In the Genome Race, the Sequel Is Personal

By NICHOLAS WADE

The race to decode the human genome may not be entirely over: the loser has come up with a new approach that may let him prevail in the end.

In 2003, a government-financed consortium of academic centers announced it had completed the human genome, fending off a determined challenge from the biologist J. Craig Venter. The consortium’s genome comprised just half the DNA contained in a normal cell, and the DNA used in the project came from a group of people from different racial and ethnic backgrounds.

But the loser in the race, Dr. Venter, could still have the last word. In a paper published today, his research team is announcing that it has decoded a new version of the human genome that some experts believe may be better than the consortium’s.

Called a full, or diploid genome, it consists of the DNA in both sets of chromosomes, one from each parent, and it is the normal genome possessed by almost all the body’s cells. And the genome the team has decoded belongs to just one person: Dr. Venter.

The new genome, Dr. Venter’s team reports, makes clear that the variation in the genetic programming carried by an individual is much greater than expected. In at least 44 percent of Dr. Venter’s genes, the copies inherited from his mother differ from those inherited from his father, according to the analysis published in Tuesday’s issue of PLoS Biology.

Huntington F. Willard, a geneticist at Duke University who has had early access to Dr. Venter’s genome sequence, said that the quality of the new genome was “exceptionally high” and that “until the next genome comes along this is the gold standard right now.”

Dr. Willard said it was “hugely better” than the consortium’s sequence, at least for his particular research interest.

“I don’t want to fan the fires but I like this, it’s a really good genome,” said Edward M. Rubin, a genome expert at the Lawrence Berkeley National Laboratory.

Dr. Venter’s race with the consortium began in 1998 when he spotted a quicker method of decoding the human genome. He tried to wrest this rich scientific prize from his academic rivals by co-founding a genome-decoding company called Celera. By June 2000, the two sides were neck and neck preparing a draft sequence of the genome. But in January 2002, Dr. Venter was abruptly fired as president of Celera. The consortium went on to claim victory when it announced its completion of the genome the next year.

But the consortium’s genome, though immensely useful to biologists, was full of gaps and only complete in the sense that it was the best that could be done with existing technology.

Dr. Venter has spent the last five years and an extra $10 million of his institute’s money in improving the draft genome he prepared at Celera. That genome was based mostly on his own DNA, and the new diploid version is
entirely so. His critics may accuse him of an egocentricity of considerable dimension, but by analyzing his own genome he has sidestepped the problems of privacy and consent that could have arisen with other people’s DNA when he made the whole sequence publicly available, as he is doing now.

Like James Watson, the co-discoverer of DNA, whose genome is also being decoded, Dr. Venter believes strongly in making individual DNA sequences public to advance knowledge and hasten the era of personalized genomic medicine.

If other experts find that Dr. Venter’s genome is the best available, could it be said that he won the human genome race after all?

“There is this long history of Craig’s vanity, which for much of the scientific community is irritating,” Dr. Rubin said, declining to give a direct answer.

Asked the same question, Dr. Venter replied: “I’m not sure I’d want to be the one to say that, but we’re not through racing yet. I’ll let you know when we’ve stopped.”

James Shreeve, author of “The Genome War,” said, “I think he already believes he’s the true winner of the genome race for what he did at Celera,” noting that the consortium, too, believed it had won.

Though there are now novel technologies for decoding DNA very cheaply, Dr. Venter’s genome sequence could set a high bar for a long time. It was decoded with an old method, known as Sanger sequencing, that is expensive but analyzes stretches of DNA up to 800 units in length. The cheaper new technologies at present analyze pieces of DNA only 200 units or so long, and the shorter lengths are much harder to assemble into a complete genome.

Dr. Watson’s genome is being decoded with a next-generation machine developed by 454 Life Sciences. But the company’s researchers are putting the pieces in correct order by matching them to the consortium’s genome sequence rather than by doing an independent assembly.

Dr. Venter’s genome could be the gold standard for many years, especially if he continues to improve it. Samuel Levy, who led the J. Craig Venter Institute team that decoded the genome, said that it was a work in progress and that new versions would be published as the remaining gaps were closed. There are 4,500 gaps where the sequence of DNA units is uncertain, and no technology yet exists for decoding the large amounts of DNA at the center and tips of the chromosomes.

Biologists studying variation in the human genome, whether to discover causes of disease or for other reasons, have mostly looked at what are called SNPs or “snips,” which are sites on the genome where a single unit of DNA is changed.

