8 When One Gene Is Too Much: At Risk for Huntington's Disease

Mike O'Brien, thirty-nine, and his brother Chris, thirty-two, wanted to become the first American brothers to reach the summit of Mount Everest together. Experienced climbers, they had previously scaled twenty-five mountains together, including Mount Kilimanjaro in Tanzania, Mount Ranier in Washington, and Cho Oyu, the sixth-highest mountain in the world, in Tibet. On the website they set up to document their Everest expedition, they described themselves as "the 4th and 7th children born into the O'Brien clan of seven. [Their parents] passed on to their children fine table manners, swimming talents, [a sense] of humor, good looks and a strong sense of pride."

On May 1, 2005, Mike called his girlfriend, Rebecca Stodola, at their Seattle home, from camp 2, above their base camp. "He sounded like a kid on Christmas—his voice sounded breathy with excitement," Stodala said. "He said, 'We're ready. We're psyched, and if the mountain lets us, we'll do it.'" But shortly after the call, Mike and Chris decided to descend to base camp because camp 3, farther up the mountain, wasn't yet ready.

Starting off from camp 2 at 21,200 feet, they reached camp 1, at 19,500 feet, and began to traverse the Khumbu Ice Fall on their way down to the base camp. Around 1:45 p.m., Blair Falahey, who was walking behind the O'Briens, shouted to Chris that his brother had fallen into a crevasse. Mike lay on his back about twenty feet below the trail. He said that he thought he had broken his leg and damaged some ribs, but he could move his head and all his limbs.

Blair and Chris climbed into the crevasse and tried to make Mike comfortable. They put a hat, sunglasses, and sun cream on him, moved a sleeping mat underneath him, and propped his head up. But Mike began asking, "How long for oxygen to arrive. It's hard to breathe." Two other

climbers raced back toward base camp to get help and oxygen. Mike's condition was stable for about thirty minutes, but then rapidly deteriorated as his breathing difficulties increased. When he stopped breathing, Blair and Chris began CPR and rescue breathing, and when oxygen arrived, they gave it to him at the highest possible flow rate. But Mike never took another breath, and at around 4:30 p.m. they gave up their efforts.

The assistant team leader, Mark Merwin, arrived on the scene around 6:30 p.m. and examined the terrain where the accident had occurred. He surmised that Mike, like most other climbers at that point in the descent, had not been "clipped to the fixed line with his safety when he fell. If he had clipped the rope I think the rope would have arrested his fall, or we would have seen a broken rope at the scene of the accident. We did not find the rope broken. Nor was his safety line nor carabiner damaged in any way, as if it might have broken in a fall. . . . I think it is possible that he simply tripped and fell while unclipped to the rope." The weather had been unusually warm, which may have caused snow to become impacted in Mike's crampons and loosen his footing.

Mike "lived adventure to adventure," Stodola said. She also said that he had decided to "live life as if he might not see forty." In fact, Mike knew full well that an early death was a fifty-fifty possibility for him. The brothers' website contained the information that David and Alice O'Brien had passed on to their children, in addition to their other gifts, "a terrible genetic disease called Huntington's." The boys' mother had died of the disease at fifty-nine; their sister Diane had died at the age of thirty-nine, after she took a fall while still in the early stages of the disease; and their youngest sister, Alice, had recently begun to develop symptoms. Mike and Chris had taken on the Everest expedition as a fundraising project: they hoped to raise $100,000 for the Hereditary Disease Foundation, which supports the search for a cure for Huntington's disease.

Huntington's disease was first described in the medical literature in 1872 by George Huntington, a twenty-two-year-old American doctor just one year out of Columbia University Medical School in New York City. Huntington drew on observations of his father and grandfather, also physicians, who described to him the involuntary shaking they had observed in some of their patients with a disease called "St. Vitus Dance." Its most well-known sufferer may be the American folksinger Woody Guthrie, who

succumbed to the disease in 1967 after spending many years in mental institutions and hospitals where he had been misdiagnosed as an alcoholic. Although he knew nothing of Mendel's work explaining how traits are inherited, Huntington accurately described the genetic mode of transmission of this horrible disease.

