9 Genes to Remember: The Growing Burden of Alzheimer's Disease

Margarita Carmen Dolores Cansino began her life in Brooklyn, New York, in 1918, at the end of the First World War. The daughter of a showgirl from Washington, D.C., and a flamenco dancer from Madrid, Cansino was destined to go on to a celebrated career punctuated by tragedy. Intensely shy and quiet as a girl, she was kept out of school by a domineering father (who also sexually abused her, according to one biographer) so that she could perform Spanish dances in Mexican casinos and on gambling boats. At the age of eighteen, Cansino married another controlling man, a thrice-divorced lounge lizard in his forties who viewed her more as an investment than a wife. To make the investment pay off, her husband willingly pushed her into the arms of any man in Hollywood who might help get her into films. To improve her chances of stardom, Cansino changed her hairline, her hair color and her name, transforming herself into Rita Hayworth.

Hayworth became instantly recognizable as one of the most glamorous screen stars of her era. She made a series of musicals with Fred Astaire and Gene Kelly, as well as erotically charged films such as *Blood and Sand*, *Gilda*, and *The Lady from Shanghai*. A photograph of her kneeling on a bed in a negligee of satin and lace that appeared in Life magazine in 1941—sent to millions of American soldiers—was rivaled in popularity only by the one of Betty Grable in a white bathing suit. When Orson Welles saw the photograph while filming in South America, he told his friends that upon his return to the United States he would marry Hayworth, even though the director of *Citizen Kane* had not yet set eyes on the actress in person. And marry her he did.

Likely a result of her painful childhood, Hayworth suffered through difficult relationships with her five husbands and her many lovers, one of whom was the aviator and tycoon Howard Hughes. Outwardly the femme

fatale, inwardly Hayworth remained a vulnerable little girl. Referring to her role as the eponymous sexual temptress Gilda in the sizzling film noir costarring Glenn Ford, she remarked, "Men go to bed with Gilda, but wake up with me."

Hayworth's career spiraled downward after she turned forty. It wasn't that her looks betrayed her or that she could no longer hold an audience. No, she was losing her mind. The cause was likely her possession of a different base at one particular position in her personal DNA code—say, where she might have had a T rather than the C that most people have there. That single difference in Hayworth's DNA would result in the production of a single altered protein, and it likely was this protein that ended her career.

On November 25, 1901, Auguste Deter, the fifty-one-year old wife of a railway worker, arrived at the Municipal Asylum for the Insane and Epileptic in Frankfurt-am-Main, Germany. Showing unusual symptoms of delusions and hallucinations, she was referred the following day to a research-oriented physician, who recorded their conversation.

"What is your name?" he asked her.
"Auguste."
"And your surname?"
"Auguste."
"What is your husband's name?"
"I think . . . Auguste."
"Your husband?"
"Oh, yes."
"How old are you?"
"Fifty-one."
"Where do you live?"
"Oh, you were so nice at our house."
"Are you married?"
"Ah, I am so confused."

Auguste's husband related the mystifying course of her illness. About eight months earlier Auguste had begun to believe that her husband was being unfaithful. She also began forgetting things, messing up her cooking, and wandering aimlessly through the house. These behaviors were soon followed by paranoia, fears of dying, and increasing forgetfulness.

At the Frankfurt clinic Auguste's condition continued to deteriorate. She became hostile and violent, striking other patients in the face. At the same

time, Auguste grew less and less animated, so that three years after her admission she simply lay curled up in bed, completely dazed. By the following year, she was totally silent. In April of 1906, five years after the appearance of her first symptoms, Auguste Deter, physically and mentally only a shadow of her former self, died in the clinic of septicemia caused by bed sores.

Decades later, however, she would become one of the most famous patients in the annals of medicine. Auguste's autopsy samples were sent to a well-known lab, the Cerebral Anatomical Laboratory in Munich, where the physician who had first interviewed her had since moved. He analyzed Auguste's brain with the latest procedures and the most powerful microscopes of the day. Two findings stood out in his analysis. First, inside the brain cells—called neurons—he observed bundles of thick fibers that came to be known as neurofibrillary tangles. Second, outside the cells he saw deposits of an abnormal substance that came to be known as amyloid. At a conference in late 1906, Dr. Alois Alzheimer presented his paper on "profound dementia in a young adult." He concluded, "I have just presented a clearly defined and hitherto unrecognized disorder." By all accounts, Alzheimer's presentation had no impact on the audience of psychiatrists who heard it.

