HUMAN GENETICS

Mapping the common variation

The haplotype map of the human genome, affectionately known as the HapMap, has been in the spotlight since the project was launched in 2002. Although the data have been available on the web throughout, the results of Phase I of the project were only published in October. The report shows how the HapMap can guide the design and analysis of genetic association studies — its principal goal — but also it reveals important information about structural variation and recombination, ultimately showing how natural selection shapes the human genome.

The aim was to create a public, genome-wide database of common human variation. In Phase I, 1 common SNP (with a minor allele frequency of at least 0.05) was genotyped per 5 kb on a genome-wide scale in each of the project's 269 DNA samples. These come from the Yoruba in Nigeria, Japanese in Tokyo, Han Chinese in Beijing and the Centre d'Etude du Polymorphisme Human collection, from Utah.

Using the HapMap data the authors confirmed that the human genome has a block structure; this is because recombination occurs mainly in short regions called recombination hotspots. They also constructed a fine-scale genetic map of the human genome, analysis of which led to an unexpected observation. Gene-rich regions that encode, for example, immune response or neurophysiological functions lie in regions of high recombination, whereas regions rich in genes that are associated with 'core cellular function' such as DNA and RNA metabolism lie in regions of low recombination. It seems therefore that the HapMap data contain information about natural selection.

The Phase I data contain more than 1 million SNPs, most of which are rare and are either present in the dbSNP database or are tightly linked with those that are. The authors show that the HapMap data capture enough common variation to provide sufficient tag SNPs for genome-wide association studies. For ancestral populations, further SNPs might be required, and it is not yet clear to what extent tag SNPs are transferable across populations. Moreover, the HapMap data can be used to maximize the power of array-based association studies, in which tag SNPs cannot be chosen by researchers, and to evaluate statistical significance and interpret results of genome-wide association studies.

As the authors say, the HapMap is a natural extension of the Human Genome Project, focusing on inter-individual variation. The project has created an unprecedented resource that will facilitate comprehensive genome-wide association studies and ultimately lead to identification of genetic determinants of complex diseases. The next step will be to understand the environmental factors that affect them.

Magdalena Skipper

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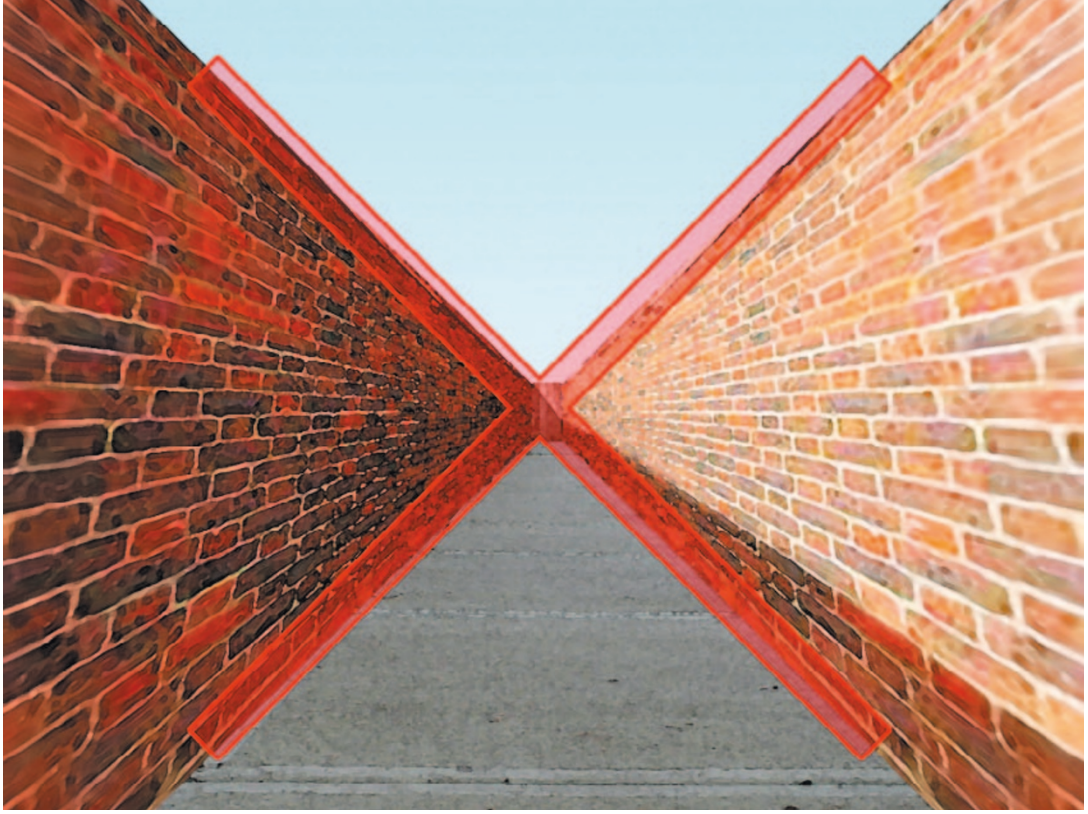
International HapMap Project: www.hapmap.org

