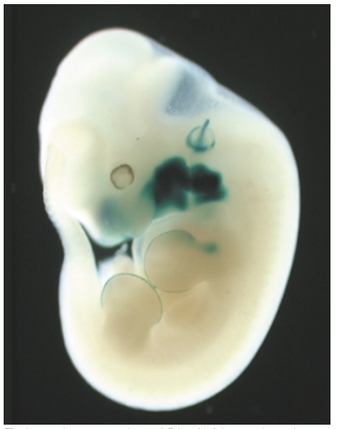
DEVELOPMENTAL BIOLOGY

Distal-less makes the leap

We're reminded almost daily that we are more like our winged, fruit-craving little friends than appearances might first suggest. The latest knock to our dignity comes from Raymond Robledo and colleagues, who have found that a family of genes homologous to those that control the outgrowth of antennae and legs in *Drosophila* also patterns limbs in mammals. The *Distal-less* (*Dll*)/Dlx family of homeobox transcription factors are known for being involved in limb formation in many insects and vertebrates; the importance of this study has been to extend this function to mammals as well, including humans.

In *Drosophila*, there is only one *Dll* gene; flies without it lack the distal portion of their appendages. Mammals, by contrast, have six Dlx genes (*Dlx1–Dlx6*), which cluster in pairs on the genome — Robledo *et al.* concentrate here on the *Dlx5/6* cluster. This is because, although all vertebrate Dlx genes are expressed in the developing limbs, the brain and the craniofacial primordia, the *Dlx5/6* cluster also maps to a region on human chromosome 7 that is associated with a severe human limb defect called split-hand/foot malformation type 1 (SHFM1). In this dominantly inherited disorder, the central limb digits are missing, giving the extremities a claw-like appearance. The phenotype of *Dlx5/6* double-knockout mice, which these authors generated, confirm their expectation that *Dlx5/6* might regulate limb development. Not only do these animals have bone, inner ear and severe craniofacial defects — as could be predicted from the expression patterns of *Dlx5/6* and as has been reported for other Dlx single- and double-knockout mice — but also they phenocopy the limb defects seen in human SHFM1.



Embryonic expression of *Dlx5/6* (shown here by β-galactosidase staining) in a wild-type mouse at embryonic day 11.5. Image courtesy of Thomas Lufkin, Mount Sinai School of Medicine, USA. Reproduced with permission from Robledo *et al.* *Genes & Development* © (2002) Cold Spring Harbor Laboratory Press.

However, Dlx genes can only be said to be functional homologues of *Dll* if the limb abnormalities of *Dlx5/6*$^{-/-}$ mice arise from defects in proximal–distal (P/D) patterning. Indeed, by embryonic day 11.5 — when most of the mutant defects become apparent — all the molecular markers for the distal medial limb are missing. The authors propose that, by reducing cell proliferation, the absence of *Dlx5/6* causes loss of cells in the apical ectodermal ridge (AER), which controls P/D patterning. Furthermore, the ectopic expression of *Dlx5* (alone) in the AER fully rescued the SHFM1 defect in *Dlx5/6*$^{-/-}$ mice.

Putting all this information together, Robledo and colleagues argue that all species with appendages owe these structures to the evolutionarily ancient *Dll*/Dlx gene family. By showing that *Dlx5/6* mutant mice can phenocopy SHFM1, they have extended the function of Dlx genes to humans, as well as creating a model for investigating the physiological basis and progression of this human limb abnormality.

Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Robledo, R. F. *et al*. The *Dlx5* and *Dlx6* homeobox genes are essential for craniofacial, axial, and appendicular skeletal development. *Genes Dev.* **16**, 1089–1101 (2002)

WEB SITE

Thomas Lufkin's lab: http://adsr13.mssm.edu/domains/dept/facultyInfo.epl?objname=biomol&user=lufkit01

IN BRIEF

CLONING

Oct4 distribution and level in mouse clones: consequences for pluripotency.

Boiani, M. *et al. Genes Dev*. **16**, 1209–219 (2002)

The transcription factor Oct4 is essential for early embryonic mouse development and is expressed only during embryogenesis and in germ cells. It is, therefore, a good marker to assess genome reprogramming in cloned blastocysts derived from somatic-cell nuclei. Here, Boiani *et al.* report that cultured cells derived from cloned blastocysts that were generated from cumulus-cell nuclei rarely express *Oct4* correctly or at levels required for normal embryonic development. The frequency of this abnormal expression alone can account for the low rates of post-implantation survival of clones.

MULTIFACTORIAL GENETICS

Simultaneous detection and fine mapping of quantitative trait loci in mice using heterogeneous stocks.

Mott, R. & Flint, J. *Genetics* **160**, 1609–1618 (2002)

Determining the molecular basis of a quantitative trait remains a challenge as current protocols for fine-mapping QTL involve scoring a large number of individuals or following the trait over many generations. The authors have used a computer simulation to show that, by examining only ~1,500 F_2 progeny from a cross between an inbred line and a heterogeneous stock of mouse (a genetic mosaic of eight known strains), a QTL can be mapped to within ~3 cM by screening with ~100 markers followed by a focused scan on the candidate regions.

GENE REGULATION

Identification of tissue-specific microRNAs from mouse.

Lagos-Quintana, M. *et al. Curr. Biol.* **12**, 735–739 (2002)

MicroRNAs (miRNAs) are non-coding RNAs that are thought to modulate gene expression at the post-transcriptional level. Here, the authors report the identification and cloning of 34 novel miRNAs from mouse, many of which are conserved in other vertebrate genomes, including human. Many of these miRNAs are expressed in a tissue-specific manner, perhaps indicating their involvement in tissue specification or cell-lineage decisions.

GENE EXPRESSION

Regulation of noise in the expression of a single gene.

Ozbudak, E. M. *et al. Nature Genet.* **31**, 69–73 (2002)

Biochemical reactions are sensitive to changes in molecular concentrations. By measuring the expression levels of a fluorescent reporter gene on a *Bacillus subtilis* chromosome in different translational and transcriptional mutants, the authors quantify the extent to which molecular fluctuations in single cells explain the differences in gene expression in a genetically identical population (which they call "phenotypic variation"). Their results show that translational efficiency is the main source of phenotypic variation.