The symptoms of Huntington's disease usually become apparent between thirty and fifty years of age, and they foreshadow a long and difficult path that leads to death. Nerve cells in certain areas of the brain degenerate, resulting in uncontrolled movements as well as cognitive and behavioral problems. People in the early stages of the disease are often irritable, depressed, anxious, and aggressive. They may have difficulty with mental processing and decision-making. Sometimes the first signs of the disease are involuntary movements or mild clumsiness or balance problems. Eventually, sufferers require major assistance with the activities of daily life, and many become unable to communicate.

About one in ten thousand people get the disease. Unlike the recessive disorder phenylketonuria, which results only if both copies of a defective *PAH* gene are inherited, Huntington's is a dominant genetic disease: a single copy of the abnormal gene (which we'll call HD^*) is sufficient to cause the disease. Any individual whose personal DNA code includes one abnormal HD^* gene will eventually succumb to the disorder. People destined to die of the disease typically have as well a copy of the normal gene, which we'll call hd^+, so they are HD^*/hd^+. Those who will not get the disease are hd^+/hd^+.

Males and females get Huntington's disease in equal numbers because the Huntington's disease gene is not located on either the X or Y sex chromosomes. Since Huntington's disease is a dominant disorder, each child of a parent with the disease has a fifty-fifty chance of inheriting the abnormal gene and developing the disease. Each also has a fifty-fifty chance of inheriting the normal gene. If a mother has Huntington's disease (HD^*/hd^+), on average, half of her eggs will carry the abnormal HD^* gene for Huntington's disease. She inherited that gene (and, therefore, the disease) from whichever of her parents had it. But half of her eggs will carry the normal version of the gene inherited from her parent who was free of Huntington's. Each time an egg is fertilized to make an embryo, there is a 50 percent chance that the egg will contain the abnormal version of the *HD* gene and a 50 percent chance that it will carry the normal version.

(Because the *HD** mutation is rare in the human population, virtually everyone who has the mutation mates with someone with the normal version of the gene.)

From Mom	From Dad	Result
HD*	*hd*$^{+}$	Suffers from Huntington's
hd^{+}	*hd*$^{+}$	Healthy

In the same way, each child whose father will succumb to Huntington's disease (*HD**/*hd*$^{+}$) also has a fifty-fifty risk of getting the disease. Half of the sperm of the father will carry a normal version of the *HD* gene and half will carry an abnormal version of the *HD* gene.

From Mom	From Dad	Result
hd^{+}	*HD**	Suffers from Huntington's
hd^{+}	*hd*$^{+}$	Healthy

Imagine you are flipping a quarter 100 times. Each time you flip, you have a fifty-fifty chance of getting either heads or tails. It's the same thing with the genetic flip of the coin. Each child born to either a mother or father with Huntington's disease has a 50 percent risk of having the disease. It does not matter which embryos have come before or will follow; with each pregnancy, the statistical chances are the same. In some families, just by bad luck, all of the children are destined to develop the illness; in other more lucky families, none do. The fate of one child has absolutely no bearing whatsoever on the fate of any other.

If you're an at-risk individual because your dad or mom developed Huntington's, what determines whether you inherited the normal chromosome, or were fated to contract the disease by inheriting the abnormal version? Although scientists can now analyze individual sperm cells and determine whether the Huntington's disease gene in them is the normal or abnormal version, to an egg cell the billions of sperm are indistinguishable. The decisive event of fertilization is random, one of the many accidents of the universe we inhabit. No force guides one sperm cell or another to a successful fertilization, any more than the heads or tails of a single coin toss is preordained. We are the products of numerous chance events that determined our personal DNA code. Neither the child born with a severe genetic affliction nor the parent is to blame.

The Huntington's disease gene lies near the tip of chromosome 4. Identification of the approximate location of the gene in 1983 electrified human geneticists because it was the first success of a new approach to map disease genes based on the knowledge of the human genome that was starting to accumulate. The discovery relied heavily on the work of Nancy Wexler, a neuropsychologist at Columbia University, and her colleagues.

