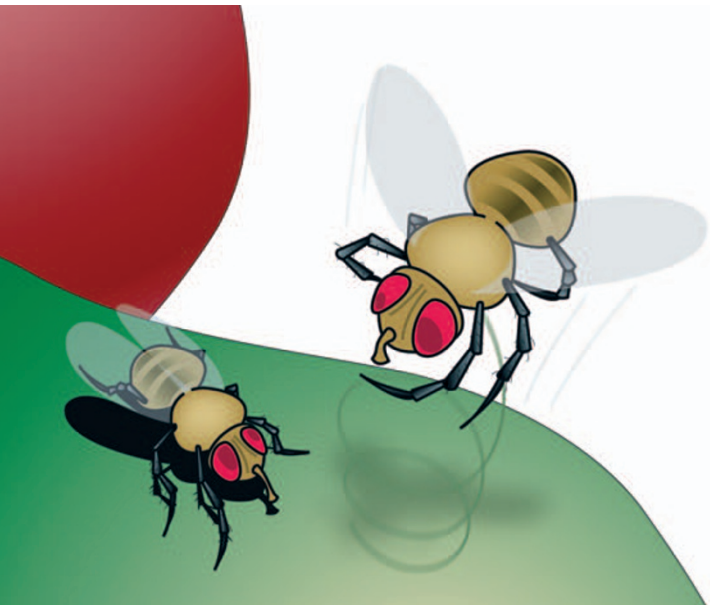
EVOLUTION

Jump-starting speciation



In the process of speciation, when two new species go their separate evolutionary ways, a critical step is reproductive isolation. This happens when groups of individuals acquire differences that prevent them from successfully interbreeding. At the genetic level, the most widely considered cause of this isolation is a change in the function of a key gene in one of the diverging groups, rendering the two populations sexually incompatible. A recent study now provides evidence for an alternative route to speciation in which the jumping of a gene that is essential for fertility to a new location in the genome is the cause.

John Masly and colleagues studied a hybrid *Drosophila* line in which all of the genome was derived from *Drosophila melanogaster* apart from the tiny fourth chromosome, which came from the closely related species *Drosophila simulans*. All females from this line are fertile, as are males that carry one copy of the fourth chromosome from each species. However, males that are homozygous for the *D. simulans* fourth chromosome are sterile as a result of sperm immotility. This provides a model of hybrid sterility, which is one route to reproductive isolation.

The authors mapped the genetic cause of this sterility to the *D. melanogaster* fourth chromosome gene *JYAlpha*, which encodes a transmembrane ion-exchange protein. Using *P*-element transposition, they created a *JYAlpha* allele that encodes a truncated protein. Male flies in which one copy of the fourth chromosome carried this null allele and the other copy came from *D. simulans* were sterile,

REPRODUCTIVE BIOLOGY

From worm sperm proteins to human infertility

A recent report details the molecular basis of male fertility through the identification of the most comprehensive list of spermatogenic proteins to date, using *Caenorhabditis elegans*. Because many of these proteins are required for male fertility in mice, this list is a useful resource in the search for the genetic causes of human infertility or targets for novel contraceptives.

The biology of sperm cells is notably unique, one difference being the way in which specific nuclear proteins are used to package sperm DNA. As this feature is conserved across many animal species, Diana Chu and colleagues hit on the idea of isolating chromatin proteins that are either specific to or enriched in *C. elegans* sperm and then looking to see whether they might be involved in male fertility in mammals. As a first step, proteins that were associated with *C. elegans* sperm chromatin were isolated: over 1,000 were identified. That number was then pared down to 132 by retaining only those that were above an abundance threshold and were not present in oocyte chromatin, a comparable meiotic population. The specific localization of many of these proteins to sperm chromatin *in vivo* confirmed that the protein enrichment protocol had indeed pulled out biologically relevant molecules.

> “…this rich database will be attractive to members of the community who are interested in identifying genes for human infertility or targets for safe contraceptives.”

So the proteins are in the right place, but what do they do? The authors carried out RNAi on all the genes that encode the identified proteins: almost 40% of the 132 genes were required for worm fertility or embryonic development, or caused defects in germline morphology, a figure that is far higher than can be detected by non-proteomic techniques such as genome-wide RNAi. What is perhaps more interesting and useful from a health perspective is the fact that about a third of the 132 *C. elegans* proteins have homologues in the mouse, in which many have been known to cause sterility when mutated or when knocked down by RNAi (some of these genes also have fertility defects in *C. elegans*). The proteins have functions in various aspects of sperm production, from DNA packaging to chromosome segregation to fertility (see the image, which shows nuclei progressing through spermatogenesis in the male gonad of *C. elegans*).

Human male infertility is an issue of medical concern, but only a handful of genes are known to be associated with this condition. The resource provided by this work will therefore be invaluable. Two-thirds of the proteins that were pulled out of this proteomics project also have homologues in humans, and

confirming the role of *JYAlpha* in hybrid male infertility.

So have the *JYAlpha* genes in *D. melanogaster* and *D. simulans* undergone a functional divergence that causes this incompatibility? When they came to mapping and sequencing the *D. simulans* version to make the necessary comparison, Masly and colleagues found that in this species the gene is located in a completely different genomic location — on the third chromosome. This provides a simple explanation of hybrid incompatibility in this model: males that are homozygous for the *D. simulans* fourth chromosome in an otherwise *D. melanogaster* background entirely lack *JYAlpha* and are sterile as a result.

As the authors point out, this example does not provide an exact model of how hybrid sterility leads to reproductive isolation: F_1 hybrids between *D. melanogaster* and *D. simulans* are sterile or inviable for other reasons and only a fraction of the F_2 generation is affected by *JYAlpha*. However, it is clear that in other situations a change in the location of a gene could lead to a more complete isolation of two populations. For example, this would occur if a Y chromosome gene that is essential for fertility relocated to the X chromosome.

