

Comment

## Fish tale

Gregory A Petsko

Address: Rosenstiel Basic Medical Sciences Research Center, Brandeis University, Waltham, MA 02454-9110, USA.  
E-mail: [petsko@brandeis.edu](mailto:petsko@brandeis.edu)

Published: 27 August 2002

*Genome Biology* 2002, **3(9)**:comment1012.1–1012.2

The electronic version of this article is the complete one and can be found online at <http://genomebiology.com/2002/3/9/comment/1012>

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OK, I promise to try to keep the fish jokes to a minimum, but it won't be easy. The draft sequence of the genome of the Japanese pufferfish, *Fugu rubripes*, has just been announced (Aparicio *et al.*, *Science*, 25 July 2002; 10.1126/science.1072104) and the temptation to humor is great. *Fugu* displaces the nematode worm as the most intrinsically humorous organism to have had its genome sequenced, the *Caenorhabditis elegans* folks having finally wriggled out of that embarrassing situation. It used to be thought that pufferfish had little to offer beyond a good dinner and an opportunity for sudden death, but now the scales, so to speak, have fallen from our eyes. Genetically speaking, *Fugu* is full of riches, right up to the gills, as it were.

The pufferfish gets its name from its habit of puffing itself up into a spiky ball three times its normal size when attacked. If this rather impressive display fails, it still has another strategy for survival. Inside its liver and ovaries lives a symbiotic bacterium, *Pseudoalteromonas haloplanktis tetraodonis*, that produces tetrodotoxin, a deadly neurotoxin that blocks voltage-gated ion channels. Most predators leave the pufferfish alone as a consequence. Despite this, *Fugu* is one of the great delicacies of Japanese cuisine, and every once in a while someone preparing it at home will die a quite unpleasant death.

I vividly remember my first encounter with *Fugu* sashimi. I was dining with some collaborators and former postdocs in a little restaurant in a back alley in Kyoto that specializes in serving the white, almost translucent slices of raw pufferfish with a variety of accompaniments. The flesh of *Fugu* has a delicate, very slightly sweet flavor with no fishy odor at all; its texture is semi-firm, somewhat like spaghetti *al dente*. It was delicious. My dinner companions assured me that there was no risk involved: by law, *Fugu* chefs must undergo thorough training in removing the poison-containing organs and have to be licensed by the state. I had just relaxed completely when one of my friends suddenly gasped, clutched his throat with both hands, and slumped over the table. I jumped up

shouting for someone to call 911 - which of course isn't 911 in Japan - only to see him suddenly sit upright with a big grin on his face, while the rest of the party burst out laughing. Apparently, this is a fairly standard initiation rite for first-time *Fugu* consumers.

Ugly and toxic it may be, but to the genomicist *Fugu* is a thing of beauty. Its inflationary tendency does not extend to its genome. *Fugu* has the smallest known genome size of any vertebrate organism, about one eighth the size of the human genome. Yet the number of genes in its 365 megabases of DNA is 35,000-40,000, about the same as in the human or mouse genomes. It would seem that, as far as gene number is concerned, an animal is an animal is an animal. One reason for the compact genome size of *Fugu* is that dispersed repetitive DNA accounts for less than one sixth of the sequence, compared with 40% in humans; another is that the genes have fewer, shorter introns and coding regions occupy over a third of the genome. Thus it is much easier to identify genes, and their controlling regions, in the *Fugu* genome than it is in mammalian ones. Even though the pufferfish and man are separated by about 450 million years of evolution from their common vertebrate ancestor, it seemed likely to fellow *Genome Biology* columnist Sydney Brenner, who with his colleagues Sam Aparicio, Greg Elgar and Byrappa Venkatesh initiated the *Fugu* genome sequencing project in 1989, that knowledge of the fish genes would aid in identifying homologs in the human genome sequence, where genes are much harder to find because they represent only a small proportion of the total DNA. And since transgenic experiments in mice and *Xenopus* had already shown that mammalian and amphibian trans-activating factors are able to interact with *Fugu cis* elements to mediate cell- and tissue-specific gene expression, he also thought that *Fugu* genomic clones would be useful in dissecting locus control regions in mammalian and other cell lines and transgenic model systems. In short, *Fugu* and human genes get along swimmingly, to coin a phrase.

As usual, Sydney was right. Preliminary analysis of the 22 pairs of chromosomes in the *Fugu* genome (the project team is expected to complete the sequence and analysis by early to mid 2003) indicates that at least 75% of known human genes have a strong homolog in pufferfish. The members of the *Fugu* consortium (about which more in a moment) have already used the easily located *Fugu* genes to find about 1,000 previously unrecognized genes in the draft human genome sequence. More such insights are sure to come.

Published reports about the *Fugu* genome sequence have stressed the fact that the pufferfish genome is free from the enormous quantity of junk DNA that bedevils the genomes of the mouse and *Homo sapiens*. I'm not so sure that this is the correct conclusion to draw. The common ancestor of *Fugu* and mammals was a fish, and over the millions of years since their lines diverged most other vertebrates have undergone enormous morphological changes. Consider human evolution alone: in less than 250,000 years Cro-Magnon man has evolved into, well, us. Fossils of pufferfish ancestors, on the other hand, look very much like the contemporary carcasses that decorate the windows of little Japanese restaurants. I think one reason *Fugu* has either shed its junk DNA or never acquired it in the first place is that *Fugu* stopped doing any sort of meaningful evolution, genetically speaking, a long time ago. From which I draw two conclusions: that junk DNA is no such thing - it may in fact be the clay from which evolution fashions morphogenetic changes - and that people looking for other compressed genomes to sequence might look in other living fossils, like crocodiles and coelacanths.

The other interesting thing about the *Fugu* genome sequence is how it came about. It was done fast - less than two years after the consortium was formed in November 2000 - and it was done cheap, for only US\$10 million. The consortium consisted of the Institute of Molecular and Cell Biology in Singapore, which actually took up *Fugu* in the early 1990s following Sydney Brenner's urgings; the Joint Genome Institute of the Department of Energy in the USA; the UK Medical Research Council's Human Genome Mapping Resource Centre at the University of Cambridge; and the Institute for Systems Biology in Seattle in the USA. A whole-genome shotgun sequencing strategy was used, and, towards the end, the consortium made use of excess sequencing capacity at several private companies, including Celera Genomics of Rockville, Maryland, and Myriad Genetics of Salt Lake City, Utah. This paid use by public sequencing initiatives of technology at private sequencing companies would seem an excellent model for further large-scale genome sequencing efforts. The entire *Fugu* sequence is being deposited in the public domain. And the project would have languished without the initial interest and support from Singapore, proving that genomics has become a truly international science.

The success of the *Fugu* consortium must be frustrating for zebrafish devotees, who have the enormous advantage of genetics in their favorite organism. Perhaps the moral is that, if they want to obtain its genome sequence in a timely manner, they should cultivate a taste for zebrafish sushi.

(Note: Some of the locutions in this column may be obscure to non-native English speakers: they don't know how lucky they are to be off the hook.)