Human Genome Project: http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml



X INACTIVATION

Imprinted inactivation: narrowing down the options

Studies in mice have been fundamental in understanding mammalian X-chromosome inactivation, but there are still important gaps in our knowledge of some of the processes that are involved. One of the missing pieces of the puzzle is how the imprinted X inactivation that takes place early in mouse development — before the onset of random inactivation — is initiated. Edith Heard and colleagues have now narrowed down the possibilities by ruling out one plausible mechanism.

In imprinted X inactivation, the paternally derived X chromosome (Xp) is silenced in all cells. One theory about how this silencing occurs is that Xp is pre-inactivated in the male germ line. In spermatocytes, the X and Y chromosomes are transcriptionally silenced in a process that is known as meiotic sex-chromosome inactivation (MSCI). Could the inactivation of Xp at this stage be carried over after fertilization?

Heard and colleagues tested this possibility in mice by examining the behaviour of a transgene that carries the gene X-(inactive)-specific transcript (*Xist*) — which is required in *cis* for X inactivation — and its surrounding sequences. When inserted into an autosome and inherited paternally, this transgene is inactivated during early development and shows epigenetic and replication-timing features that are similar to Xp, which indicates that it contains all the *cis* sequences that are necessary for imprinted X inactivation.

But can this inactivation be explained by MSCI? In spermatocytes, chromatin marks that are typical of MSCI were absent from the transgene, which was also transcriptionally active, unlike Xp. Moreover, inability to undergo pairing during meiosis does not seem to have a role in inactivation: the transgene was inactivated whether it was inherited from males that were hemizygous or those that were homozygous for the autosome that carried it.

Gene-expression studies also argued against a role for MSCI in establishing imprinted inactivation as it seems that silencing of Xp genes takes place in the embryo itself, and not before fertilization. Cysteine-rich hydrophobic domain 1 (*Chic1*), which is ultimately silenced on the inactive X chromosome, was initially expressed from both Xp and the *Xist* transgene in the early mouse embryo, and only became silenced from the 8-cell stage onwards. Similar patterns were seen for global transcription from the Xp and the transgene-carrying autosome.

So what event triggers imprinted inactivation early in embryogenesis? Heard and colleagues showed that only low levels of *Xist* mRNA are expressed from Xp at the 2-cell stage, and the transcript only later accumulates on the chromosome. This indicates that it might be *de novo* expression of the *Xist* transcript from Xp that initiates imprinted inactivation.

While ruling out MSCI as the cause of imprinted X inactivation, this study leaves important questions open. What leads to the expression of *Xist* from Xp early in development? And why is the maternal allele repressed? Whether a feature of the male germline other than MSCI is involved or a different mechanism entirely is operating awaits further investigation.

Louisa Flintoft

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IN THE NEWS

Stem cell therapy jumps another ethical hurdle

Two new methods for producing embryonic stem (ES) cells without destroying embryos provide a boost for the technology, tackling the main ethical objection against its use.

The first technique, reported in *Nature* (16 October 2005), involves taking 1 cell from an 8-cell embryo and coaxing it to become an ES cell in culture. The remaining 7 cells don't go to waste, as they go on to produce a normal embryo when implanted. This could open the way for banking cell lines for children who are born from the transferred embryos. "The procedure has been done hundreds of thousands of times, so we know it has a minimal or negligible effect on the embryo," said Robert Lanza, who led the research (*New Scientist*, 16 October 2005).

