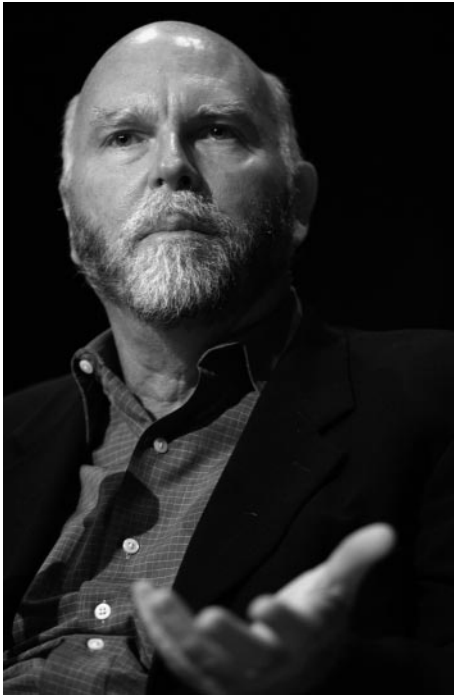
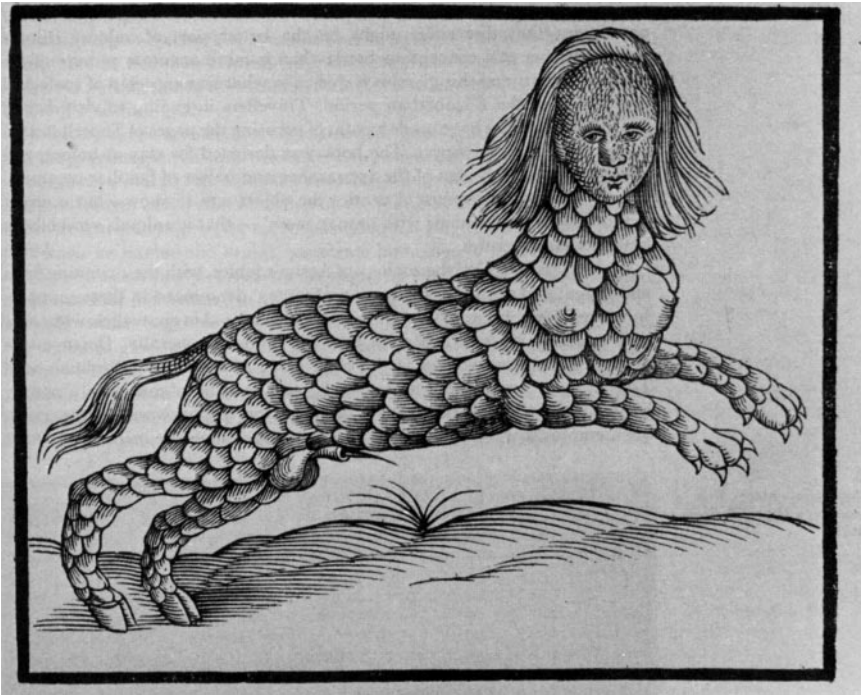


Mortal and Immortal DNA: Craig Venter and Keats' "Lamia"



Craig Venter (Getty images)



"Lamia" From Edward Topsell's *History of Fourfooted Beasts* (1607), courtesy MBL/WHOI Library (Woods Hole, MA, USA).

First Individual Diploid Human Genome Published By Researchers at J. Craig Venter Institute. Sequence Reveals that Human to Human Variation is Substantially Greater than Earlier Estimates.

Press Release: September 3, 2007 (1)

This theory suggests that only the differentiating cells will inherit the newly "photocopied" DNA strands, which contain errors. The stem cells retain the unmodified original DNA strands, which consequently remain "immortal" after repeated cell divisions.

G. Cossu, S. Tajbakhsh *Cell*, 2007 (2)

The capacity to blunder slightly is the real marvel of DNA. Without this special attribute, we would still be anaerobic bacteria and there would be no music.