Because Auguste displayed symptoms at only fifty-one years of age, her disease—dubbed Alzheimer's disease a few years later by Alzheimer's mentor, Emil Kraepelin, the father of modern psychiatry—was classified as a presenile dementia, defined then as occurring before sixty years of age. This disorder stood in contrast to the much more common senile dementia displayed by older patients. This distinction between dementia in a younger person and dementia in the aged would confound the field for half a century, during which time Alzheimer's disease attracted hardly any attention from researchers.

Whereas presenile dementia showed characteristics that caused it to be considered a disease, senile dementia was thought to be to the result of the normal deterioration of old age. Instead of giving credence to the idea of a physical illness, psychiatrists fostered a model of dementia in the aged that pinned the cause on some combination of personality, emotional trauma, mandatory retirement, social isolation, and the breakup of the family. In the 1940s and 1950s they linked social pathology to brain pathology, viewing the former as the cause of the latter. To psychiatrists of that era, it was all nurture, and no nature.

By the 1970s, however, society had come to appreciate that people should not be discriminated against on the basis of their advanced age any more than because of their race or sex. As a consequence, the stereotype of aging individuals as inevitably succumbing to dementia began to fade. Meanwhile, on the scientific front, Martin Roth, Bernard Tomlinson, and Gary Blessed at Newcastle University, in the U.K., demonstrated that the degree of dementia in a person correlated best not with age but with the number of deposits of amyloid and neurofibrillary tangles observed in the brain, suggesting that specific pathological changes, and not the general aging process, were the culprit. Because the clinical and pathological manifestations of the early-onset (presenile) and late-onset (senile) dementias were the same, both disorders were classified as Alzheimer's disease.

These findings led to a much greater realization of the burden of Alzheimer's disease, which until then had been thought to be relatively small. In 1976, Robert Katzman of the University of California in San Diego made the bold estimate that Alzheimer's disease afflicted 1.2 million Americans and accounted for sixty thousand to ninety thousand deaths each year. Those numbers startled the public and galvanized the research community, stimulating big increases in funding for research into the causes of the disease and the development of therapies. The numbers from thirty years ago pale compared to those of today: about 5 million Americans currently suffer from this horrible disease; by 2050 it is expected to be between 11 million and 16 million.

Inside the cell, neurofibrillary tangles of protein fibers; outside the cell, deposits of amyloid protein. The actual makeup of those defining structures and the process by which they form remained mysterious for eighty years after Alois Alzheimer's examination of Auguste Deter's brain. Indeed, whether the tangles or deposits cause the disease or merely appear as a byproduct of the real toxic event remained an open question for much of the last century. Maybe dying cells in the brain accumulate broken-down bits of worn out proteins, and these are what form these two structures, long after the cells have quit functioning for completely different reasons.

But over the last two decades, Alzheimer's disease research has made remarkable leaps, and the geneticists can take much of the credit. Their studies of rare hereditary forms of Alzheimer's disease, although comprising less than 1 percent of all cases, have provided insight into the more

prevalent so-called "sporadic" cases (whose cause is unknown). These studies have revealed the pathways that produce the tangles and deposits seen in the common forms of the disease. The proteins implicated by these rare familial cases of Alzheimer's disease provide targets for developing medication to treat Alzheimer's.

Before plunging into the genetics of Alzheimer's disease, we first need to consider its cast of proteins. In 1984, George Glenner, a pathologist at the University of California in San Diego, identified the small protein present in the amyloid deposits, which he named amyloid-beta. Not long after that, amyloid-beta was found to be derived from a much larger protein called amyloid precursor protein that sits on the cell surface with just a short tail of amino acids protruding into the cell. The protein gets clipped in two places to produce amyloid-beta. The scissors that do the clipping are two other proteins that researchers named presenilin-1 and presenilin-2.

