

Rudolph E. Tanzi and Ann B. Parson

# DECODING DARKNESS

THE SEARCH FOR THE GENETIC CAUSES OF  
ALZHEIMER'S DISEASE

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*The Search for the Genetic Causes of  
Alzheimer's Disease*

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Rudolph Tanzi is a principal scientific founder of Prana Biotechnology, Ltd.; Genoplex, Inc.; and Neurogenetics, Inc. Dr. Tanzi has equity in all three companies as well as the publicly traded companies Elan Pharmaceuticals and Bristol-Myers Squibb.

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When the word *impossible* especially threatened, family and close friends vanquished it. Please know—each one of you—how much your steadfastness has meant.

RET & ABP

# Introduction

Few real nightmares on earth compare to the terror wrought by Alzheimer's disease. That this fatal brain disorder not only annihilates a person's mind, but starts doing so years before it takes their life is surely its most insidious aspect. Its initial symptoms of forgetfulness and personality changes lie so close to normalcy that they typically go unnoticed; and, once noticed, too long unexplained. As the victim's grasp further slides, it can bring nothing but tormenting confusion for both the patient and those close to him. What can be worse than watching someone you love cognitively flailing, until eventually they no longer recognize faces, surroundings, or even themselves?

More razor-sharp than Alzheimer's physical distress is this emotional pain felt by patient and helpless bystanders. "No one not saddled with it can understand it, not even my best friend," says Julie Noonan-Lawson. Along with her four sisters and five brothers, Julie watched their mother Julia Tatro Noonan succumb to a rare form of Alzheimer's that strikes in middle age and is passed down to 50 percent, on average, of offspring. Consequently, all ten of Julia's children, who currently span the ages of thirty-six to fifty-eight, bear the burden of being genetically at risk.

Framed in their recollections of their mother is how much she loved to sing. Growing up, they would cram into the family station wagon on hot summer days, swimsuits in tow, and led by Julia's strong lilt sing one song after another full throttle all the way to Manomet Beach on Massachusetts' South Shore. When, in her early forties, Julia inexplicably began singing less and lapsing into depressed moods, her children followed her into a mire of anxiety, trouble, and hurt. Her lost song was their lost song.

The Noonans' response to the disease has been to not take it sitting down. So admirably, they and hundreds of other at-risk families have made invaluable contributions to research, helping the thousands of us who make up the Alzheimer's scientific community to try to extrapolate the disorder's molecular roots. Without their aid, the following account of the inestimable progress we've made in a remarkably short time wouldn't exist for the telling. Faced with the prospect of the disease's

bull run through generations of their large family, the Noonans made their DNA available to investigators at Massachusetts General Hospital in Boston. It's primarily under that roof that I've been involved in researching Alzheimer's causes since the early-1980s, currently as the director of the Genetics and Aging Unit. From this vantage point emerges the following story. Although words can't fully describe the fears and losses an Alzheimer family is up against, some small sense of the Noonans' ordeal appears between these chapters.

When a doctor recognized Julia's illness in 1967, its brand of dementia was thought to be confined to middle age. It wasn't long before the true boundaries of Alzheimer's emerged. Researchers realized that its classic lesions—the microscopic *amyloid plaques* and *neurofibrillary tangles* that overrun brain tissue—also appeared in elderly people who suffered from senile dementia, and with alarming frequency. Since then, the disease has been perceived in two guises. The extremely rare type, which first manifests in people under sixty, is known as *early-onset* Alzheimer's. This is what plagues the Noonans. When the very same plaque-and-tangle pathology descends on people sixty or older, it is referred to as *late-onset*. So common is this late variety that in this country it afflicts 20 percent of people age seventy-five to eighty-four, and reportedly over 40 percent of those eighty-five and over. No other neurodegenerative disease takes so many lives.

Although its extensive toll stood revealed, by the 1980s Alzheimer's was still considered a backwater disease, one that didn't attract much research attention. Those who studied it were coming round to believing that its early form was inherited, and therefore the result of a genetic error. Late-onset cases, on the other hand, were thought to be caused by environmental stressors, not mutations in genes.

