WEB WATCH

Genetic tests: the fun and the factual

- http://www.sciona.com
- http://www.genetests.org

What does the future hold for you, genetically speaking? Does your genetic make-up mean that you should avoid the sun or eat more greens? How long can you expect to stave off wrinkles and keep your own teeth?

If these are the kinds of question that interest you, numerous companies are lining up to provide you with the answers. For example, Sciona, a company based in the United States, offers genetic profiling to provide you with: "Personalized diet and lifestyle advice based on your body's real needs." Just do a DIY cheek swab, fill in a lifestyle survey, and a few weeks later you'll get a report explaining how your genetic profile and eating habits might influence your health.

However diverting this might seem, such tests have raised concerns about validity and regulation (see our Ethics Watch article from July 2005). Another issue is whether the public is sufficiently informed to understand the implications of the results, especially when tests for medical conditions are involved.

Gene Tests, an information service funded by the US National Institutes of Health, takes a more measured approach towards evaluating genetic tests. Aimed at physicians and researchers, this web site contains peer-reviewed articles about genetic conditions, focusing on what is known about mutations and their use in testing, as well as providing links to companies that offer the relevant tests.

The Gene Tests approach allows a more informed view of genetic tests, but the information on offer is squarely aimed at users with some knowledge of genetics. The question therefore remains: is it acceptable to offer mail-order genetic tests to a public that is not fully equipped to evaluate the implications?

Louisa Flintoft

PLANT GENETICS

Tailor-made crop improvements

Tapping into natural allelic variation has always been an important means of crop enhancement. A recent study has now identified a new and powerful way of improving rice yield — by combining loci that increase grain production and plant height.

Starting from two rice varieties that were variable with respect to agronomically important traits, Ashikari and Sakakibara identified 4 QTLs for plant height *(Ph)* and 5 QTLs for grain number *(Gn)*. *Ph1*, the strongest of the four height QTLs, turned out to encode gibberellin 20 oxidase. *Gn1*, on chromosome 1, accounted for 44% of the difference in grain production between the two varieties used.

***Gn1* contained two loci. Positional cloning of one of these, *Gn1a*, revealed that it encoded cytokinin oxidase/dehydrogenase (CKX). Sequence analysis of *OsCKX2* from several varieties revealed that in one variety, a small 11 bp deletion introduces a premature stop codon. Reasoning that perhaps a reduced activity of this enzyme would increase the grain yield, the authors created transgenic rice plants that express different levels of CKX. As expected, lower levels of CKX meant more grain. But how does it work?**

***OsCKX2* is most abundantly expressed in inflorescence meristems and young flowers. As the *OsCKX2* relative from *Arabidopsis thaliana* reduces the number of flowers when overexpressed, the authors propose that the same mechanism operates in rice — that low CKX levels lead to higher yield by increasing the number of flowers.**

CANCER GENETICS

A screen success

Screening human cell lines for genes involved in cancer can be tricky — such genes are often recessive and the mechanisms through which they are inactivated can be complex. RNAi screens provide a potentially powerful way to identify genes that are involved in cancer by investigating the effects of reduced gene expression on specific cellular phenotypes. Now, two independent groups have verified the importance of RNAi-based screening in human cell lines by using this approach to identify novel tumour-suppressor candidates.

Both groups produced libraries of retroviral vectors that contain short hairpin RNAs (shRNAs); each construct was complementary to a single human gene and 8,000 or so genes were represented in total. The researchers transduced these vectors *en masse* into engineered human cells lines that were poised for transformation — the rationale being that knocking down a candidate tumour suppressor would be enough to tip these cells over into the transformed phenotype.

Because most cancers arise from epithelial tissues, Elledge and colleagues chose an immortalized mammary epithelial cell line for their screen. For normal growth *in vitro*, these cells need support from the extracellular matrix, but when they are transformed, they become 'anchorage-independent' and can simply be screened for proliferative ability on soft agar. Elledge's group also took the opportunity to carry out the first test of the use of 'genetic barcodes' in mammalian cells. By adding a unique 60-nucleotide barcode to each shRNA vector, they used microarrays to successfully identify the shRNA responsible for the knockdown.

Reassuringly, several of the genes that Elledge and colleagues picked up are well-known tumour suppressors, such as transforming growth factor-β receptor II (TGFBR2) and phosphatase and tensin homologue (PTEN). But they also found a new candidate tumour-suppressor gene — RE1-silencing transcription factor (*REST*) — which (like *TGFBR2*) resides in a locus that often suffers loss of heterozygosity, a frequent chromosomal characteristic of human tumour suppressors.

REST is often downregulated in prostate and small-cell lung cancers, and is frequently deleted in colon tumours. The authors present evidence that REST downregulation augments phosphatidylinositol 3-kinase signalling, an important pathway in cancer progression. Furthermore, the fact that REST is responsible for repressing neuronal genes in non-neuronal tissues provides another clue to its potential function in cancer. Several human tumours aberrantly express neuron-specific genes, and the authors reasoned that this might have an important role in cancer, with REST potentially playing a part.

Agami's group introduced their shRNA vectors into an immortalized fibroblast cell line that required only the deregulation of RAS for transformation. RAS proteins convey growth signals from the cell surface to the nucleus, and their overexpression or aberrant activation is an important cause of cancer. Although activating mutations of *RAS* are frequent in human cancers, many tumours still retain wild-type copies of the gene, prompting Agami and colleagues to look for genes that, when inhibited, activate RAS.

They identified the gene paired-like homeodomain transcription factor 1 (*PITX1*), which is frequently downregulated in bladder and prostate tumours. Although it is not yet known whether *PITX1* is mutated or deleted in human cancers, the authors present some intriguing evidence that loss of PITX1 can lead