But there are other kinds of variation, all of which can have consequences for a person. One type is called indels, where a single DNA unit has either been inserted or deleted from the genome. Another is copy number variation, in which the same gene can exist in multiple copies. There are also inversions, in which a stretch of DNA has been knocked out of its chromosome and reinserted the wrong way around. Dr. Venter’s genome has four million variations compared with the consortium’s, including three million snips, nearly a million indels and 90 inversions.

“This is the first time that anyone has had an accurate representation of how much variation there is in a human genome,” said Stephen W. Scherer of the University of Toronto, a co-author of the study.

Biologists had estimated that two individuals would be identical in 99.9 percent of their DNA, but the true
The genome is being made publicly available on the database operated by the National Center for Biotechnology Information and is free for any use. Dr. Venter said he would add phenotypic information to the version on his own Web site, meaning medical records and other data to help researchers correlate his bodily characteristics with his DNA.

What little is understood about the human genome at present consists mostly of medical variants that put people at risk of disease. So interpreting a genome brings mostly adverse news. Dr. Venter reports that he has variants that increase his risk of alcoholism, coronary artery disease, obesity, Alzheimer’s disease, antisocial behavior and conduct disorder.

But these predictions are far from certain. As more individual genomes are decoded, the information from them will become more valuable, Dr. Venter said, provided that people can overcome “irrational fears of even seeing their genetic code.”

Although Dr. Venter has decoded the DNA sequence inherited from both of his parents, he does not yet know which sequences are from his mother and which from his father. The issue could be resolved by analyzing DNA from his mother, who is alive and well, and the matter is under consideration, Dr. Levy said. Dr. Venter has traced his ancestry for three generations and found that his mother’s and father’s ancestors came from England.

Next month, Dr. Venter will publish an autobiography, “A Life Decoded.” The book describes the twists and turns that led him down the unlikely path into scientific research. “Rebellious and disobedient,” as he describes himself, he dedicated his teenage years to the pursuit of young women and the California surf, to the detriment of his academic career.

He was drafted at the time of the Vietnam war and enlisted in the Navy. Because of a high I.Q. score, he was given a choice of any Navy career, from nuclear engineering to electronics. He chose the hospital corps school, because it was the only course that did not require any further enlistment. Only too late did he discover the reason. Corpsmen in Vietnam did not usually survive long enough to re-enlist — the half-life of medics in the field was six weeks, he writes.

Learning how to manipulate the Navy bureaucracy, he got himself assigned to the Navy hospital in Da Nang, where chances of survival were better. But the work was harrowing. He witnessed several hundred soldiers die on his operating table, mostly when he was massaging their heart or trying to breathe life into them.

“I learned more than any 20-year-old should ever have to about triage, about sorting those you can salvage from those you cannot do anything for except ease their pain as they died,” Dr. Venter writes in the autobiography.

He escaped from Vietnam with his life and an interest in medical research. With his lack of academic skills, this was a hard field for him to break into, but by 1975 he had a Ph.D. By the late 1980s, he was starting to make his mark as one of the few scientists who could get useful results out of the first DNA sequencing machines that were then becoming available.

He was the first to sequence the genome of a bacterium, Hemophilus influenzae, even though his grant application was turned down by the National Institutes of Health on the advice of experts who said his method would not work. With the human genome, an even greater prize, the pace of competition was intense, especially when his approach turned out to be more efficient than the one his rivals had chosen.
In the book, Dr. Venter says that detractors badmouthed his work, pressured other scientists not to cooperate with him and tried strenuously to block publication of his report, of which they had earlier maneuvered to be made co-authors.

“Like most human endeavors, science is driven in no small part by envy,” he writes.

Dr. Venter has never fully lost his youthful disrespect for authority and establishments. His investment in himself — choosing his own genome to sequence, naming his laboratory the J. Craig Venter Institute — may come across as vainglorious, but it can also be seen as a signal of survival, defying the establishments he believes have sought to crush him. However nettlesome he may seem to some of his colleagues, he has the charm and the personal skills to have recruited many highly able researchers to his teams.

Another reason for his success has been his skill at raising private finances to achieve research goals after being denied support from the National Institutes of Health. That a scientist of his ability has been forced to work outside the N.I.H.’s peer-review system puts peer review in a strange light. If his diploid human genome should become a standard, the success is one that he will have earned by perseverance and defiance of long odds.