DEVELOPMENTAL BIOLOGY

New tricks for an old dog

Notch signalling is involved in cell-fate decisions in many organisms, and the molecular events that underlie these decisions are well established. But no pathway acts in isolation and there have been intriguing reports that another signalling pathway — mediated by Wingless — might interact with Notch signalling. New evidence in support of this cross-talk comes from Ramain *et al.* who, through their analysis of new dominant Notch alleles, reveal the existence of a novel Notch pathway in *Drosophila* and show that it is antagonized by Wingless signalling.

Notch, a transmembrane receptor, is best known for mediating lateral inhibition — a mechanism that allows neighbouring cells to adopt one of two different cell fates. Consistent with the function of Notch in preventing neural fate, lateral inhibition through Notch specifies the number and positioning of microchaetae — short sensory bristles — on the adult body of the fly. When Ramain and colleagues characterized several dominant Notch mutants (N^{Mcd}) that they had identified in a genetic screen for loss of microchaetae, they were surprised to find that the mutant phenotype was independent of the classical lateral inhibition pathway. So, how is the Notch signal transduced in microchaetae? Previous reports indicated that the cytoplasmic protein Deltex (Dx) can bind to the intracellular portion of Notch; Ramain *et al.* showed that mutations in *Dx* suppress the N^{Mcd} gain-of-function phenotypes, indicating that this non-canonical Notch pathway requires Dx.

This new microchaetae-repressing function of Notch would be expected to be inhibited in wild-type flies. Dishevelled (Dsh), another component of the Wingless pathway, had been previously reported to interact physically with Notch, and so the authors proposed that Dsh antagonizes the Dx-dependent function of Notch on the adult body. *In vivo* and *in vitro* analysis showed not only that Dsh is involved, but also that it binds to the intracellular portion of Notch that is missing in the N^{Mcd} mutant proteins.

Ramain *et al.* propose that, in wild-type flies, the newly discovered Dx-dependent pathway acts early to prevent neural-cell differentiation, and cell-fate choice through lateral inhibition occurs only after the Dx-dependent pathway has been blocked by Dsh — allowing microchaetae to develop. More tissues in *Drosophila* and in vertebrates will need to be examined to determine how widespread the functioning of this new Notch pathway really is.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Ramain, P. *et al.* Novel *Notch* alleles reveal a Deltex-dependent pathway repressing neural fate. *Curr. Biol.* **11**, 1–20 (2001)

MULTIFACTORIAL GENETICS

Wafer thin diversity

One of the biggest challenges that faces human genetics is to uncover the genetic basis of common disease. Although the idea that underpins this quest is relatively simple — study the genomes of many individuals and identify the genetic variants that distinguish those with disease from those without — to actually do this is a very difficult and expensive undertaking. However, a team of scientists from Perlegen Sciences, Inc. have now taken a step towards this goal in a large pilot study to identify all the single nucleotide polymorphisms (SNPs) on human chromosome 21 using high-density oligonucleotide arrays. Importantly, they've found that the SNPs can be grouped into haplotype blocks, each of which can be defined by just three common haplotypes for 80% of all human chromosome 21s — indicating that much less haplotype diversity exists than previously thought. They also show that screening the human genome for genetic variation relating to disease is an achievable goal.

Patil *et al.* began this mammoth undertaking by isolating 20 different haploid copies of chromosome 21 — derived from 24 ethnically diverse individuals — in rodent–human somatic-cell hybrids. They did this so that they could directly assess the haplotypes of the chromosomes. From each hybrid, they amplified 3,253 DNA fragments, which span most of the non-repetitive DNA of chromosome 21 and cover 32.4 Mb. These PCR products were then pooled and hybridized to high-density oligonucleotide arrays — Perlegen's so-called wafers — that carried chromosome 21 sequence corresponding to that in the pooled samples. By using pattern-recognition software to detect altered hybridization signals on the wafers, the team found ~36,000 SNPs from the 20 chromosomes sampled.

Next, the authors identified ~24,000 SNPs with a minor allele present in more than one sample, only 4,705 of which overlapped with SNPs identified by The SNP Consortium. They used these SNPs, together with a new algorithm, to find the smallest number of SNPs that could define each chromosome 21 haplotype. Surprisingly, they found that, on average, three common haplotypes can define a block of consecutive SNPs and that, within these blocks, all the common haplotype information can be captured by genotyping only 4,563 selected SNPs.

This work has several important implications for future whole-genome studies for mapping common disease genes. It shows that, although a few SNPs can define most haplotypes, a very dense SNP map is needed to capture all haplotype information because of the unpredictable nature of haplotype structure. It also shows that such large-scale studies are feasible, taking us one step closer to finding the genetic variants that predispose us to disease. Pui-Yan Kwok, however, sounds a note of caution in an accompanying Perspective with respect to drawing broad conclusions about human haplotype structure from so few chromosomes.

Jane Alfred

References and links

ORIGINAL RESEARCH PAPER Patil, N. *et al.* Blocks of haplotype diversity revealed by high-resolution scanning of human chromosome 21. *Science* **294**, 1719–1723 (2001)

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WEB SITE

Perlegen Sciences, Inc.: www.perlegen.com/haplotype