Meanwhile, geneticists collected blood from families around the world whose members exhibited the early-onset form of Alzheimer's disease. They subjected the DNA of these family members to intense scrutiny, using new powerful tools for DNA analysis that were being developed.

In 1987, the gene for amyloid precursor protein was identified. Intriguingly, it lies on chromosome 21, an extra copy of which causes Down syndrome. That is significant because people with Down syndrome typically exhibit symptoms of Alzheimer's by age forty, possibly because of extra amyloid-beta protein produced from their extra amyloid precursor protein gene on their extra chromosome 21.

The geneticists eagerly examined their Alzheimer's family pedigrees, hoping to find mutations that cause the disease in the newly discovered amyloid precursor protein gene. In 1991 they found one in a British family with a rare form of Alzheimer's. A few other mutations in this gene have since been identified, most of which change amino acids near the sites in the protein that get clipped by the presenilin scissors in the process of generating amyloid-beta. The key fact about these mutant versions of the gene is that they lead to an abnormal accumulation of amyloid-beta, and therefore implicate amyloid-beta as a cause, not just a consequence, of the disease.

But mutations in the gene encoding amyloid precursor protein are the least frequent cause of familial Alzheimer's disease. Most familial cases are

due to mutations in the genes encoding the presenilin-1 and presenilin-2 scissors. The first of these was found in the mid-1990s after an enormous amount of work on pedigrees of families with Alzheimer's disease (the use of pedigrees will be discussed in more detail in chapter 13). Some mutations in the presenilin genes cause the scissors to be hyperactive, resulting in the production of excess amyloid-beta, strengthening the case that amyloid deposition is a cause of Alzheimer's disease.

Geneticists conclusively demonstrated that amyloid-beta contributes to Alzheimer's disease, but that still left the question of the cause of the neurofibrillary tangles that accumulate in neurons in the brain of people with the disease. The major component of the tangles is a protein known as tau, part of a network of protein cables that move materials around the cell, much as the cables of a chairlift move skiers up the mountain. Since neurons are large cells with long extensions, they are especially reliant on these cables to move cellular materials long distances.

In 1998 geneticists identified disease-causing mutations in the gene that encodes tau protein, but not in patients with Alzheimer's disease. Rather, they found the tau mutations in patients suffering from a neurological disorder called frontotemporal dementia and Parkinsonism linked to chromosome 17, or FTDP-17 for short. People with this disorder have intracellular deposits of tau, but no deposits of amyloid-beta. The hypothesis that tau plays a role in this disease supports the idea that altered forms of tau cause neurodegeneration. But they do not seem to be a cause of Alzheimer's disease.

The mutations in the genes that encode amyloid precursor protein, the presenilin scissors, and tau shed much needed light on the etiology of Alzheimer's disease. But the laurels will go to those who identify mutations that contribute to the common, sporadic form of the disease. Many such mutations must exist, but so far only one major genetic risk factor is known: the gene encoding apolipoprotein E (apoE), a protein that shuttles cholesterol around the body, including to the brain. The particular form of apoE specified by your personal DNA code influences your disposition to Alzheimer's disease, but it doesn't strictly determine your fate: people carrying one copy of the apoE4 form of the gene are only about three times more likely to get the disease. Those with two copies are nine times more likely, but some people with two copies live into their eighties and never get the disease. Furthermore, Alzheimer's disease is common, and apoE is

only one risk factor; only about half of Alzheimer's sufferers have the apoE4 form of that gene.

Rita Hayworth lost her career and her life to Alzheimer's disease. Like many people, both of us have seen loved ones suffer this awful disease, which takes a heavy toll on the family as well as the patient. Most Alzheimer's researchers think that amyloid-beta is one of the culprits that rob victims first of memory and, eventually, of almost all other thought processes. The accumulating amyloid-beta somehow gums up the works of cells in the brain, eventually killing them.