A second study published in the same issue of *Nature* used a modified form of nuclear transfer. The new twist lies in inactivating a key gene in the donor nucleus. This prevents the development of a placenta so that a *bona fide* embryo is never produced. As one of the authors explained: "…our goal was to create a cellular system unable to establish the basic body pattern of a human embryo but able to generate fully functional ES cells." (*The Scientist*, 17 October 2005)

While it remains to be seen whether these technical advances will satisfy critics, the opening of a stem cell research centre in South Korea shows the strength of support for the technology among potential patients. When the World Stem Cell Hub in Seoul announced that it was beginning patient registration a surge of applications overloaded its web site. "I'm pinning all hopes on this," said one applicant, among the many who have few other options for treatment (*CBS News*, 1 November 2005).

Louisa Flintoft

IN BRIEF

HUMAN DISEASE

Sequence variants in *SLITRK1* are associated with Tourette's syndrome.

Abelson, J. F. *et al*. *Science* **310**, 317–320 (2005)

Tourette syndrome (TS) has been associated in linkage studies with regions on several human chromosomes, but this paper is the first to study a specific candidate gene. SLIT and NTRK-like 1 (*SLITRK1*) was identified because of its proximity to a chromosomal inversion in a child with TS. In other patients, a frameshift mutation and a microRNA-binding site mutation in *SLITRK1* were found. Expression patterns in the brain of *SLITRK1* and the microRNA, and the ability of wild-type SLITRK1 to promote dendritic growth, further support a role for *SLITRK1* in TS.

MOUSE MODELS

The homeodomain transcription factor Irx5 establishes the mouse cardiac ventricular repolarization gradient.

Costantini, D. L. *et al*. *Cell* **123**, 347–358 (2005)

The rhythmic beating of the heart depends on waves of depolarization and repolarization, with defects in the latter leading to arrhythmia. This study demonstrates that mice that lack the Irx5 transcription factor are susceptible to fatal arrhythmias because they overexpress the $K_v4,2$ potassium channel. Irx5 negatively regulates $K_v4,2$ and is expressed in an opposing gradient. Together these two proteins establish the potassium gradients that ensure repolarization.

RNA WORLD

DICER-LIKE 4 is required for RNAi and produces the 21nt siRNA component of the plant cell-to-cell silencing signal.

Dunoyer, P., Himber, C. & Voinnet, O. *Nature Genet.* 6 November 2005 (doi:10.1038/ng1675)

In plants, the production of 21-nt small interfering RNAs (siRNAs) leads to the degradation of homologous RNAs, and this silencing signal can also move between cells. This paper reports the long-awaited identification of the Dicer protein that is involved in the silencing process. By analysing *Arabidopsis thaliana* mutants that are deficient in cell-to-cell silencing, the authors showed that DICER-LIKE 4 is required to produce the 21-nt siRNAs that mediate this form of RNA interference.

COMPUTATIONAL BIOLOGY

Genomic variability within an organism exposes its cell lineage tree.

Frumkin, D. & Wasserstrom, A. *et al*. *PLoS Comp. Biol*. **1**, e50 (2005)

Reconstructing the cell-lineage tree of *Caenorhabditis elegans* was a tremendous feat, and was made possible by the transparency of the organism and its relatively few cells. The paper shows that it is feasible to accurately determine the cell-lineage trees of complex organisms by analysing the pattern of microsatellite mutations that accumulate during somatic cell divisions. Although the approach is currently only applicable to small cell populations, it might one day be powerful enough to reconstruct the cell-lineage tree of an entire human.

GENE EXPRESSION

Something for a stressful day

The genome has developed numerous ways to regulate the expression of the genes it harbours, and a new mechanism has recently been reported by David Spector and colleagues in *Cell*. They have identified an RNA that is normally retained in the nucleus but, in response to stress, is cleaved to release an mRNA into the cytoplasm and is subsequently translated into protein. This indicates a role for the nuclear retention of RNA in controlling gene expression in the mouse.

Intrigued by the earlier observation that poly(A)$^+$ RNA is enriched in distinct subnuclear structures known as nuclear speckles, the Spector group set out to isolate and characterize the population of poly(A)$^+$ RNA molecules in nuclear speckles. They showed that one RNA — which they named CTN-RNA, and is encoded by the mouse cationic amino-acid transporter 2 (*Cat2*; also known as *Slc7a2*) gene — colocalizes only partially with nuclear speckles, but colocalizes completely with adjacent nuclear domains, known as paraspeckles.

