HUMAN GENETICS

An accomplice, by (Di)George!

There is nothing more frustrating than thinking you've got the answer to a problem only to find there is much more to it than you originally thought. The quest for the genetic cause of DiGeorge syndrome is one such vexing problem that now, thanks to Ingeborg Stalmans, Diether Lambrechts and colleagues' identification of a modifier of the syndrome, is one step closer to being solved.

When it was shown that most DiGeorge syndrome patients had a 3 million base-pair deletion in chromosome 22, it seemed obvious that haploinsufficiency of one or more genes in the hemizygous region (22q11) was the cause. Mouse studies nailed down the transcription factor gene *Tbx1* — orthologous to *TBX1* in humans — as the prime suspect.

However, it turned out that the rare DiGeorge syndrome patients without the large deletion apparently had normal *TBX1* genes. The syndrome's extreme phenotypic variability also suggested *TBX1* might have an accomplice, or accomplices, that remained unknown. Some more detective work in mice was required.

DiGeorge syndrome is characterized by life-threatening cardiovascular birth defects, as well as craniofacial, thymic and parathyroid defects. Therefore, the authors targeted the gene encoding vascular enthothelial growth factor (VEGF) because its crucial role in angiogenesis marked it as a potential accomplice.

Promisingly, birth defects of homozygous *Vegf*-mutant mice ($Vegf^{120/120}$ and $Vegf^{188/188}$) were strikingly similar to those seen in DiGeorge patients. Moreover, the authors found that hot spots of *Vegf* expression correlated with sites affected in del22q11 individuals.

The mouse work provided good evidence that VEGF was involved in DiGeorge syndrome, but the most direct evidence came from zebrafish. Stalmans, Lambrechts and colleagues showed that progressive knock-down of *vegf* expression, against a background of a constant dose of *tbx1*-specific morpholino, resulted in increasingly severe heart defects.

The evidence from animal models was strong, but the authors needed some evidence to confirm that *VEGF* was similarly important in humans with DiGeorge syndrome. They targeted single nucleotide polymorphisms (SNPs) in the promoter and 5′ untranslated region of *VEGF* that are known to downregulate expression. Genotyping 91 DiGeorge cases and 316 unrelated controls for these polymorphisms showed a crucial role for one allele (–1154A) in determining the susceptibility of DiGeorge patients to cardiovascular defects, but didn't rule out the involvement of other SNPs.

The case is now sound: *VEGF* — which maps outside the chromosome 22 region that is deleted in most del22q11 patients — is a modifier of birth defects in the syndrome. However, perhaps the most interesting aspect of the study is the potentially general approach it models. Rather than using a genome-wide scan to track down modifiers of the DiGeorge phenotype, the authors used the evidence from mouse and fish to generate a specific hypothesis that they went on to test in humans.

Although their association data remains to be confirmed in additional larger study populations, the success of the authors' combined genetic approach raises the possibility that perhaps we should be using a similar approach to disentangle the genetic influences on other complex diseases. Regardless, we should keep in mind that no matter how obvious the genetic culprit responsible for a specific disorder seems we should never discount the possibility of an accomplice on the outside!

Nick Campbell

References and links

ORIGINAL RESEARCH PAPER Stalmans, I. *et al. VEGF:* a modifier of the del22q11 (DiGeorge) syndrome. *Nature Med.* 21 Jan 2003 (10.1038/nm819)

IN BRIEF

BIOINFORMATICS

Trait-to-gene: a computational method for predicting the function of uncharacterised genes.

Levesque, M. *et al. Curr. Biol.* **13**, 129–133 (2003)

This group have developed algorithms to infer gene function based on correlations between the presence of genes and a particular phenotype. The algorithms were tested in a search to find genes involved in flagella development, and successfully identified genes already known to be involved in flagella function, as well as two uncharacterized genes that if inactivated in *Bacillus subtilis* result in impaired motility.

GENOMICS

Release 3 of the *Drosophila* genome.

Genome Biol. **3**, research0079-0088 (2002)

The Berkeley *Drosophila* Genome Project, FlyBase and colleagues have produced this collection of 10 papers covering the completion of the *Drosophila* genome sequence and its annotation, along with a description of functional studies and computational tools. The new release of the genome sequence confirms the utility of the whole-genome shotgun strategy but also highlights flaws in the initial method of repeat assembly. Furthermore, it has some immediate practical benefits, allowing defective clones to be weeded out from the collection of full-length *Drosophila* cDNAs (the *Drosophila* Gene Collection). The bioinformatic strategies and software used to annotate the sequence are among the most sophisticated available, yet manual curation is still an essential step in the annotation process. Nonetheless, the sequencing and annotation strategies accurately defined the intron–exon structures of 30 known protein-coding genes and 267 protein-coding gene models in the notoriously difficult heterochromatic sequences. The new release also has the first characterization of transposable elements in the euchromatic genome sequence. *Drosophila* developmental genomics gets a boost with the embryonic expression patterns of 2,179 genes being examined in fixed *Drosophila* embryos. Comparative genomics and the computational identification of core promoters in the fly genome are also covered in this comprehensive collection that, having been available online, is now published in print.

TECHNOLOGY

A lentivirus-based system to silence genes in primary mammalian cells and transgenic mice by RNA interference.

Rubinson, D. A. *et al. Nature Genet.* 18 February 2003 (10.1038/ng1117)

Although RNAi works efficiently in many organisms, including mammals, some cell types remain refractive to it, mainly because of transfection problems. Rubinson and colleagues show that lentiviral delivery of short hairpin RNAs overcomes this problem and leads to efficient functional gene silencing *in vivo* and *in vitro* in many cell types, including mitotic and post-mitotic cells, stem cells and zygotes. The authors suggest that, if used to silence disease-causing genes, this method might have a therapeutic potential.