection of any 23 of the 46 chromosomes. Rather, one of each chromosome pair is taken. Thus, the egg and the sperm cells resulting from this process of reduction have a single copy of each of the 23 chromosomes. When a sperm cell unites with an egg cell, a complete complement of 46 chromosomes is restored in the fertilized egg. If the fertilized egg has 22 pairs plus two X chromosomes, one from Mom and one from Dad, it will become a female. If it has 22 pairs plus an X chromosome from Mom and a Y chromosome from Dad, it will become a male.

A fortunate consequence of having two copies of each chromosome is that we have two copies of every gene (except for genes on the X and Y chromosomes in males)—think of it as a backup if a certain gene is defective. For nearly all of these genes, one copy is sufficient: it doesn't matter if the other copy carries a mutation and therefore produces a defective protein, because the good copy provides a normal, functional protein. Thus, we can sleep soundly, safe in the knowledge that most mutations can't hurt us because we have a backup copy of every gene.

The second principle of heredity is that genes are apportioned to sperm and egg cells independently. That is, a particular gene in a man's sperm cell is equally likely to have come from his mom as from his dad; the same is true for any particular gene that ends up in a woman's egg cell. How this independence occurs—even for genes that reside on the same chromosome—will be considered in chapter 12.

Around the same time that the American mother in China was coping with her daughter's retarded development, another young woman, Borgny Egeland of Oslo, Norway, gave birth to two children, a girl in 1927 and a boy in 1930. Both children failed to develop normally: Liz, at age six, was able to say only a few words; Dag, at four, was unable to talk at all. Borgny and her husband, Harry, visited numerous specialists, but none was able to explain the cause of the children's condition. The parents also noticed

that both Liz and Dag produced urine with a strange musty odor, and wondered whether this smell was associated with their developmental defects.

Eventually the Egelands went to see Asbjørn Følling, an Oslo physician with an interest in metabolic disorders. Følling examined the children and, like the other doctors, could not make a diagnosis. But when he conducted a routine test of their urine for the presence of ketones—chemicals that in elevated concentration can be a symptom of many illnesses, including diabetes—Følling made a remarkable discovery. The test he used involves the addition of ferric chloride, an iron-containing compound, to the urine. If no ketones are present, the urine turns brown; if ketones are present, it turns purple. But the urine from the Egeland children did something Følling had never seen: it turned dark green when ferric chloride was added to it, indicating the presence of an unusual chemical.

Følling asked Mrs. Egeland to bring him urine samples every other day for two months. Eventually she brought him a total of twenty liters, a heroic feat considering that Dag was not toilet trained.

Følling purified the substance in the urine that reacted with the ferric chloride and identified it as phenylpyruvic acid. To determine whether other children who were mentally impaired also produced this substance, Følling tested more than four hundred institutionalized patients in Norway. He found eight more with phenylpyruvic acid in their urine, including two other sibling pairs. He also noted other traits in these patients, including fair skin, eczema, broad shoulders, and a stooping carriage.

Følling later identified thirty-four more patients from twenty-two families, and by 1945 he was able to report the genetic basis of this disease, which was given the name phenylketonuria, or PKU. The disease is due to the failure of these children's metabolism to break down surplus phenylalanine, one of the twenty amino acids found in proteins. The result is an increased amount of phenylalanine in the blood, which eventually spills over into the urine as phenylpyruvic acid. The excess phenylalanine leads to severe problems in the developing central nervous system, for reasons that are not well understood even today, resulting in diminished intellectual abilities in affected children.

The specific defect that is the cause of PKU is a mutation—a DNA sequence change—in a gene that encodes a protein known as phenylalanine hydroxylase, or PAH. The defective *PAH* gene directs the production

of a defective PAH protein that cannot do its job, which is to serve as an enzyme that converts phenylalanine to another amino acid, tyrosine.

Long before the gene for this enzyme was identified, babies who failed to produce PAH could be identified by a simple test for phenylalanine, first by measuring it in their urine and then later by measuring it in their blood by means of a test that could be done even before infants left the hospital. These advances led to the adoption by the 1950s and 1960s of routine screening of newborns, which became mandatory in many countries.