The mechanism for nuclear retention of RNA molecules is unknown, but it could occur as a result of an RNA-editing process known as adenosine (A) to inosine (I) editing. Could CTN-RNA be a target for RNA editing? Sequence comparison of several CTN-RNA clones revealed that A-to-I editing takes place in the 3′ UTR. However, reporter-gene analysis showed that the CTN-RNA 3′ UTR is not sufficient for retention, but that the entire transcript is required. This could indicate that specific folding of the entire RNA, as well as A-to-I editing of the 3′ UTR, is important for nuclear retention.

To explore the function of CTN-RNA, Spector and colleagues knocked down CTN-RNA using antisense oligonucleotides and found that this was accompanied by a reduction in the level of *Cat2* mRNA. The CAT2 protein functions in the nitric-oxide synthesis pathway, which is induced by stress conditions. Cells that were exposed to stress showed a decrease in the level of CTN-RNA, which, in contrast to the knockdown situation, was accompanied by an increase in the level of *Cat2* mRNA. Northern blot analysis revealed that, under conditions of stress, the CTN-RNA is cleaved at its 3′ UTR, releasing the protein-coding mRNA. So, in unstressed cells, CTN-RNA is nuclear retained and regulates the level of *Cat2* mRNA, whereas in stressed cells, the CTN-RNA is released as translation-competent mRNA for the rapid production of the CAT2 protein.

The identification of CTN-RNA and its mechanism of action unveils a new model in the regulation of gene expression, and Spector and colleagues propose that this type of regulation allows for a rapid response to environmental signals. These findings also implicate A-to-I editing as a mechanism for nuclear retention of RNA, and indicate a role for paraspeckles as a reservoir for A-to-I-edited nuclear RNA molecules.

Arianne Heinrichs, Chief Editor, Nature Reviews Molecular Cell Biology

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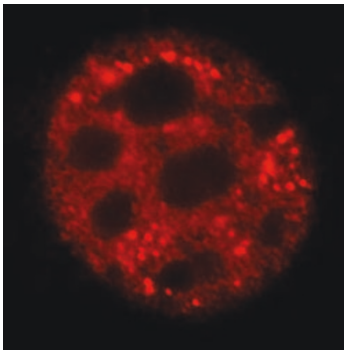
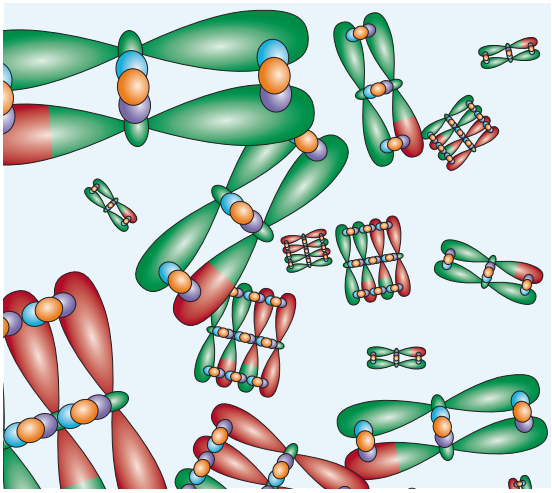
WEB SITE
David Spector's laboratory: http://spectorlab.cshl.edu



RNA fluorescence *in situ* hybridization showing the diffuse nuclear localization of CTN-RNA as well as its presence in paraspeckles in a mouse-embryo fibroblast. Image courtesy of Kannanganattu V. Prasanth and David L. Spector, Cold Spring Harbor Laboratory, USA.

CHROMOSOME BIOLOGY

Meiotic functions for a histone modification



Genetic analysis of a *Drosophila melanogaster* female sterile mutation has provided some of the first insights into the mechanisms that control the morphological changes that chromosomes undergo during meiosis, and into functional requirements for histone modifications during oogenesis.