Generally, Alzheimer's grip on older people cooled the interest of researchers. The unfortunate sentiment was, why work on a disease whose victims were close to the end anyway? More to the point, the technology available for exploring the mysterious complex of the human brain was limited. Even today, despite two decades of tremendous strides in neuroscience, a central irony persists. The human brain has festooned Earth with amazing objects of its own making—high-speed computers, Boeing jets, buildings that touch the sky, powerful medicines—even elaborate scanners such as MRI (magnetic resonance imaging) and CAT (computerized axial tomography) that further our attempt to un-

derstand the brain as well as we do the heart and lung. Yet as Stephen Vincent, a neuroscientist at McLean Hospital outside Boston, so aptly puts it, “Our brain is having a devilish time figuring itself out. It remains totally ignorant of how it works as a unified organ to make us so uniquely human.” Even a slug’s brain, and how it enables a slug to be a slug, eludes scientists, notes Vincent. If the trappings of a healthy brain are hard to decipher, imagine the murky picture a diseased brain presents.

In the early 1980s, the genetic revolution’s fantastic inroads into the biological world’s two crucial elements—*genes* and *proteins*—began making possible a more introspective investigation of human diseases, including those that rob the brain.

Genes, composed of the molecule DNA (deoxyribonucleic acid), are the basis of all inherited traits in every living organism on Earth. Each gene is a linear chemical script, a special cryptogram made up of DNA’s four nucleotide bases—adenine (A), guanine (G), thymine (T), and cytosine (C). And each is part and parcel of a far longer DNA filament—a chromosome. So genes simply amount to codes of inherited information that are intermittently spaced out on chromosomes. A human has twenty-three pairs of chromosomes—one in each pair inherited from mom, one from dad—which present us with two copies of roughly 100,000 genes. This full complement is found inside the nucleus of most every cell. Although we each inherit two copies of every type gene, there are, in fact, several different versions of each gene floating around in the population’s overall gene pool, any of which may be inherited. Versions of the same gene can differ by just a few bases.

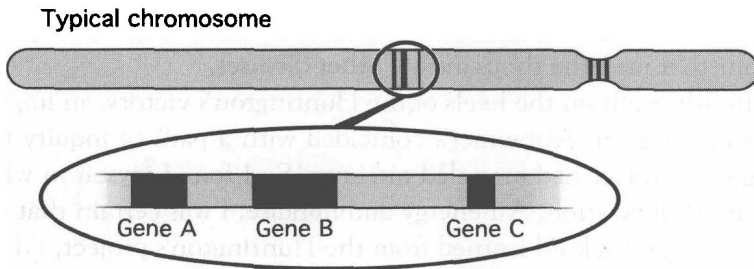


FIGURE I.1 Genes interspersed along a chromosome.  
Illustration: Robert D. Moir



Since genes and proteins are so central to the story that follows, pretend, as I often do, that they're characters in a play. Like kings, genes more or less stay seated on their thrones inside the nuclei of cells. But most every gene imparts its crucial code for the making of a protein, proteins being the slaves of the biological world. Once encoded by genes, proteins take care of nearly every function necessary to an organism's survival. In humans, this work ranges from building tissues for organs, to making enzymes that exert chemical changes for food digestion and other necessities, to practically everything else that keeps the body's trillions of cells happy and ticking.

Most important, genes provide the instructions for proteins. The structure of a gene and its corresponding protein therefore are interrelated. If a gene happens to contain a serious flaw, or mutation, in its lineup, the making of its protein can be aborted. Sometimes, however, a defective protein survives, and its faulty amino-acid structure mars its normal activity. Depending on how much it deviates, this can lead to a specific disease.