Lewis Thomas "The Medusa and the Snail", 1979 (3)

DNA STRIKES BACK

When news arrived that the 2007 Nobel Prizes for Medicine or Physiology had been awarded to Mario Capecchi, Martin Evans, and Oliver Smithies for targeting genes in mice, it crowned the comeback of DNA (4). For two

decades now, fans of RNA have been lording it over those who study its deoxygenated sibling. Ever since Wally Gilbert announced the "RNA world" (5), and Sidney Altman and Thomas Cech discovered its enzymatic properties (6), RNA has been flying high. First, RNA interference (RNAi) became the molecule of the year (7); last year, RNAi picked up its glittering prize in Stockholm (8), and pretty soon, RNAi was roiling the stock market (9). That hadn't happened to DNA for a while. Like the Korean War, Crick and Watson's double helix goes back to 1953; Meselson and Stahl worked out the chemistry of its replication in 1958; Roberts and Sharp defined the ins and outs of the DNA lexicon back in 1977 (10). Even the Capecchi/Evans/Smithies work dates to 1989 (4), and the knockouts they made can now be ordered on-line. By the time the haploid human genome was announced to great fanfare in 2001, a lot of us thought that DNA was old news. It may have been the "Book of Life" for geezers, but young folks viewed all of those megabytes in the GenBank as just another on-line catalogue (11). Canonical runs of DNA were good enough for Post-Docs making photocopies, but for a kinetic, 3-D look at how genes work, the smart money was on RNA.

All that changed in the last two years. In the first place, Craig Venter added a surprising companion to the genome catalogue: The Book of Life turned out to contain more typos and misprints than anyone predicted (1). Equally unexpected was the discovery that the dull routine of DNA replication has a novel twist: One strand of the double helix turns out to be “immortal,” at least in stem cells (12).

DIPLOID DNA

In September, J. Craig Venter and colleagues (13) made public the DNA sequence of his own 46 chromosomes. The original human genome sequences, reported in 2001—that Book of Life—relied on data from a haploid set of 23 chromosomes derived from a pool of donors. Venter’s diploid genome, derived from one paternal and one maternal set of chromosomes, suddenly made DNA much more interesting. Earlier genome sequencing projects, which attributed the bulk of human-to-human variations to single-nucleotide polymorphisms (SNPs; changes in single DNA bases), had stopped with sequences of approximately 13,000 bases. However, Venter’s group was able to define runs of DNA hundreds of thousands of bases long. Comparing alternate alleles with those registered by the National Center for Biotechnology Information, Venter and colleagues (13) identified more than 4.1 million DNA variants. Encompassing 12.3 megabases, the variants yielded a surprise: 44% of the genes Dr. Venter inherited from his mother were different from those that came from his father. One-third of these variations had never been described and were by no means limited to SNPs.

Venter’s institute soon spread the news that human beings turn out to be much less alike than we ever suspected, at least five times less. Human-to-human variation, it proclaimed, is clearly greater than the 0.1% difference found in 2001. The new estimate was that genomes vary between individuals by at least 0.5% (13). The large number of variations has implications for genetic screening. In the near future, it seems likely that we will be able to choose whether or not to know our own diploid genome. Should we? Variation gives hope to the genetically challenged: If one parental strand has a spelling error, it is always possible that there is a SpellCheck[®] hidden in the other.

Venter told the press, “I might want to know: Do I have an additive risk from the genomes from both my parents, or did I get some helpful ones from her that counteract the ones from him?” (14). Others may not want to know: At a recent public event Charlie Rose asked Nobelist Joseph Goldstein of Dallas whether he was curious to know his genetic print-out. Goldstein replied, “Look, if there is no more than a 15–20% concordance for colon cancer between identical twins who have 100% identical genomes, I’d get a colonoscopy” (15).

IMMORTAL COILS

*“For in that sleep of Death what dreams may come
When we have shuffled off this mortal coil. . . .”*
Hamlet

Perhaps it’s not surprising that two parental genomes compete for our phenome, as we all have two parents. What’s more astonishing is that the two complementary strands of DNA don’t always uncoil equally when our cells divide. In 1975, John Cairns of Oxford (16) floated the notion of “immortal DNA.” He noted that our tissues contain stem cells and differentiating cells, and since differentiating cells replicate quicker than stem cells, their DNA is a better target for the slings and errors of frequent replication. Stem cells, which replicate very slowly, would be likely to hold on to the original, error-free strands of DNA. That seemed a reasonable explanation for why the most rapidly replicating cells in our body (e.g., in skin, gut, or mammary glands) are more likely to become malignant. In this process, now defined as “asymmetric self renewal” (12), each adult stem cell undergoes a division that yields a new, pristine adult stem cell and its error-prone sister, which is the progenitor of the differentiated cells in the tissue. The mechanism of asymmetry is obscure (17).

