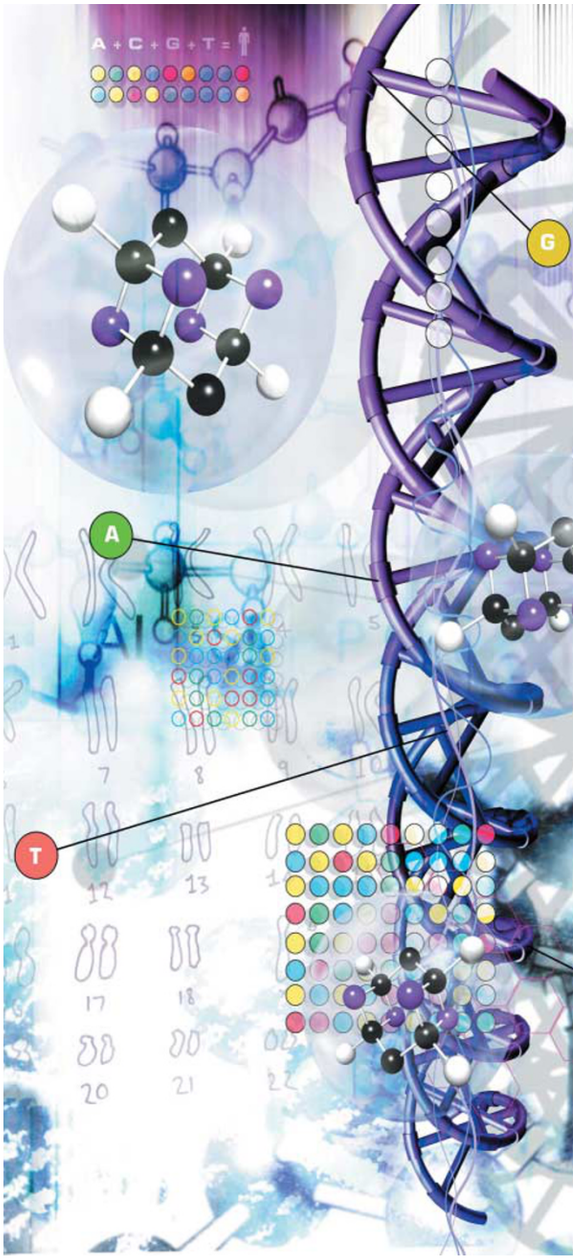
TECHNOLOGY

Making history



The study of the genetic past is often associated with heroic attempts to extract age-old genomic fragments that have been locked away in resin for thousands of years. But there is another way of getting our hands on our ancestors' DNA — creating it ourselves. Joseph Thornton and colleagues used the members of a modern gene family to infer the ancestral sequence that existed hundreds of millions of years ago, which was then reconstructed in the laboratory and functionally analysed.

The gene in question encodes the ancestor of six modern-day nuclear steroid receptors (SRs) — ligand-binding transcriptional activators through which sex and adrenal hormones affect biological responses such as sexual differentiation. SRs are found in all vertebrate genomes; however, they are missing from the invertebrate species that have been sequenced so far, including flies and worms. Could SR genes have been lost from these invertebrates? That depends on the answer to the question: were SRs present in the ancient ancestor of flies, worms and humans?

Short of that ancestor turning up in a blob of resin, this matter could only be answered by looking at present-day SR sequences. The authors were able to clone a mollusc orthologue of one particular vertebrate SR gene — the oestrogen receptor (ER). The existence of a true ER orthologue in an invertebrate and the position of the mollusc sequence on the phylogenetic tree make it possible to affirm that the ancestor of ER genes existed at least 600 million years ago in the ancestor of all bilaterally symmetrical animals.

A surprise, however, came when the mollusc ER was tested *in vitro*: although it could efficiently bind oestrogen response elements on DNA, it activated transcription constitutively — that is, unlike all known ERs, it functioned independently of oestrogen or any other ligand. So, although cloning the mollusc ER answered one question, it threw up the related problem of whether the ancestor of all SRs was ligand-sensitive or ligand-insensitive.

This time there was no living ancestor the sequence of which could be interrogated, so the authors decided to infer the sequence of an ancestral SR by applying sophisticated statistical algorithms to a large number of modern-day SR sequences. Not only was the sequence inferred, it was actually built. When tested, this great grandmother of all existing SR genes responded specifically to oestrogen *in vitro*, activating transcription in a dose-dependent manner.

Therefore, according to the revised version of evolutionary events, the ancestral ligand-sensitive ER gene would have been inherited intact by vertebrates, and gradually evolved by gene duplication and divergence into the six SR-types. By contrast, ERs would have been lost entirely in some invertebrate lineages and would have lost their hormone sensitivity in the mollusc lineage.

This study establishes a powerful method for uncovering our genetic history. It also shows that science is often only as good as the thinking behind it: if the analysis had been limited to, say, *Drosophila* and *Caenorhabditis elegans*, which have lost their ER genes, we would now be convinced of a completely different story.

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References and links

ORIGINAL RESEARCH PAPER Thornton, J. W. *et al*. Resurrecting the ancestral steroid receptor: ancient origin of estrogen signaling. *Science* **301**, 1714–1717 (2003)

WEB SITE

Joe Thornton's laboratory: http://www.uoregon.edu/~joet