Huntington's disease is prevalent in the communities around Lake Maracaibo, in Venezuela; up to half the residents of some small villages are ravaged by it. It's not unusual to see villagers there walking around with legs and arms flailing about in wild, uncontrolled movements. This extreme prevalence of Huntington's is due to a woman with the disease who lived there about two hundred years ago and gave birth to ten children. Because of the isolation of these communities, the descendants of this woman now make up much of the current population, a phenomenon known as a founder effect. The advantage to geneticists of such a population is that all those with the disease carry the same mutation, and the contribution of the environment is minimal because all the residents share the same living conditions.

Wexler and her colleagues constructed an extensive family tree of the thousands of Huntington's sufferers in this region. She took the first of many trips to the Lake Maracaibo region in 1979, taking blood samples and skin biopsies from the residents and tracking the progression of the disease in those showing symptoms. Her older sister, Alice, who accompanied Nancy in 1983 and 1984, wrote in her book about the disease, *Mapping Fate*, "Nancy is physician, nurse, ethnologist, psychologist, diplomat, photographer, neurologist, geneticist, and general all rolled into one." Collection of these samples in the primitive conditions in the Venezuelan villages required overcoming numerous logistical hurdles, like timing the days for blood draws to coincide with the departure dates of members of the team so they could hand-carry the tissues back to the United States. These samples proved crucial both for localizing the gene to a region of the human genome and then, ten years later, for identifying the DNA sequence of the gene.

The *HD* gene encodes a protein called Huntingtin. The change in the protein caused by the mutation in the HD^{*} gene is unusual. In the normal (hd^{+}) gene, there is a stretch of DNA where the bases CAG, which specify

the amino acid glutamine, are repeated: CAGCAGCAGCAGCAGCAG and so forth. Individuals with the normal (*hd*$^{+}$) version of the gene have between seven and thirty-five copies of CAG at this point in the gene, resulting in seven to thirty-five glutamines all in a row in the Huntingtin protein. The *HD** (abnormal) versions of the gene have forty or more copies of CAG, resulting in a longer run of glutamines in the Huntingtin protein. It's not clear why, but those extra glutamines in Huntingtin cause the protein to poison brain-cell function, ultimately leading to an early death. (Some people with thirty-five to thirty-nine copies of CAG in the gene may develop the disease; others will escape it.)

Why do we term the mutation that causes Huntington's disease "dominant"? For recessive mutations like the one that causes phenylketonuria, the amount of protein produced by a single functional copy of the *PAH*$^{+}$ gene is sufficient for its normal function in development. Both copies of the gene must be defective for the disease to occur:

From Mom	From Dad	Result
Functional *PAH*$^{+}$	Defective *pah*$^{-}$	Healthy (carrier)

Huntington's disease, however, occurs even though one of the copies of the gene produces normal Huntingtin protein in each cell of the body:

From Mom	From Dad	Result
Altered *HD**	Normal *hd*$^{+}$	Huntington's disease

The altered Huntingtin protein with those extra glutamines is toxic, possibly because those amino acid residues cause the protein to associate abnormally with other proteins in the cell, resulting in clumps of proteins that effectively gum up the works of the cell (a more precise description of the phenomenon can't be given because its basis is not well understood). Certain brain cells are especially susceptible to this protein clumping, causing the disease to be manifested largely as a neurological disorder.

Dominant mutations like these are called "gain-of-function" mutations because they confer on a protein an activity it doesn't normally have (in this case aggregation of Huntingtin with other proteins):

From Mom	From Dad	Result
Altered (gain-of-function) *HD**	Normal *hd*$^{+}$	Huntington's disease

Recessive mutations like those in the *PAH* gene typically cause a "loss of function" of the protein they affect.

From Mom	From Dad	Result
Functional PAH^{+}	Defective (loss-of- function) pah^{-}	Healthy (carrier)

Since about 1 in 10,000 people carry the HD^{*} mutation, the likelihood that an individual will inherit two copies of a defective HD^{*} gene is about 1 in 100 million (1/10,000, the chance that Mom carries the mutation, times 1/10,000, the chance that Dad carries the mutation). Such individuals are found around Lake Maracaibo because of the large number of people carrying the abnormal form of the gene.

