NEWS

All about Craig: the first 'full' genome sequence

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Controversial genomics pioneer Craig Venter has sequenced his own genome. In a preliminary analysis published this week (S. Levy *et al. PLoS Biol.* **5**, e254; 2007), Venter's team has picked apart the sequences belonging to both chromosomes in each of the 23 chromosome pairs found in his cells, providing the first glimpse of the variation found within a single genome.

The paper also highlights some features of Venter's genome. The sequence of his *ABCC11* gene, for example, indicates that Venter is likely to have wet earwax, as opposed to dry. In a finding likely to disappoint some critics of the maverick scientist, Venter has four repeat sequences located just before his *MAOA* gene. Having only three of the repeats is associated with an increased risk of antisocial behaviour. On a more sobering note, Venter's *APOE* sequence is associated with a higher risk of Alzheimer's and cardiovascular diseases, and his *SORL1* gene also contains several variants that are associated with Alzheimer's disease.

For more about his personal genomic and family history, Venter aficionados can refer to his upcoming book, *A Life Decoded*. Venter has placed references to how his genome sequence may have affected his life throughout the book, says Jan Witkowski, executive director of the Banbury Center at Cold Spring Harbor Laboratory in New York, who is reviewing the book for the 4 October issue of *Nature*.

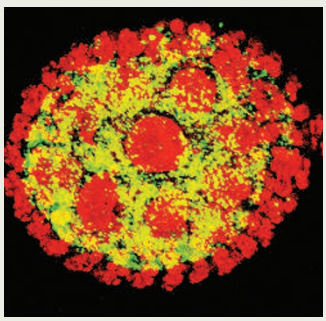
Venter's sequence also provides important new information about the human genome. Previous sequencing efforts have not distinguished between the two copies of each chromosome, or even between DNA from different donors. "What we were doing was mixing up alleles," says Samuel Levy — who led the study at the J. Craig Venter Institute in Rockville, Maryland — referring to DNA sequences from specific spots on the chromosome. "We were creating Frankenstein versions of chromosomes."

This time, armed with an additional 13 million sequences — added to the 19 million generated from Venter's own DNA during the first genome project — and fresh algorithms designed to pick apart sequences from different versions of the same chromosomes, Levy and his team could look at the variation within the genome. They found more than 4 million vari-

Genomes within genomes

Another team of genome researchers at the J. Craig Venter Institute in Rockville, Maryland, which has been investigating the DNA of a rather less salubrious organism, this week reports a surprise discovery: the DNA of fruitfly *Drosophila ananassae* contains the entire genome of a parasitic bacterium of the *Wolbachia* genus. Smaller parts of the parasite's genetic material also turned up in worms and wasps.

Bacteria commonly swap DNA with each other. But transfer of bacterial genes into animals was thought to be rare. The new work, published in *Science* (J. C. Dunning Hotopp *et al. Science* doi:10.1126/science.1142490; 2007), suggests that gene flow from bacteria to animal hosts happens on a larger scale and more commonly than suspected. And it hints that the bacterial genome may have provided some sort of evolutionary advantage to its host. "You're talking about a significant portion of [the fruitfly] DNA that is now from *Wolbachia*," says Julie Dunning Hotopp, who led the study. "There has to be some sort of selection to carry around that much extra DNA."



Invader: *Wolbachia* bacteria (yellow) inside a developing fruitfly egg (red).

SCIENCE

But Dunning Hotopp's former colleague Jonathan Eisen of the University of California, Davis, contests this. "One cannot conclude that some DNA is advantageous simply because it is there," he says.

Up to 75% of insect species are plagued by *Wolbachia*, which lives inside testes and ovaries and passes from one female generation to another through infected ova. To ensure its spread, *Wolbachia* can skew insect birth ratios towards females and even prevent infected males from successfully mating with disease-free females. The bacterium's close association with egg cells means there's ample opportunity for bacterial DNA to get permanently sewn into a host's nuclear genome, says Dunning Hotopp.

When Dunning Hotopp and her colleagues analysed the DNA of *D. ananassae* uninfected by *Wolbachia*, they found 44 of the 45 *Wolbachia* genes they searched for. Because these selected genes are so widely spread throughout *Wolbachia* DNA, this suggests that the rest of its more than 1-million-base-pair genome is also likely to be found in fruitflies.

Many of the *Wolbachia* genes were infiltrated by strands of insect DNA that jump around the genome, and so are unlikely to be functional. But the researchers showed that at least 28 of the bacteria's 1,206 genes are active in the flies. More genes that have seeped from bacteria into animals are certain to be found, the researchers say, particularly in reptiles and amphibians. But finding bacterial genes in mammals is unlikely because no bacteria are known to infect their sperm and egg cells. ■

