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Zebrafish genome helps in hunt for treatments

Sequencing boosts research on organism increasingly useful for modelling human diseases.

Ewen Callaway

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When scientists began sequencing the zebrafish genome in 2001, the model organism was a favourite of biologists studying early development of the brain and other organs. Few others found much use for the small, stripy fish with see-through embryos. More than a decade later, with its genome finally unveiled today, the zebrafish (*Danio rerio*) has become the go-to animal for researchers studying many human diseases — as well as those investigating new treatments.

“We have been waiting for this [genome] for some time,” says molecular geneticist Nicholas Katsanis at Duke University in Durham, North Carolina. He and his team use the fish to understand the effects of mutations they find in the genomes of sick children. “It’s going to help us accelerate what we have been doing”, which is to systematically study human paediatric diseases by looking at zebrafish analogues, he says.

A rough draft of the zebrafish genome was first made public in 2002, and researchers have updated the database periodically in the years since. The latest version, published online today in *Nature*[1], shows that zebrafish have more than 26,000 protein-making genes — the largest gene set of any vertebrate sequenced so far — and reveals their arrangement across the organism's 25 chromosomes. The genome sequence is now comparable in quality to the published human and mouse sequences, says project leader Derek Stemple, a genome scientist at the Wellcome Trust Sanger Institute near Cambridge, UK.

Mighty model

The updated genome underscores why this tropical freshwater fish has become so useful to human-disease researchers. Stemple’s team found that about 70% of human genes have a counterpart in zebrafish — a figure that jumps to around 80% for human genes implicated in disease.

The number of genes pegged to particular diseases is set to rise, as researchers increasingly sequence the individual genomes and exomes (the part of the genome that encodes protein) of patients who have mysterious diseases of unknown cause. In many cases, sequencing turns up mutations that have never been seen in humans before.

Katsanis and a growing number of researchers are now able to mimic the effects of these mutations into zebrafish to observe their effects and determine whether they might cause a similar disease to that seen in the original patient.

In December 2012, for example, Katsanis and medical geneticist Han Brunner at Radboud University Medical Centre in Nijmegen, the Netherlands, together with their colleagues, used this approach to identify a new genetic syndrome in humans. They described two unrelated boys, both of whom had an intellectual disability and strikingly similar facial features, including arched eyebrows and rounded noses. Exome sequencing showed that the boys shared a mutation in the gene *PACS1*. Expressing mutated *PACS1* in zebrafish embryos caused facial deformations in the fish, supporting the gene's key role in the boys' condition[2].

Using this technique, Katsanis and his team can identify the mutations underlying mysterious paediatric diseases in 80% of cases, he says. Zebrafish are especially useful for modelling childhood conditions, Katsanis says, because many such diseases originate during developmental stages, and it is easy to alter the activity of genes in zebrafish embryos. The genome released today will hasten such work, he says, because it will make it easier to match human and zebrafish genes.

Zebrafish are also speeding the search for treatments to diseases both common and rare, says Leonard Zon, a physician-scientist at Boston Children's Hospital in Massachusetts. The fish's small size makes it easy to screen thousands of drugs for the ones that improve zebrafish versions of human diseases. Using zebrafish, his team has identified two drugs that are now in early clinical trials in cancer patients.

And in unpublished work, Zon and his team have discovered a drug that might help to treat Diamond–Blackfan anaemia, a genetic disorder of the bone marrow that affects several hundred children worldwide. They did so by studying the zebrafish analogue of the mutation, and finding a molecule that altered its effects. "Having a small molecule that could rescue a fish mutant could make a difference to these children," he says.

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References

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2. Schuurs-Hoeijmakers, J. H. M. *et al. Am. J. Hum. Gen.* **91**, 1122–1127 (2012).