Children who test positive are put on a phenylalanine-restricted diet, which prevents the severe symptoms of PKU. Nonetheless, because the diet prohibits milk products, meat, egg, beans, lentils, and many other foods, and because some of the food that can be eaten is a bit unpalatable, it is difficult to follow. And even patients who adhere to the diet have somewhat elevated levels of phenylalanine, and often score lower on intelligence tests and have some emotional and behavioral problems. Despite the imperfection of the treatment, discovering the basis of the disease and developing a simple test for PKU (and subsequently for many other metabolic disorders) must nevertheless be considered one of the triumphs of modern medicine.

In the Egeland family lurked a mutation in the gene we'll call *PAH* on chromosome 12. Both copies of the gene in Liz and Dag must have carried this mutation because they didn't appear to have a good backup gene and their cells could produce no functional phenylalanine hydroxylase protein, hence their developmental problems. Their parents, Borgny and Harry Egeland, were free of the disease, but in their personal DNA codes both must have carried a mutation in one of their two copies of the *PAH* gene, and each parent passed on a defective copy of the gene to their children. Borgny and Harry Egeland are "carriers" of the mutation: they show no sign of the disease but carry a mutation in one of their two *PAH* genes.

Both Egeland parents had one normal copy of the gene (PAH^+) to direct production of a functional phenylalanine hydroxylase protein, and one copy of the gene with a mutation that directs production of a non-functional PAH protein. We'll denote the gene with the mutation as pah^-. The parents did not have the disease because all of their cells possessed functional PAH protein. The amount of good PAH protein that comes from only a single good copy of the gene was enough enzyme for them to thrive.

The effect of the normal *PAH*$^+$ gene dominates over the effect of the *pah*$^-$ gene with the mutation that directs production of a defective PAH protein. That is, the normal *PAH*$^+$ gene is "dominant" over the mutant *pah*$^-$ gene; the *pah*$^-$ mutation is said to be "recessive" because its effect (loss of PAH protein function leading to abnormal development) recedes into the background in the presence of a normal *PAH*$^+$ gene that encodes a functional PAH enzyme. (Throughout this book, dominant genes will be written in uppercase letters and recessive genes in lowercase.)

Only when both copies of the defective *pah*$^-$ gene are inherited, one from Mom and one from Dad, as happened to Liz and Dag Egeland, is the effect of this recessive mutation manifested with such severe results. Half of their mother's egg cells received the chromosome 12 with the defective *pah*$^-$ gene, as did half of their father's sperm. The consequence is that half of the time the egg that is fertilized and develops into a child is one that carries a defective *pah*$^-$ gene from the mother. Half of those fertilizations will be by a sperm carrying a defective *pah*$^-$ gene from the father; thus, half of one half, or one fourth, of the fertilized eggs will have defective versions of *both* copies of the gene.

We can see this clearly by listing all of the possible combinations of the *PAH* genes the children of Borgny and Harry Egeland could have received:

From Mom	From Dad	Result
PAH$^+$	*PAH*$^+$	Healthy
PAH$^+$	*pah*$^-$	Healthy (carrier)
pah$^-$	*PAH*$^+$	Healthy (carrier)
pah$^-$	*pah*$^-$	Suffers from phenylketonuria

Although statistically only one in four children of two carriers will get the disease, any given family may be lucky or unlucky. The Egelands were unlucky because, by the luck of the draw, both their children inherited two copies of the defective *pah*$^-$ gene (the fourth combination above). The statistical probability was that three quarters of the Egeland offspring would have been healthy. Fortunate carriers of the *pah*$^-$ mutation will produce no children with the disease.

If Liz or Dag had been put on a phenylalanine-restricted diet, it's likely that they would have led nearly normal lives and they themselves would have married and had children. Since Liz's personal DNA code included two defective copies of the *PAH* gene, if she had had children with

someone having two normal copies of the *PAH* gene, all of her children would have been carriers:

From Liz	From Partner	Result
pah^-	PAH^+	Healthy (carrier)

If Liz's partner was a carrier (unlikely, because the mutation is rare in the population), then the chance of each child's having PKU is one half:

From Liz	From Partner	Result
pah^-	PAH^+	Healthy (carrier)
pah^-	pah^-	Suffers from phenylketonuria