In 1980, by a stroke of considerable luck and timing, I happened to join a team that went on to demonstrate a novel technique for finding disease genes and their proteins. Back then, very few human genes had been identified. They lay in the blackness of a cell's nucleus, absolutely tiny and inscrutable. For a twenty-one-year-old who was enthralled with genes to begin with, to land on the doorstep of this undertaking (headed by James Gusella at Mass General) was beyond any dream I had for a career. The experiment involved trying to locate the gene defect that underlies Huntington's disease, a neurodegenerative disease, which like Alzheimer's probably has damaged humanity since Cicero's day. The extraordinary outcome not only put the Huntington's gene and its defect within reach, but gave researchers a trick that sent them chasing the gene faults that underlie thousands of other diseases.

Fortuitously, right on the heels of the Huntington's victory, an important breakthrough in Alzheimer's coincided with a path of inquiry the Huntington's project had funneled me onto. So I found myself in what seemed an ideal position. All energy and impulse, I was certain that if I applied the same trick I'd learned from the Huntington's project, I'd locate the mutant gene responsible for the rare, early-onset form of Alzheimer's—a first step that might lead to a treatment for both early and late forms of the disease.

Little did I or others embarking on the same investigation realize the morass we were heading into. The total detective work into Alzheimer's since then, which has been carried out by a swelling universe of scientists from different disciplines and continents, has been anything but straightforward. Yet in less than two decades we've gone from knowing little about what causes Alzheimer's dementia—which is the outward manifestation of severe brain-cell degeneration—to knowing what goes wrong on several fronts. Exactly *how* it happens still eludes us nevertheless.

The thread for this book is the evolution, clue by clue, of one particular hypothesis that has gained widespread support. It poses such a believable explanation that not only have hundreds of us sold our souls to it, but nearly every large pharmaceutical company and countless biotech companies are in the process of crafting a new generation of drugs based on its general principle. As the year 2000 begins, the first of these treatments, having shown promise in mice, are just beginning the ultimate challenge—testing in humans. Even those of us who have contributed to the backbone of this hypothesis are apt to blink in amazement. Not long ago the idea of curbing cognitive loss seemed as futile as trying to stop a spring tide from going out. To now be at the point of testing drugs woven from this credible theory seems nothing short of a miracle.

Anchored in molecular genetics, the hypothesis in the spotlight has to do with amyloid plaques, the microscopic deposits of protein that abnormally inundate the brain tissue of Alzheimer victims. The premise behind the *amyloid hypothesis* is that these deposits—or their subunit fibril—are directly to blame for the brutal wasting of neurons. This theory represents the dominant viewpoint, but keep in mind it's only a theory. You might think because it's backed by such heavy betting there would be general agreement over it, but this is far from the case. Numerous experts from inside and outside the field still view any drug prototypes arising from it as a misinformed long shot.

While the amyloid hypothesis may be the most popular explanation for Alzheimer's, plenty of other theories and resulting drug designs still undergoing research and development have come into existence. Although *Decoding Darkness* examines these potential therapies in less depth, it endeavors to show that this rich range of prospects represents the true prize. There have been times when our field has been criticized

for crowing prematurely about how close we are to effective drugs. Yet today, derailing this scourge of an illness is no longer a dream but a distinct possibility.

Finally, the Alzheimer research field has gained a certain notoriety for being a fiery, truculent, and driven lot—moments of which we've allowed in here. What isn't talked about and written about is the considerable camaraderie that, through the years, has grown up among so many of us. While we may not always see eye to eye, we are stuck together like Velcro against a much bigger foe. Hats off to all those many colleagues, and may we soon know the answer.

The proud father relayed the news over a candlestick-style telephone to family and friends in Agawam, Massachusetts, and beyond. “It’s twins! God Bless! Lil has given birth to identical twin girls!” Before long, tiny Julia and Agnes Tatro were taking their first tottering steps and trailing each other into mischief. They were the spitting image of each other, from their wispy flaxen locks to their knobby knees—except for the deep dimple that Julia wore on her left cheek and Agnes wore on her right. It was the 1920s, the days of new-spinning Victrolas and sporty Model Ts; of old-fangled doctors whose black bags contained, first and foremost, a stethoscope and vials of morphine. Medicine’s reach was skin-deep; the source of most ills too complex to grasp. People knew about genes—in the case of identical twins, their identical set—but they were as distant as magma at the earth’s core, and no one knew what they were made of or the good or bad extent of an individual’s inherited array. And so, even as Julia and Agnes Tatro blossomed into pretty, spunky girls who reached out to life, no one suspected what lurked beneath the surface. And it gave no sign of itself. It inched along its harmful course in too quiet a way, just as, in all likelihood, it had been doing even before their mother knew she was pregnant.