Although Cairn’s theory has led to lively and at times amusing debate (12, 17), recent studies support immortal DNA. Jim Sherley’s laboratory (18) at Massachusetts Institute of Technology (Cambridge, MA, USA) was the first to show that individual mammalian cells in culture can undergo asymmetric self-renewal, and the process was soon documented in neural cells (19). Further confirmation came one year ago from the Institut Pasteur (Paris, France). By following the fate of mouse satellite cells (muscle stem cells) in the course of cell division, the laboratory of Shahragim Tajbakhsh (20) confirmed that stem cell DNA strands are distributed asymmetrically, but the chemistry of DNA asymmetry remains as much of a puzzle in Paris as it was in Oxford. Tajbakhsh confessed, “How the cellular machinery distinguishes old DNA from new is still a mystery. For me, it is one of the most fascinating questions regarding DNA since the double helix was first described” (21).

Not to worry, *cher maitre*, I’d say. The mystery of asymmetry between mortal and immortal coils has been around a lot longer than the double helix.

THE CADEUCEAN CHARM

The serpentine image of DNA has resonance with others in our collective history. From Apollo to Adam and Eve, Aesculapius to Moses, and Hygea to Hermes, the coiled serpent has guarded mystery, knowledge, and healing. The caduceus, winged at the top and encircled by twin serpents, is the symbol of Apollo’s

power and the eternal magic of snakes. The pythons who guarded Apollo's temple were believed to share with their master the divine arts of prophecy and healing, *i.e.* of prognosis and therapeutics. Aesculapius appeared in the dreams of his patients as an undulant snake, and Hygea was depicted with cup and adder. The caduceus was Apollo's gift to Hermes in trade for a stolen lyre, and Hermes used his wand to transmute species and to spell out their fate.

Nowadays, we've learned to play Hermes in the lab. Over 50 years ago, Joshua Lederberg discovered homologous recombination in bacteria. Then Capecchi, Evans, and Smithies taught us how to recombine genes to engineer mice. Their Nobel citation explained, "It is now possible to introduce mutations that can be activated at specific time points, or in specific cells or organs, both during development and in the adult" (4). Transmutation and fate: what concordance between the myths of the ancient world and the latest news from Stockholm!

What we've also learned from knock-out and knock-in experiments is that if you know the genome, you can predict those "mutations that can be activated at specific time points" to affect you or your offspring. However, do we really want to know what mutations are entwined in our own diploid genome? Venter and colleagues (13) addressed those doubts in their *PLoS Biology* paper:

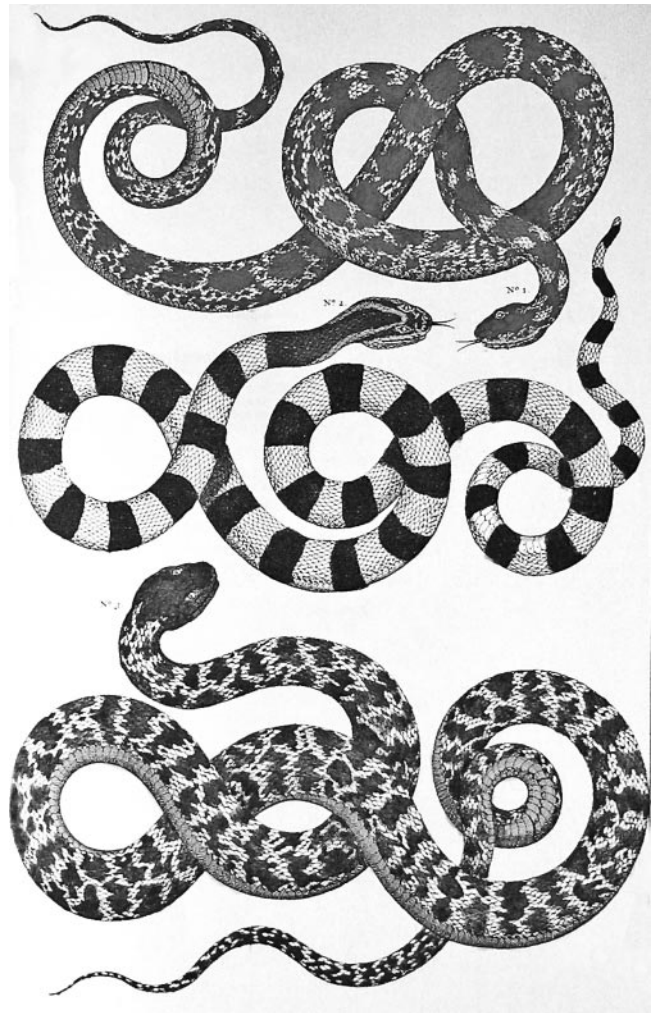
There are often concerns that individuals should not be informed of their predisposition (or fate) if there is nothing they can do about it. It is possible, however, that many of the concerns for predictive medical information will fall by the wayside as more prevention strategies, treatment options, and indeed cures become realistic. The cycle, in fact, should become self-propelling, and reasons to know will soon outweigh reasons to remain uninformed.