Ivanovska *et al.* studied female sterile fly mutants, hoping to learn more about the ill-understood mechanisms that control the architecture of meiotic chromosomes. They found that embryos laid by females that carried one particular mutation — Z3-0437 — showed abnormal chromosome dynamics. It turns out that the mutation maps to the gene *nkh1*, which encodes a kinase that specifically phosphorylates histone H2A. The mutation is probably hypomorphic and results in an amino-acid substitution in the kinase domain.

Detailed analysis revealed that NKH1 is required for several meiosis-specific events; for example, the formation of the karyosome — an oocyte-specific chromosomal structure that forms in prophase I — and of the metaphase I spindle. To dissect the mechanisms behind the mutant phenotype, the authors first looked at homologous recombination in early prophase I. They found that NKH1 is required for the disassembly of the synaptonemal complex (a structure that holds homologous chromosomes together during meiotic recombination), but not for double-strand break repair. Later on, NKH1 is required for the loading of condensin onto the chromosomes, which is required for chromosome condensation and consequent karyosome formation.

In addition, the results indicate a specific role for histone modifications in meiosis. The authors found evidence of a meiotic histone modification cascade — although some modifications are unaffected in *nkh1* mutants, others are absent. It remains to be seen what the function of a meiosis-specific histone modification pathway might be. One possibility is that, consistent with the general role of histone modification, it might control access of key factors to the chromosomes at crucial stages during meiosis.

Magdalena Skipper

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GENE EXPRESSION

Which mean do you mean?

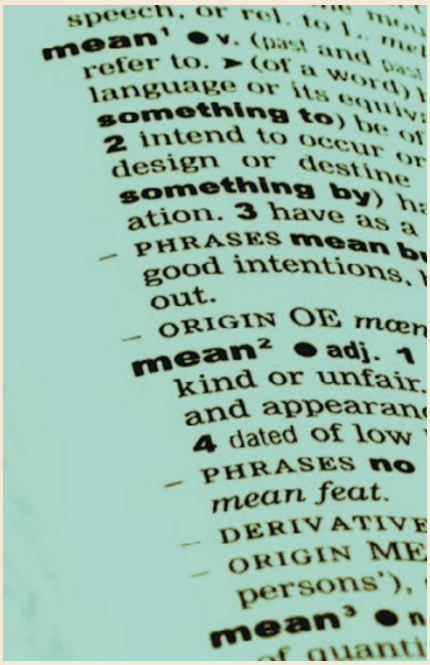
There is considerable variation in gene-expression levels between individual cells. Bengtsson *et al*. show that these levels are distributed log-normally rather than normally, which implies that the arithmetic mean does not represent the situation in a typical cell. They also show that the levels of expression of different genes in the same cell do not generally correlate, and suggest that mechanistic conclusions can be drawn when they do.

Using reverse transcriptase quantitative real-time PCR, they measured the transcript levels of 5 genes in 169 mouse pancreatic cells. For each gene the results were distributed log-normally across the sample cells, making the geometric mean a more appropriate representation of the data than the more commonly quoted arithmetic mean. For the insulin genes, *Ins1* and *Ins2*, up to 9-fold differences were found between the arithmetic and geometric means.

Of the five genes studied, only *Ins1* and *Ins2* expression levels correlated at the level of the individual cell. Levels of *ActB*, the β-actin gene, correlated with these two only at the overall population level, whereas levels of the final two genes did not correlate with any of the others. This indicates that expression-level differences in individual genes are not due to cells having different levels of overall transcription. The authors suggest that genes that correlate at the individual cell level are co-ordinately regulated, whereas those that correlate at the population level merely respond to the same environmental stimuli.

The importance of these findings is demonstrated by the fact that we might have underestimated the effect of glucose on insulin expression by almost 4-fold, which could be important in the administration of therapeutic insulin.

Patrick Goymer



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SYSTEMS BIOLOGY

Linked-up loops: a reliable means of control

Depending on how you look at it, large gene-expression networks are dauntingly complicated or, if you're a mathematical modeller, elegantly simple and reducible to a discrete number of meaningful ON/OFF switches. A modelling study has begun to link these network 'building blocks' together by showing that an optimal output is obtained when two such switches are combined.

There are several well-characterized classes of switch-like elements, but this study concentrated on positive-feedback loops, in which *A* activates *B* and *B* activates *A*. Feedback loops operate in many signalling pathways, with some processes — such as oocyte maturation in frogs and the polarization of yeast cells — relying on more complicated switch arrangements, such as the coupling of two positive-feedback loops. This arrangement is initially rather puzzling: why combine two switches when a single one will carry out exactly the same function?

