WEB WATCH

Bioinformatics lessons

• http://s-star.org

If you can't tell your Needleman–Wunsch from your Tulla algorithm, then, like me, this is the web site for you. With lectures on basic to advanced bioinformatics topics, this web-based teaching resource offers hope and enlightenment to the computationally confused.

S-Star is an international alliance of teaching institutions that includes Stanford University, Sydney University and Sweden's Uppsala University. Its goal is to provide a unified, bioinformatics learning environment — comprising institution-approved lectures and courseware in genomics, bioinformatics and medical informatics — to all.

The bioinformatics lectures range from introductory overviews — such as the overview on computationally analysing sequence data — to in-depth presentations on specific topics, for example, on algorithms for computational biology. The lectures vary in length from 40 minutes to over an hour and can be viewed by installing Microsoft's Windows Media Player. A synchronized presentation of the instructor's slides accompanies each video, and a dropdown menu lets you choose between the different topics that are covered. The lectures are not just restricted to DNA-based topics either, but also cover proteomics, and protein structure and prediction.

Another part of the site — Self Tuition — provides worksheets on specific topics and problems to work through. One such worksheet tackles BLAST searches — it provides a sequence for a search and then assesses, through questions, how well you understand the results.

S-Star is clearly at an early stage of development, but has the potential to be a great web resource, providing much-needed tuition and guidance on the fast-evolving field of bioinformatics.

Jane Alfred

HUMAN GENETICS

Myotonic dystrophy comes into focus

In 1992, when it was discovered that myotonic dystrophy — a common adult muscular dystrophy — is caused by an expanded CTG repeat that affects the non-coding regions of two adjacent genes (*DMPK* and *SIX5*), it raised some intriguing questions. Which gene causes the disease, or do both? Or are mutant *DMPK* transcripts, which accumulate abnormally in nuclear foci, responsible for the varied, seemingly unrelated, symptoms of the disease? With evidence supporting each of these theories, the myotonic dystrophy field hit an impasse.

However, one of the outcomes of this discovery was a genetic test for myotonic dystrophy, the use of which revealed another genetic cause of the disease — DM2 — a chromosome-3-associated form of myotonic dystrophy that is clinically very similar to DM1 (the originally discovered form). Could the identification of this second gene finally shed light on the disease's pathology? With the recent discovery that DM2 is caused by enormous expansions of a tetranucleotide repeat in an intron of *ZNF9* — a zinc-finger gene — it would seem so. Because *ZNF9* and its neighbouring genes bear no resemblance to those at the *DM1* locus — and because mutant *ZNF9* RNAs also accumulate in nuclear foci — it now seems very likely that these expanded mutant transcripts significantly contribute to the pathology of myotonic dystrophy.

Liquori *et al.* focused their gene hunt by identifying an ancestrally conserved region of chromosome 3. They then noticed that a *DM2*-linked marker had an unusual segregation pattern — DM2 individuals always seemed to be homozygous, and affected children appeared not to inherit an allele from their DM2 parent. Southern-blot analysis revealed that affected individuals carry expanded marker alleles that are too large to amplify by PCR, leading the authors to a CCTG repeat that was expanded in DM2 samples to 75–11,000 copies — the largest repeat number found in control samples was 26. The authors also noticed that older individuals often had the largest expansions, owing to the repeat's time-dependent somatic instability.

So, how can mutant RNA transcripts bring about the myotonia, cataracts, heart-conduction defects and muscular dystrophy that characterize DM1 and DM2? The authors propose that expanded CCUG-containing transcripts could sequester into nuclear foci the same RNA-binding proteins that bind to the CUG repeats in *DMPK* mutant RNAs, causing similar global disruptions to RNA splicing and cell metabolism. Abundant *ZNF9* expression in heart and skeletal muscle might also explain why these tissues are most affected in the disease. A recent

discovery reported in *Nature Genetics* sheds further light on the pathological effects of such expanded mutant transcripts. This study found that DM1 individuals inappropriately express an isoform of the insulin receptor in their skeletal muscles, perhaps accounting for their muscle tissue's decreased sensitivity to insulin. Wild-type cells can be induced to make this isoform by exposing them to increased levels of a CUG-binding protein — levels of which are increased in DM1 skeletal muscle tissue — indicating that increased levels of this protein cause an alternative-splicing switch and the misexpression of the insulin receptor isoform in DM1 skeletal muscles.

With these important discoveries, the impasse affecting myotonic dystrophy research could soon be breached, speeding our understanding of the molecular and cellular defects that cause the disease.

Jane Alfred

References and links

ORIGINAL RESEARCH PAPERS Liquori, C. L. *et al*. Myotonic dystrophy type 2 caused by a CCTG expansion in intron 1 of *ZNF9*. *Science* **293**, 864–867 (2001) | Savkur, R. S. *et al*. Aberrant regulation of insulin receptor alternative splicing is associated with insulin resistance in myotonic dystrophy. *Nature Genet.* **28**, 40–47 (2001)

WEB SITE

International Myotonic Dystrophy Organization: http://www.myotonicdystrophy.org/