Nature Reviews Genetics | Published online 14 December 2015; doi:10.1038/nrg.2015.26

GENOMICS

Fishing for the ageing secret

Two independent papers in *Cell* report *de novo* assembly of the reference genome of the shortest-lived vertebrate that can be bred in captivity — the African turquoise killifish (*Nothobranchius furzeri*) — opening doors for the use of these fish as model organisms in ageing and biological research.

"Research on ageing is hampered by the relative long lifespan of the standard vertebrate model organisms," notes Matthias Platzer (Leibniz Institute on Aging, Germany), the lead author of one of the studies. The African turquoise killifish has a captive lifespan of only 4–6 months, can be bred in laboratory conditions, allows rapid genome editing and, importantly, mimics many aspects of human ageing. With the assembly of its reference genome, these characteristics now put the African turquoise killifish in a great position to become a new vertebrate model for ageing.

Teams led by Platzer and by Anne Brunet (Stanford University) independently set out to sequence the genome of the inbred GRZ strain of *N. furzeri*, which exhibits only a low percentage of heterozygosity. Both groups achieved good coverage and assembly of the coding regions, but the genomes remained fragmented, mainly owing to repeat-rich areas. Platzer and co-workers reported a genome assembly of 1.24 Gb with ~26,000 annotated protein-coding genes, whereas this was 1.02 Gb and ~28,000 in the report by Brunet and colleagues. Both reference genomes and transcriptomes are publicly available and will become a great resource for the scientific community.

To understand the evolution of features unique to short-lived fish, Valenzano *et al.* compared the *N. furzeri* genome with seven longer-lived fish species and identified >200 genes under positive selection, including genes involved in insulin and insulin-like growth factor signalling, as well as genome maintenance. Interestingly, several of these genes were found to also be under positive selection in exceptionally long-lived species (including bowhead whales, naked mole rats and some bats), but the specific protein residues under selection differ between the long-lived and short-lived species. Although this supports the hypothesis that the same proteins regulate compressed and extended life trajectories, Brunet warns that these genes could have been selected for traits other than lifespan, for example, stress resistance.

By using comparative genomics and linkage analysis based on a cross between shorter-lived and longer-lived *N. furzeri* strains, Valenzano *et al.* revealed candidate genes associated with lifespan differences. Interestingly, both teams found that the genetic regions associated with the differences in lifespan are not spread randomly, but are grouped together. More specifically, Valenzano *et al.* found that these genes map to the sex chromosome, although they are distinct from the sex-determining region. "This finding could suggest a link between lifespan determination and sex determination, which might be beneficial in a 'life in the short lane'-type of animal, which has to reach sexual maturity fast," proposes Brunet.

Platzer's team also identified several intra-species Y chromosome polymorphisms in *N. furzeri* that might represent different stages of sex chromosome formation, thus providing insights at high resolution into the early steps of sex chromosome evolution. Further studies will need to assess whether the most successful Y chromosome will sweep through the population, leading to minor sequence variations that mark Y haplotypes in most species.

Genome assembly of *N. furzeri* potentiates the usefulness of these fish as a model organism. "The genome sequence facilitates the comparison between closely related species that differ in lifespan and ageing phenotypes," says Platzer. Functional confirmation of the biological role of the genes implicated in ageing and sex determination by transgenic technologies is nonetheless needed.

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Nature Reviews Disease Primers

ORIGINAL ARTICLES Reichwald, K. *et al.* Insights into sex chromosome evolution and aging from the genome of a short-lived fish. *Cell* **163**, 1527–1538 (2015) | Valenzano, D. R. *et al.* The African turquoise killifish genome provides insights into evolution and genetic architecture of lifespan. *Cell* **163**, 1539–1554 (2015)