The inheritance of PKU is precisely like that of many other diseases caused by recessive mutations. Most metabolic abnormalities show recessive inheritance because a single copy of a gene encoding an enzyme that carries out a step in metabolism is generally sufficient to provide enough of the protein for normal life; the loss of half of the amount of enzyme due to one bad copy of the gene usually has no ill effect. Fortunately for us, most of these diseases are rare because it's not often the case that both parents will carry a mutation in the same gene. Some mutations are incredibly rare; for example, only about twenty cases of a type of congenital insensitivity to pain with anhidrosis (inability to sweat), caused by a mutation in a gene that codes for a protein that stimulates nerve growth, have been reported. Others, however, are not so rare. Gaucher disease—whose symptoms include joint degenerations, bone fractures, and bleeding problems—occurs in about one in fifty thousand people and is caused by two defective copies of the gene encoding an enzyme called beta-glucosidase.

The most common recessive disease among Caucasians is cystic fibrosis, which is caused by a mutation in a gene known as *CFTR* (which codes for a protein called the cystic fibrosis transmembrane conductance regulator). About 3 percent of Caucasians carry a mutation in the *CFTR* gene.

Recessive inheritance of disease can also occur for genes on the X chromosome, as we saw in chapter 5 for the *IL2RG* gene, whose mutation causes SCID, severe combined immunodeficiency syndrome. Because females have two X chromosomes, both copies of a gene on this chromosome must be defective for a recessive disease to be manifest, just as for genes on any

of the other chromosomes. But males, with their lone X chromosome, have no backup copy of the genes it carries, so a mutation in a gene on the X can cause major problems for boys. For example, Duchenne's muscular dystrophy is due to a mutation in a gene on the X chromosome that specifies a protein important for muscle function. About 1 in 3,500 boys inherit the defective gene from their carrier mothers (their fathers give them a Y chromosome).

Young Carol, back in 1920s China, was afflicted with phenylketonuria. Her mother, Pearl S. Buck, of course knew nothing of this disease, whose name would not be coined for another two decades. Buck knew only of her child's failure to develop normally. She visited institutions all over the United States to find a home for Carol, eventually deciding on the Training School in Vineland, New Jersey, because the staff treated the children with dignity and carried out research on the causes of mental disabilities. After leaving Carol at the school, Pearl Buck did not see her again for three years.

To earn money for Carol's care, Buck obtained five hundred dollars from the Presbyterian Mission Board in New York to write a children's story about missionaries. This work led to other writing, and in 1931, two years after Carol began life at Vineland, Buck published *The Good Earth*, a tale of peasant life in China, for which she won the Pulitzer Prize. In 1938, Buck became the first American woman to win the Nobel Prize for Literature.

In *The Good Earth*, Wang Lung and his wife O-lan have a baby girl who is profoundly retarded. This would not be the only work of Buck's to feature children with mental deficiencies, but it was not until 1950, with the publication of *The Child Who Never Grew*, that she revealed her daughter's—and her own—history. Buck's efforts on behalf of children with mental retardation spurred others to action, including Eunice Kennedy Shriver, sister of President John F. Kennedy, who wrote about their sister Rosemary, and Dale Evans Rogers, the wife of the cowboy actor Roy Rogers, who wrote about their child with Down syndrome.

In 1960, a pediatrician involved in PKU research visited Pearl Buck at her home in Pennsylvania, and asked her to smell a vial containing phenylacetate crystals, which produce the odor of stale urine from PKU patients. Buck immediately remembered that Carol produced this same characteristic odor, indicating that her mental disability was indeed due to PKU.

Carol Buck lived at Vineland for more than sixty years; she died of cancer in 1992 at the age of seventy-two. Progress in medical research over her lifetime has largely answered the questions that so puzzled Pearl Buck and the Egelands. Why did these children get phenylketonuria? Because their personal DNA codes included two copies of a defective *PAH* gene, one inherited from each of their unsuspecting carrier parents. How did they come to be so profoundly disabled? Because the buildup of phenylalanine in the blood inhibits development of an infant's nervous system. What can be done about the disease? A diet designed to minimize the intake of phenylalanine heads off the cognitive deficiencies and allows those with the disease to lead nearly normal lives. Because these questions could not be answered in 1920, the world got one of its literary treasures.

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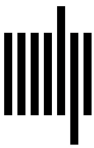

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