WEB WATCH

Human Ageing Genomics Resources

• http://genomics.senescence.info/index.html

If you are working on or are interested in human ageing, you should know about the Human Ageing Genomics Resources (HAGR): a web site that brings together databases and computational tools to help understand the biology of ageing.

The resource started in 2002 as a collaborative project at the University of Namur, Belgium. A searchable and browsable database of genes that are related to human ageing, GenAge, forms the core of the resource. Each gene page contains nomenclature, cytogenetic and protein information. Among other useful features are links to relevant publications and a list of orthologues with links to NCBI Entrez. There are also further external links to OMIM, Swiss-Prot and GeneCard, to name but a few.

Another database, AnAge, caters for those who work on ageing in other species. It has information on ageing in *Drosophila melanogaster*, *Caenorhabditis elegans*, red and purple sea urchin, and 2,469 chordate species!

But databases are not all the HAGR has to offer: there is also the Ageing Research Computational Tool — ARCT. This Perl-based toolkit allows you to generate phylogenetic profiles locally or through NCBI's BLAST, to data-mine multiple sequences to find regulatory or functionally important regions, to display protein–protein interactions and phylogenetic trees, and to access other data-analysis programs such as ClustalW and Gibbs.

The project team is busy making continuous improvements to HAGR. For example, the inclusion of gene-expression information is on the cards. The team plan to include genes that are differently expressed between young and old tissues, focusing mainly on microarray data.

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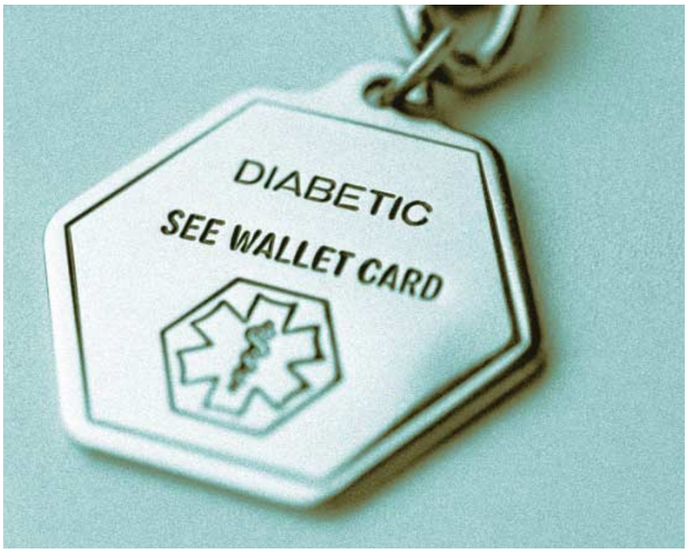
HUMAN GENETICS

Dissecting diabetes



Two new association studies have revived hopes that research into unusual monogenic forms of diabetes can provide pointers to the genetic basis of susceptibility to the common multifactorial form of the disease.

Maturity-onset diabetes of the young (MODY) is an autosomal dominant form of the disease that usually develops before an individual reaches 25 years. The hepatocyte nuclear factor-4α gene (*HNF4α*) that underlies one form of MODY encodes a β-cell transcription factor that is involved in insulin secretion. The hope has been that variation in this gene might also help to explain susceptibility to type 2 diabetes (T2D) — the much more common late-onset form.

Despite linkage evidence for a susceptibility locus in the *HNF4α* region, previous attempts to identify *HNF4α* variants associated with T2D, which focussed on the coding sequence of this gene, had failed. Now, however, Latisha Love-Gregory and Kaisa Silander, with their respective colleagues, have independently gathered convincing evidence for a link between T2D and variation in the region of an alternative promoter for *HNF4α* (P2) that drives transcription of what is probably the gene's dominant splice variant in pancreatic β-cells.

Love-Gregory *et al.* used linkage disequilibrium (LD) to map a 78-kb candidate region that included *HNF4α* and P2. They identified haplotype tagging SNPs (htSNPS) that would represent the most common haplotypes across this region in Ashkenazi Jews. The authors then compared frequencies of the nine

DEVELOPMENT

A new twist to bone formation

The identification of a novel anti-osteogenic domain by Gerard Karsenty and colleagues, reported in *Developmental Cell*, has revealed that the differentiation of osteoblasts — the cells that are responsible for bone formation — is more complex than was previously suspected.

Building on work that identified *Runx2* as the master gene for osteoblast differentiation, the authors wanted to find out why it is expressed four days before osteoblasts appear. Taking this delay as evidence for the involvement of other regulatory proteins, and considering that some developmental bone diseases result from increased (presumably premature) bone formation, they wondered if *Runx2*, which encodes a transcription factor, might be negatively regulated.

Increased bone formation in cranial sutures is seen in *Twist1*$^{+/-}$ mice and also in Saethre–Chotzen patients who are heterozygous for *TWIST1* inactivation. So, Karsenty and co-workers hypothesized that Twist1 (and perhaps its relative, Twist2) negatively regulates Runx2 — and therefore osteoblast differentiation.

***In situ* hybridization in embryonic day (E)12–15 mice confirmed that osteoblast differentiation is seen only after the decrease of *Twist* gene expression. In addition, they found that when the *Twist* genes are not expressed, osteoblasts differentiate prematurely. Moreover, the authors showed that inactivation of the *Twist* genes can rescue a *Runx2* haploinsufficiency phenotype. So, it seems that *Runx2* interacts with both *Twist1* and *Twist2*.**

Twist1 was found to inhibit osteoblast differentiation without affecting *Runx2* expression, so how exactly do the Twist proteins exert their effect? DNA co-transfection experiments revealed that Twist1 and Twist2 specifically inhibit the transactivation function of Runx2. Using Twist1 deletion mutants in these experiments, Karsenty and colleagues identified the domain responsible for the inhibition — the Twist box. It turns out that this novel anti-osteogenic domain of 20 amino acids, which is only present in Twist1 and Twist2, binds directly to the Runt DNA-binding domain of Runx2, and