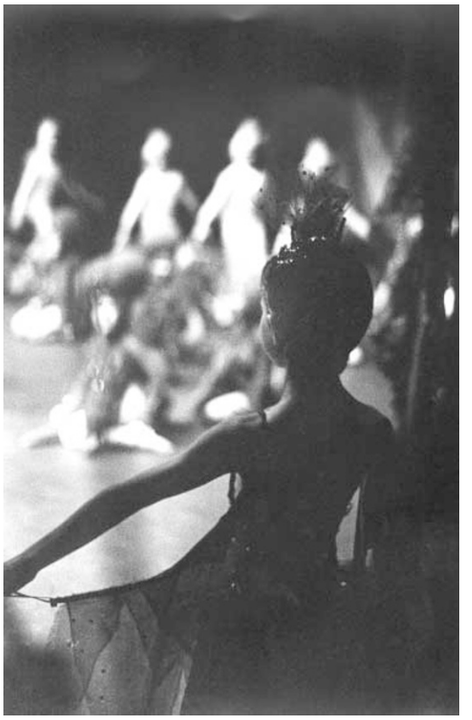
HIGHLIGHTS

FUNCTIONAL GENOMICS

Elegant tour de force



When the draft human genome sequence was published it was referred to as the blueprint. But, as with any design plan, the challenge is in establishing how the plan is executed. This task lies at the heart of functional genomics, and now Kamath *et al.* provide an important contribution to this field with their tour de force systematic RNAi analysis of the *Caenorhabditis elegans* genome. Not only do they uncover the function of scores of worm genes, but they also provide important information on the worm genome structure and its evolution.

To determine RNAi phenotypes for as many *C. elegans* genes as possible, the authors constructed a library of 16,757 bacterial strains (equivalent to 86% of all currently predicted worm open reading frames; ORFs), each of which expressed double-stranded RNA (dsRNA) corresponding to a single worm gene. When worms feed on these bacteria (*Escherichia coli* is their normal diet) the dsRNA is internalized and mediates sequence-specific knock down of the endogenous gene. One by one, the phenotypes were scored, and 10.3% of the analysed ORFs gave consistent phenotypes, which the authors grouped into three classes: nonviable (Nonv), growth defects (Gro) and viable post-embryonic phenotypes (Vpep). The first class contains many universal eukaryotic genes, for example, those that encode essential components of the basal cellular machinery. By contrast, most of the genes in the Vpep class probably represent animal-specific genes, and their products affect processes such as behaviour or body shape.

A closer look at the genomic distribution of genes in each class revealed that genes with similar functions tend to be co-localized in large domains of the genome and are co-transcribed. The size of these clusters, however, suggests that any large-scale transcriptional co-regulation must be mediated by a mechanism other than the previously described open-looped chromatin.

Another interesting finding concerns the X chromosome. The fact that Nonv genes are underrepresented on the X chromosome, whereas those that encode components of signalling pathways and transcription factors are overrepresented, suggests that very different selection pressures operate on genes on the sex chromosomes compared with genes on the autosomes.

Two other studies, in which the same approach was used to address more specific biological questions, have also been recently published. Ashrafi *et al.* used the same RNAi library to look for genes that regulate fat storage and mobilization. Among the 305 genes that reduce body fat stores and the 112 that increase them, they identified those genes that have mammalian homologues, some of which have already been implicated in fat metabolism. The worm fat-regulating genes fall into three main pathways (insulin, serotonin and tubby) confirming that fat metabolism is conserved in metazoans and that the worm can be used as a model of human fat metabolic disorders.

The authors of the second report, published in *Nature Genetics*, sought genes that, when inactivated, increased the *C. elegans* lifespan. Lee *et al.* followed up their RNAi screen with a classic forward genetics screen and, together, the results showed that worms with impaired mitochondrial and certain metabolic functions tend to be long-lived.

IN THE NEWS

Clone baby?

Doubts have started to surface over the truth of claims that the first human clone has been born, after Clonaid — the company that made the original 27 December announcement — backed away from an independent verification by genetic tests.

The *New York Times* reported that Clonaid's self-imposed one-week deadline expired with no evidence forthcoming. Clonaid's chief executive Brigitte Boisselier said "The parents told me that they needed 48 hours to decide yes or no — if they would do it" (*New York Times*).