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# Cleave, Zap, Blot, Probe

*It came like a lightning flash, like knowledge from the gods.*

—Edward O. Wilson, “Naturalist,” on

Watson-Crick 1953 discovery of DNA’s structure

At twenty-one and fresh out of college, I entrusted myself to the Taoist philosophy that the less you interfere in Nature’s course, the more likely you will find your true path in life. This wisdom flowed from a slip of a book I’d discovered in high school—the *Tao Te Ching*. In retrospect, it would seem that giving myself up to “the way of things” succeeded, because that fall, out of the blue, an opportunity of a lifetime presented itself, one that introduced me to a spectacular new scientific method and later prompted my investigation into the genetic wrongs of Alzheimer’s disease.

It was a cloudy September Saturday in 1980, and after the quiet of summer, Boston seemed energized by autumn’s return. Beacon Hill’s narrow streets were clogged with cars, its crooked-brick walks filled with residents and students who seemed all business. On the Charles River even the sailboats crossing the watery line between Boston and Cambridge flew forward at a clip. A few blocks east on Blossom Street, which curves behind Massachusetts General Hospital, members of the rock band Fantasy and I moved more like laden barges. Sleep-deprived and hungover from the previous night’s fling, we nonetheless managed with an elevator’s aid to move the band’s musical equipment into the Flying Machine, the nightspot atop the Holiday Inn that attracted everyone from visiting Portuguese sailors to the occasional Brahmin.

Four months earlier, in May of 1980, the University of Rochester had sent me into the world with what I hoped would be sufficient padding—



bachelor's degrees in both history and microbiology. The one, Time Past, had filled me with an indelible impression of the patterns and trends that span recorded centuries. The other, Emergings of Time Future, had left me startled by the phoenix soaring out of the present—the molecular-genetics revolution. Biology's horizon was filled with elaborate possibilities far beyond the imaginings of such tour-de-force microbe hunters as Louis Pasteur, Robert Koch, and Paul Ehrlich.

In the course of my history studies, I'd devoured Thomas Kuhn's *The Structure of Scientific Revolutions* and taken away his valuable model. One set of beliefs ascends over time, then falls under the weight of a crisis, which inevitably ushers in yet another belief system that rises and similarly collapses, and so on, until there's a sense, as from a wave rolling forward, that you can extrapolate the nature of the next crisis and the new visions it will unfold. Now a scientist, I'm even more aware that the models we put our faith in are mostly wrong. Someday they will be as outmoded as the idea, imagined by Franz Mesmer in the eighteenth century, of how to relieve people of disease: Stand them across from healthy folk in a tub of water, have both groups grasp a long metal chain, and let the positive forces of animal magnetism flow from the healthy into the infirm, miraculously curing them. For scientific revolutions to take flight, current theories have to be questioned, the status quo disrupted. Since my years at Rochester, I've always wanted to induce the next crisis, inspire the next paradigm shift. This is the challenge of science—to shed dogma and get closer to the truth.

But scientific revolutions were the furthest thing from my mind that Saturday atop the Holiday Inn. I was in the throes of a postcollege existentialist crisis. Why did I exist? What *was* life? Living life as a bushy-haired, scruffy musician and playing keyboard once again with my musician friends from high school days seemed the best way to regain some perspective. When I was ten, my Uncle John had let me fold and unfold the huge red accordion he played in old-age centers around our hometown of Cranston, Rhode Island, and from then on I'd been glued to the keys of pianos, electric organs, and synthesizers. Blues, jazz, rock, punk, improv, some classical. One form fed another. I'd come to realize that when I played music on a daily basis—even on an informal basis, as I had throughout college—life was always better. When I didn't, disaster struck.