Ever since the *HD* gene was discovered in 1993, people like Mike O'Brien who are at risk of the disease can take a genetic test to find out if the abnormal gene is part of their personal DNA code and learn whether or not they are destined to develop symptoms of Huntington's disease. Genetic counselors isolate DNA from cells in a tissue sample (obtained by swabbing the inside of the cheek or drawing a bit of blood), and determine the precise number of CAG repeats in each of the two copies of the gene. There is no indication that Mike ever took such a test, or that his DNA was tested after he died. His sister Meghan concealed her true identity because of concerns about insurability in the event the test showed that she had inherited the abnormal gene. But she did not receive the disease-causing mutation, and she is now raising a family, having escaped from under the dark cloud of Huntington's disease.

The specter of taking a genetic test to establish the likelihood of falling victim to a progressive, incurable disease like Huntington's can be overwhelming to those at risk, whose worst fears may be confirmed by the test. Knowledge that the abnormal gene has been inherited brings a considerable penalty, removing that fifty-fifty probability and replacing it with the certainty of a slow, agonizing death. On the other hand, taking the test can be a source of relief if only the normal version of the gene is found, lifting the anxiety of a life in limbo and the daily stress of not knowing how much of a future to plan for.

For some individuals, the prospect of gaining peace of mind warrants the risk of certain knowledge of an awful fate. But even a test that provides

good news can bring a heavy burden, including survivor's guilt over the other family members who are less fortunate, and the loss of a driving force to accomplish something that may have been motivated by one's genetic inheritance. Beyond the emotional stakes for at-risk individuals of learning their fate, there are potential practical risks, such as loss of employment or insurance, and even social stigma.

Nancy Wexler, the neuropsychologist who played a major role in finding the *HD* gene, and her sister Alice know the emotional stakes well. Their mother, Leonore, was stopped by a Los Angeles police officer in 1968 because she was walking erratically and was thought to be inebriated. But alcohol was not the problem; her poor balance was a consequence of Huntington's disease, which claimed her life a decade later. Their father, Milton, got together with the two girls, then in their early twenties, to tell them that their mother had "'a progressive, degenerative, neurological illness, that it often caused madness, that it was always fatal, and that both [of you] . . . have a fifty-fifty chance of inheriting the illness yourselves.' He went on, 'You know what you both said? "Fifty-fifty? That's not so bad." That took a terrific load off my mind.'"

The awareness that Leonore Wexler had Huntington's disease unearthed hidden family secrets—a not uncommon occurrence in such families. The sisters learned that their maternal grandfather and all three of their mother's brothers had succumbed to the disease. Her mother had watched the inexorable decline of her father. When she was just fifteen she had read a textbook of neurology and noted that it stated that only males inherit the disease. Hoping to find a cure for her older brothers before it was too late, she studied genetics in college and worked in the laboratory of the Nobel Prize–winning geneticist Thomas Hunt Morgan.

When a genetic test for the disease became available, Nancy and Alice Wexler had to confront their own ambivalence about the issue. Heated family discussions took place in 1984. Alice described her decision to forego the test: "'Talking about it concretely—moving from the realm of abstract possibility to planning the logistics of it—terrifies me. . . . The thought of learning that I carry that gene—that my brain is already deteriorating—is just too horrendous. I'm not sure that I could go on.'"

Their father, Milton Wexler, a psychoanalyst who treated many notable Hollywood figures, founded the Hereditary Disease Foundation in 1968 in an effort to uncover the cause of the disease that would kill his wife

and that threatened his daughters. He vowed to use the funds of the Foundation, for which his daughter Nancy now acts as president, to fund treatments and cures for this horrific illness, and he dedicated the next forty years of his life to finding the gene and making progress toward a cure. This is the organization for which Mike and Chris O'Brien were raising funds with their Everest expedition. A year after Mike O'Brien's untimely fall on the mountain, his family and friends succeeded in topping their $100,000 goal. But we are still awaiting a cure for Huntington's disease.