The credibility of the claims took another hit when Michael Guillen — the freelance science journalist organizing the genetic tests — pointedly distanced himself from Clonaid after the tests did not go ahead. "It's entirely possible [that] Clonaid's announcement is part of an elaborate hoax to bring publicity to the Raelian movement," he said (*The Guardian*).

Claude Vorhilon (aka 'Rael'), leader of the pseudoscientific sect that funds Clonaid, suggests that a Florida court action aimed at placing the baby under the court's protection might explain the company's reticence. "…to take away this poor baby from a mother, I think this is completely crazy, just because she was cloned. So I called Doctor Boisselier, and I said, 'If I was you, I would not test anything.'" (*The Washington Times*).

The increasing scepticism of the media has not prevented Clonaid from expanding their claims: according to them a further three human clones will be born in the next month, in addition to the trio already born (*The Guardian*).

Perhaps the biggest concern for geneticists arising from the whole media furore is the spur it is likely to provide for efforts in the US Congress to ban human cloning (*The Guardian*).

Nick Campbell

Apart from the important biological insights, Kamath *et al.* have given the community an important resource — the bacterial RNAi library that can be used over and over again. Many more reports of screens such as those by Ashrafi *et al.* and Lee *et al.* are bound to follow, the results of which will provide a more complete picture of individual biological processes. The hope is that, as RNAi technology improves, similar systematic screens will also be feasible in mammalian cells.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPERS Kamath, R. S. *et al.* Systematic functional analysis of the *Caenorhabditis elegans* genome using RNAi. *Nature* **421**, 231–237 (2003) | Ashrafi K. *et al.* Genome-wide RNAi analysis of *Caenorhabditis elegans* fat regulatory genes. *Nature* **421**, 268–272 (2003) | Lee, S. S. *et al.* A systematic RNAi screen identifies a critical role for mitochondria in *C. elegans* longevity. *Nature Genet*. **33**, 40–48 (2003)

FURTHER READING Dillin, A. *et al.* Rates of behavior and aging specified by mitochondrial function during development. *Science* **298**, 2398–2401 (2002)

EVOLUTIONARY GENOMICS

Compensation or innovation

Gene duplications are often seen as an opportunity to evolve new functions through the accumulation of mutations leading to functional diversification. But, they can also be thought of as a back-up or a buffer against loss-of-function mutations in one of the duplicates. Using yeast as a working example, Gu *et al.* have shown that gene duplications considerably contribute to genetic robustness against null mutations.

A previous study of genetic robustness — the ability to withstand null mutations — concluded that it was redundant metabolic pathways and networks, rather than duplicate genes, that mainly fulfil this function. However, these conclusions were based only on a few genes, so Gu *et al.* revisited this problem — this time addressing it on a genome-wide scale. They made use of a previous study in which almost all of the genes of *Saccharomyces cerevisae* were knocked out and the fitness of the mutants was assessed under five different conditions (see Highlights section in September 2002 issue). When the authors compared the fitness of strains deleted for unduplicated genes with those deleted for duplicates, they found a significant difference — deletions of duplicates were significantly less likely to cause lethality and more likely to have mild effects, or no effects, under each of the five experimental conditions. These observations indicated that duplicated genes compensate for each other, a conclusion that was supported by the fact that deletions of either gene from a duplicate pair showed similar fitness effects. Furthermore, the smaller the divergence between the duplicates, the better they compensate for each other. It also turns out that deleting duplicate genes with higher expression levels has a greater effect on fitness than deleting those that are not as highly expressed.

These data provide strong evidence for the role of gene duplication in genetic robustness against null mutations. Whether this contribution is more or less important than the interactions between unduplicated genes that function in alternative pathways remains to be seen. The role of duplicates in genetic buffering might explain why these genes do not 'decay' into pseudogenes as quickly as expected. But, Axel Meyer — the author of the accompanying *News and Views* — suggests that their incorporation into new networks and pathways also prevents such decay. So, does this mean that we were wrong about duplications being the prerequisite for innovation? Gu *et al.* believe that gene duplication is still the most common path for innovation, and that a duplicate gene is maintained because it might be able either to improve part of the original function or to perform a new function. The buffering effect of duplicates is largely caused by their partially overlapping function. Axel Meyer argues for a dual role for duplicate genes, but further whole-genome-sequence comparisons and functional genetic analyses are needed before we can really address this question.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Gu, Z. *et al.* Role of duplicate genes in genetic robustness against null mutations. *Nature* **421**, 63–22 (2003)

FURTHER READING Meyer, A. Duplication, duplication. *Nature* **421**, 31–32 (2003)