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Gourmet's Delight, A Poisonous Fish Offers Streamlined Genome Project

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By *Tom Hollon*

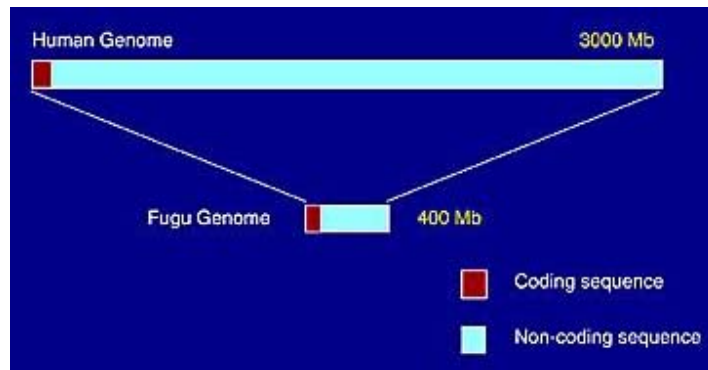
Preparing to eat a platter of Japanese puffer fish—the gastronomic equivalent of bungee jumping—requires confidence in the chef. That's why not just anyone can prepare them. A special license is required as proof the cook knows his chops, and so won't let puffer on the palette become a mouthful in the morgue. For the wrong morsel of Fugu rubripes between chopsticks means a taste of tetrodotoxin, a deadly nerve poison. Served raw, broiled, or in soup, dinner companions like to kid each other about the fish parts they hope aren't there—"Do you feel the tingling?" Dining on puffers is so popular in Japan that restaurants rely on fish farms to keep the costly delicacy in steady supply.



Sydney Brenner's involvement with puffer fish comes from his interest in their scientific value rather than their exotic cuisine. Brenner, one of the founders of molecular biology, sees them not so much as fish on a plate as genes in a database. And their availability from fish farms is for him a practical matter, weighed in his decision to launch a project to sequence the puffer fish genome.

The reason for a Fugu genome project, Brenner avows, is that "it's the quickest way to find all the [human] genes." Years ago, he realized that vertebrates were too complex and closely related for there to be many differences in their structural genes. Vertebrates' morphological differences follow from differences in gene regulation. "You have the same alphabets, all the same words, if you like, but you write different stories with them," he says. Brenner also realized that a genome project for a model vertebrate, ideally one with a small genome, would be valuable for interpreting the human genome. The ideal he found is Fugu.

Gene coding sequences are about the same size for Fugu and humans; both have about 50,000 genes, by Brenner's estimate. The fish's lure for Brenner is that the rest of its genome is streamlined: introns are small; genes are close together; repetitive DNA sequences are few. Fugu's genome is compressed into one-eighth as many bases as homo sapien's.



And compaction is a compelling virtue for genome exploration: "You can discover the genes more easily because there is no junk," says Brenner, "and then you can go and find them in man." He says human gene hunting will be harder and costlier with mouse or zebra fish genes because of their more abundant non-coding DNA. And he notes that locating human genes by homology comparisons with yeast, fruit flies and nematode

genes (genome sequences are finished for all three) is also harder, because their greater evolutionary separation from humans means gene sequences are less conserved.

Another asset is that genes located close together in Fugu are frequently similarly situated in humans. Brenner estimates linkages of up to 10 genes at a time will be conserved between the two species. The Fugu project has already exploited conservation of location to pinpoint human genes.

With so much in favor of a Fugu genome project, Brenner unfortunately reports less than 1% of its sequence has so far been completed.

The reason is that Fugu is starved for public support. Part of the problem is that money is already committed for mouse and zebra fish genome projects. Short of cash for sequencing, Brenner and his colleagues are doing related experiments, like demonstrating that Fugu genes are correctly expressed in transgenic mice. Their work is being carried out at the Human Genome Mapping Project Resource Center in Great Britain, the Institute of Molecular and Cell Biology in Singapore, and Brenner's lab at the Molecular Sciences Institute in Berkeley, CA.

With empty pockets, Brenner has called his the only privately owned genome project in the world. But he remains encouraged. He figures there is a lot of surplus sequencing capacity around, and believes he needs only patience: "I'm pretty sure that sooner or later, someone will see the virtue of Fugu. Any one of the large sequencing organizations would have the capacity to do it in a matter of months."

Tom Hollon is a science writer and editor based in Rockville, MD. He was the founding editor of the journal *Modern Drug Discovery*. Prior to that, Tom conducted research at the National Institutes of Health, the Pasteur Institute, and the University of Washington. Tom can be reached at thollon@starpower.net.

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