KEATS' LAMIA

*The ever-smitten Hermes empty left
His golden throne, bent warm on amorous theft;
For somewhere in that sacred island dwelt
A nymph, to whom all hoofed Satyrs knelt. . .
Lamia (22).*

Nowhere in literature are Venter's "reasons to know" better defined than by John Keats' poem *Lamia*. These days, *Lamia* can be read as a commentary on DNA itself: the split between mortal and immortal coils, the tricks of homologous recombination, and the penalty of remaining uninformed.

Lamia begins with the ever-smitten Hermes leaving golden Olympus to chase a nymph over hill and dale in Crete. The nymph becomes lost, and Hermes is forlorn, but suddenly, the messenger stumbles across a coiled creature,
. . . a palpitating snake,
Bright, and cirque couchant in a dusky brake.
Her head was serpent, but ah, bitter-sweet!
She had a woman's mouth with all its pearls complete
(22).



From Albertus Seba, *Cabinet of Natural Curiosities*, 1734–1765, courtesy MBL/WHOI Library (Woods Hole, MA, USA).

The reptile, a hybrid of mortal and immortal strands, exacts a promise from Hermes to transmute her into human form. In return for the gift of recombination, Lamia will tell Hermes where his nymph is hidden. It all works as promised: The nymph is found, Hermes exults, and hybrid Lamia swoons. Fulfilling his part of the bargain, Hermes turns with snake-entwined wand,
*To the swoon'd serpent, and with languid arm,
Delicate, put to proof the lythe Caducean charm. . .
Left to herself, the serpent now began
To change; her elfin blood in madness ran. . . .*

What a romantic precedent for homologous recombination and rapid differentiation! However, Lamia is more than just a pretty, transgenic face. As she was constructed to retain and express on induction the serpentine genes of passion, she became:

*A virgin purest lipp'd, yet in the lore
Of love deep learned to the red heart's core. . .*

Thus, equipped, Lamia hurries to Corinth, where she ensnares a young philosopher (read: scientist), Lycius. The two become enraptured with each other, but Lycius deliberately ignores the different worlds they

have inhabited. Soon enough, they exchange vows of wedlock.

Yet, at a drunken prenuptial feast, their fate is sealed. One of the wedding guests is Apollonius, a sophist, who has been Lycius' mentor. This "bald-head philosopher" (read: thesis advisor) spots Lamia instantly as a dangerous demon and fixes her in his withering gaze. When Apollonius denounces Lamia as a dangerous serpent, the beauty blanches. Lamia turns white, then cold, and suddenly vanishes into thin air. She has reverted to the demon world.


Lycius cannot bear this loss; he dies a languorous death of grief, having paid the final penalty for remaining willfully uninformed. The tale could be read as an augury of Venter's prediction that the reasons to know will soon outweigh the reasons to remain uninformed.

Keats (22), like many Romantics, worried that the Newtonians of the Royal Society had destroyed the beauty of the rainbow itself:

... Do not all charms fly
At the mere touch of cold philosophy?
There was an awful rainbow once in heaven:
We know her woof, her texture; she is given
In the dull catalogue of common things
Philosophy will clip an Angel's wings. . .
Unweave a rainbow, as it erewhile made
The tender-person'd Lamia melt into a shade.

Keats was afraid that exact knowledge of material nature, the dull catalogue of common things, would destroy not only esthetics but ethics as well. These days, we'd call that dull catalogue of common things our diploid genome ($\pm 0.5\%$) and hope that our ethics can cope with its challenge.

I find Venter's peroration in *PLoS Biology* (13) reassuring:

Ultimately, as more entire genome sequences and their associated personal characteristics become available, they will facilitate a new era of research into the basis of individuality. The opportunity for a better understanding of the complex interactions among genes, and between these genes and their host's personal environment will be possible using these datasets composed of many genomes. Eventually, there may be true insight into the relationships between nature and nurture, and the individual will then benefit from the contributions of the community as a whole. 

Gerald Weissmann
Editor-in-Chief
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