The early stages of Rita Hayworth's disease brought mood swings, tantrums, and violent outbursts that were attributed to alcohol abuse. The memory deficits soon became apparent. When Hayworth was tapped to replace Lauren Bacall in the Broadway production of *Applause,* she discovered she couldn't remember a whole play's worth of dialogue, and she had to pull out of the production. By 1971, the fifty-three-year old actress had trouble retaining even short bits of dialogue. During the filming of *Wrath of God*, she had to be fed one line at a time. Some years later Orson Welles ran into her at a hotel and went over to her and kissed her. "My blood ran cold," Welles recalled, as he realized that Hayworth had no idea who he was.

The early onset of Rita Hayworth's Alzheimer's disease indicates that it was likely caused by a mutation in her personal DNA code: a substitution of one base-pair for another that changed one of the base triplets of a gene, causing a different amino acid to be inserted at that position in a particular protein chain. That amino acid change at that particular spot in the protein altered its chemical properties and disrupted its structure, causing it to kill neurons. We don't know which of Rita Hayworth's genes suffered that fateful mutation—perhaps it was one of the presenilin genes—but it's likely that a change in only one of her 6 billion base-pairs led to the buildup of the amyloid-beta that shortened her dazzling career and prematurely ended her life.

When Hayworth died in 1987 at the age of sixty-eight, a fellow actor was occupying the White House. "Rita Hayworth was one of our country's most beloved stars," Ronald Reagan said. "Glamorous and talented, she gave us many wonderful moments on the stage and screen and delighted audiences from the time she was a young girl. . . . Nancy and I are saddened by Rita's death. She was a friend whom we will miss."

The president also praised Hayworth and her daughter, Princess Yasmin Aga Khan, for publicly confronting Alzheimer's disease. "The courage and sincerity shown by Rita and her family have done us a great public service by calling the world's attention to a disease that all of us hope will soon be curable." Alas, the cure did not come soon enough for Mr. Reagan: he himself succumbed to the disease in 2004, ten years after telling the American public of his own diagnosis.

Unlike Hayworth's disease, the Alzheimer's disease that we typically confront in our parents or grandparents, our aunts or uncles, does not strike the young. The Alzheimer's Association estimates that about one fifth of Americans who reach the age of seventy-five will suffer from the disease in their next decade of life; for those eighty-five and older it's more than two fifths.

Research in recent years has provided clues to the risk determinants, protective factors, and possible targets for drugs against this disease. The greatest risk factor is obvious: age. Before life expectancy in modern societies reached nearly eight decades, Alzheimer's disease had little impact. As more of us enjoy longer lives, more of us suffer from this devastating disease.

Another risk factor is also clear: one's parents. People with a parent or sibling with the disease are two to three times more likely to develop it themselves.

Several environmental risk factors have also been identified. Severe head injury increases the likelihood of getting the disease. Boxers who suffer years of blows to the head often end up with dementia. Other factors include the same ones that contribute to vascular disease—a high-cholesterol diet, high blood pressure, and diabetes.

Protective factors are also being identified. An intriguing one is high educational attainment, suggesting that a cognitive reserve, created over a lifetime of challenging mental activity, protects against Alzheimer's disease. People who are on statin drugs (for treatment of high cholesterol) or who take nonsteroidal anti-inflammatory drugs (for treatment of pain) seem to have a decreased risk in some studies, though these therapies have yet to prove useful in drug trials for those who already have the disease.

Since Alzheimer's disease generally develops in a person's seventh or eighth decade of life, a drug that staves off the symptoms for even a decade

would be a blockbuster. Advances in understanding the basis of Alzheimer's disease have provided several proteins that seem like good targets for a drug. These include the presenilin proteins that cleave the amyloid precursor protein, proteins that contribute to the formation of amyloid-beta deposits, and proteins that remove amyloid-beta from the brain. Other approaches focus on tau, apoE, or growth factors active in the brain.

Rita Hayworth did not lose her memory, judgment, and language to alcohol abuse, as was first suspected. No, she succumbed to a neurodegenerative disease first diagnosed by Dr. Alois Alzheimer in Munich. Millions of other aging individuals who demonstrate failing memory are showing the effects of this disease, not of the aging process. Millions more will be affected before a cure is found.

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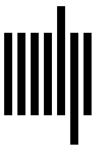

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