Ewen Callaway

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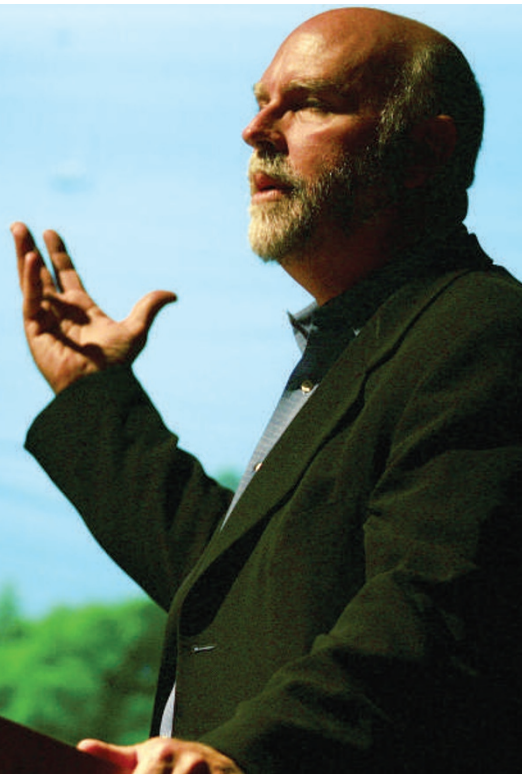

The man within: enthusiasts will be able to examine the genetic make-up of Craig Venter.

ations between the two sequences, including single nucleotide differences, sequence insertions and deletions, and differences in the number of copies of a given gene. Some 44% of Venter's genes contained a genetic difference between copies found on each chromosome. Venter's two sets of chromosomes differed by 0.5%, suggesting that there may be seven times more DNA variation than previously expected, says Levy.

This approach provides a clearer picture of the human genome, says Edward Rubin, director of the Joint Genome Institute in Walnut Creek, California. Before, the sequence gave a "statistical view" of the genome, Rubin says. "And in fact the genome is not statistical, it's really a linear array of bases."

Venter notes that single genetic changes are unlikely to seal his fate. "I take it very seriously," he says. "But most diseases are going to be some huge compilation of human factors and environmental factors." Witkowski agrees, but says that reading about someone's genome can strike an emotional chord. "Somehow there's a sense that when you tell people that sequence, you're telling them in a very deep way about yourself," he says. "It's like looking at their medical records." ■

Heidi Ledford

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DNA probe finds hints of human

A groundbreaking analysis of Neanderthal DNA that suggested they interbred with humans was based on samples contaminated with human DNA, a new study suggests.

The study[1], published on 28 August in *PLoS Genetics*, reanalysed about one million base pairs of fossilized Neanderthal DNA that had been analysed in a paper published last November in *Nature*[2]. The *Nature* paper and a paper in *Science*[3] published the same week on 65,000 base pairs were the first reports on Neanderthal nuclear DNA.

But around 80% of the sequences in the *Nature* paper are modern human DNA, not Neanderthal, claims Jeffrey Wall, an evolutionary geneticist at the University of California, San Francisco, who led the *PLoS Genetics* study. This indicates that human genetic material was somehow introduced into the samples. This known risk is increased by the closeness of the two species — the 3-billion-base-pair genomes of a human and a Neanderthal differ by less than 0.5%.

The results in the *Nature* paper suggested that there was interbreeding among Neanderthals and humans in their common European home ground before Neanderthals became extinct 30,000 years ago. The *Science* article found no genetic evidence of interbreeding.

Svante Pääbo, senior author of the *Nature* paper, concedes that his group at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, had problems with contamination. These prompted him to change laboratory procedures and to add controls late in 2006, after the paper was published. "I agree with [Wall's] analysis," Pääbo says. "Their observations are formally correct."

J. TRUEBA/MSF/SPL

Neanderthal DNA has been reanalysed, leading to suggestions of human DNA contamination.

Pääbo's co-author Michael Egholm, who is research vice-president at 454 Life Sciences in Branford, Connecticut, adds: "There is no denying contamination. It was one of the dangers of doing this." But ongoing analysis indicates that human contamination in their study was just 30%, Egholm adds.

There had been intense debate over the contrasting results in the *Nature* and *Science* papers, which analysed the same 38,000-year-old Neanderthal bones from Croatia using different sequencing methods. Pääbo's group used 454's rapid 'direct sequencing' approach, whereas the *Science* team, led by Edward Rubin of the Joint Genome Institute in Walnut Creek, California, used a traditional method using cloned DNA and bacteria to generate the base pairs.

The studies gave different estimates for the time Neanderthals diverged from humans — the *Science* article pegged it at 706,000 years ago, whereas the *Nature* paper set it at 516,000 years ago. Wall's study confirms the 706,000-year divergence date. The probable human DNA contamination led to the more recent date and may have led to the suggestion of later interbreeding, Wall says.

The *Nature* paper also found more similarities between genetic variations called SNPs (single nucleotide polymorphisms) in Neanderthal and human DNA than the *Science* paper, even after allowing for the *Nature* group's larger number of base pairs. Pääbo's team reported that about 30% of the SNPs in the Neanderthal DNA are derived — that is, the mutations occurred — in today's humans.

Pääbo acknowledges there is "a potential problem" with the presence of these human SNPs in the Neanderthal sequence. These same discrepancies were noted by Rubin's group. "We had concerns," says Rubin. "We suspected some of the issues raised by Wall."

Both Pääbo's and Rubin's groups expect to publish further Neanderthal sequences from other specimens that each group is studying. Pääbo and Egholm say their analysis will address the anomalies in their *Nature* paper. ■

Rex Dalton

1. Wall, J. D. & Kim, S. K. *PLoS Genet.* doi:10.1371/journal.pgen.0030175.eor (2007).
2. Green, R. E. *et al. Nature* **444,** 330–336 (2006).
3. Noonan, J. P. *et al. Science* **314,** 1113–1118 (2006).