Previous studies that have looked for divergences of gene function as a cause for reproductive isolation have so far found few examples. This study suggests that searching for changes in the genomic location of genes could prove a fruitful approach for future studies that aim to understand the genetic basis of speciation.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Masly, J. P. *et al.* Gene transposition as a cause of hybrid sterility in *Drosophila*. *Science* **313**, 1148–1150 (2006)
FURTHER READING Wu, C. I. & Ting, C. T. Genes and speciation. *Nature Rev. Genet.* **5**, 288–298 (2004)
WEB SITE
Allen Orr's laboratory: http://128.151.242.156/~orrlab/orrhome-2002.html

two of these map to genes — a topoisomerase and a helicase — that are implicated in human infertility.

Perhaps even more interesting are those proteins that, despite being involved in sperm production in worms, have homologues in mammals with no known function. Therefore, this rich database will be attractive to members of the community who are interested in identifying genes for human infertility or targets for safe contraceptives.

Tanita Casci

ORIGINAL RESEARCH PAPER Chu, D. S. *et al.* Sperm chromatin proteomics identifies evolutionarily conserved fertility factors. *Nature* 30 August 2006 (doi:10.1038/nature05050)
FURTHER READING Cooke, H. J. & Saunders, P. T. K. Human genetics and disease: mouse models of male infertility. *Nature Rev. Genet.* **3**, 790–801 (2002) | Kimmins, S. & Sassone-Corsi, P. Chromatin remodelling and epigenetic features of germ cells. *Nature* **434**, 583–589 (2005)
WEB SITES
Diana Chu's laboratory: http://online.sfsu.edu/%7echud
Barbara Meyer's laboratory: http://mcb.berkeley.edu/faculty/GEN/meyerb.html
John Yates' laboratory: http://fields.scripps.edu

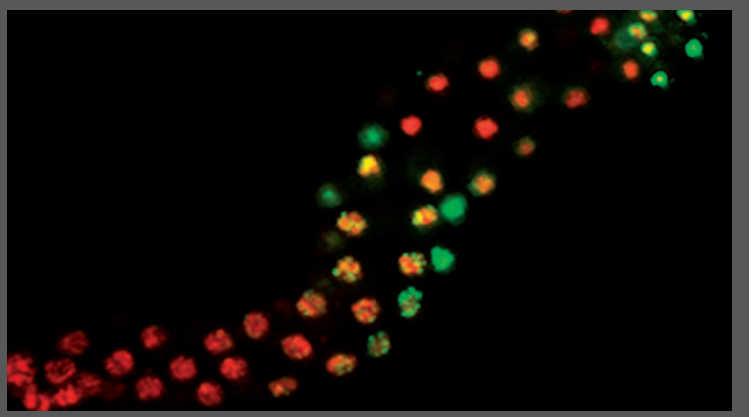


Image courtesy of Barbara J. Meyer, Howard Hughes Medical Institute, University of California, USA, and Diana S. Chu, San Francisco State University, USA.

IN BRIEF

DEVELOPMENT

A segmentation gene in *Tribolium* produces a polycistronic mRNA that codes for multiple conserved peptides.

Savard, J. *et al. Cell* **126**, 559–569 (2006)

Gap genes control the segmentation pattern along the head–tail axis of insect embryos. Savard *et al.* characterized a novel gap gene from *Tribolium*, *mille-pattes* (*mlpt*), knockdown of which results in embryos with extra pairs of legs due to the transformation of segmental identities. Unlike the other gap genes, *mltp* does not encode a transcription factor, but a polycistronic peptide coding mRNA (ppcRNA), which is predicted to produce four short, conserved peptides. *mltp* therefore seems to be the prototype for a new class of regulators.

GENE FUNCTION

Toward a molecular understanding of pleiotropy.

He, X. & Zhang, J. *Genetics* **173**, 1885–1891 (2006)

A pleiotropic gene affects many phenotypic traits. Pleiotropy could arise either when a gene has different functions or when a single gene function is involved in different contexts. By carrying out a genome-wide analysis of 741 genes — in which the degree of pleiotropy was determined by correlating the effects of deleting a gene with the biological processes in which it is involved — the authors show that the second hypothesis is the more plausible: highly pleiotropic genes in *Saccharomyces cerevisiae* are not attributable to an excess of molecular functions but to multiple consequences of a single function.

PLANT BIOLOGY

Visualizing plant development and gene expression in three dimensions using optical projection tomography.

Lee, K. *et al. Plant Cell* 11 August 2006 (doi:10.1105/tpc.106.043042)

Three-dimensional imaging provides the much needed data to analyse growth and development. Lee *et al.* used optical projection tomography (OPT) to capture three-dimensional data from a range of plant tissues at different developmental stages. The advantage of OPT is that it allows for visualization of large, thick specimens and large cells. It can also be used to visualize domains of gene expression, using reporter genes or *in situ* hybridization. The resulting data can be visualized and interrogated using specially developed software tools.

CANCER GENETICS

The consensus coding sequences of human breast and colorectal cancers.

Sjöblom, T. *et al. Science* 7 September 2006 (doi:10.1126/science.1133427)

In this paper the authors provide a systematic analysis of genetic alterations in 13,023 well-annotated human protein-coding genes in two types of cancer: breast and colon. Developing high-throughput methods for genome-wide analysis of cancer genes enabled the authors to describe the spectrum of somatic mutations in human tumours and to identify new cancer genes and pathways. Among the 189 genes that are frequently mutated in tumours, the majority were not previously known to be mutated in cancer, providing potential diagnostic and therapeutic tools.