A computational modelling approach revealed a reason for the extra layer of complexity: slow loops are stable switches, but cannot transit between states quickly; by contrast, fast loops make for unstable (noisy) switches, but are quick at switching between states. Coupling two switches of the same kind together brings no overall benefit over having a single switch, but combining a fast and a slow switch yields an optimal output — that of a fast yet robust, reliable switch.

This type of dual positive-feedback loop is the one that is seen in the sub-circuits of many biological systems, and we now understand why this might be. This work also highlights the comforting thought that the details of a circuit are in fact dispensable, provided we have a good handle on the wiring.

Tanita Casci

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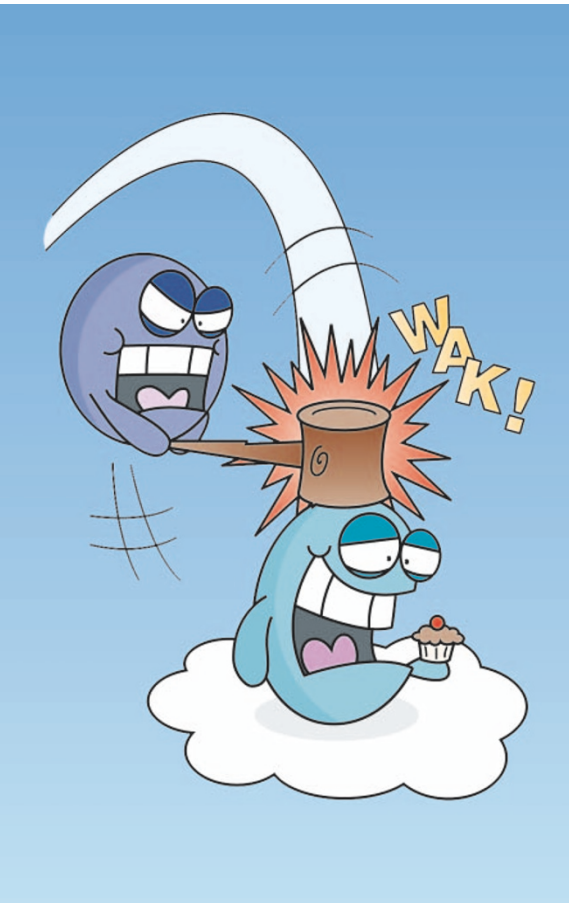
CANCER EPIGENETICS

Dangerous unmarked genes



Loss of imprinting (LOI) at specific loci has been implicated in several cases of tumorigenesis, probably as a result of imbalanced expression of potential imprinted tumour-suppressor genes and oncogenes. Previous studies have demonstrated that LOI is associated with tumorigenesis, not that it causes it. The consequences of a global LOI have not been addressed either, merely the consequences of single-gene LOI or imbalanced imprinting (having an entirely maternally or paternally imprinted genome). Now, Rudolf Jaenisch and colleagues have demonstrated that global LOI leads to tumour formation.

They used conditional mutants of DNA methyltransferase to transiently remove methylation from mouse embryonic stem (ES) cells. When methylation was restored, imprinting patterns were lost — the maternal and paternal genomes were no longer differentially methylated. The authors derived fibroblasts from these ES cells and found that they were immortalized, grew at an increased rate and resisted inhibition by transforming growth factor β, a cytokine that inhibits the growth of various cell types.

Several tumour-suppressor genes, such as *Igf2r*, *Tsp1* and *p57*, were underexpressed in the fibroblasts, and oncogenes, such as *Peg3*, *Peg5* and *Igf2* were overexpressed. When the non-imprinted fibroblasts were injected into immunodeficient mice there was some tumorigenesis, compared with none in the controls. However, when the fibroblasts were also transfected with constitutively active Ras, tumorigenesis was much faster. The authors suggest that this is because Ras and LOI cooperate to form tumours.

Chimeric mice that were created from a mixture of non-imprinted and normal ES cells all had tumours by 18 months of age, in contrast to the controls in which there was only one case of tumour formation. All the tumours in the chimeric mice were derived from the non-imprinted cells. Importantly, tumours were not seen in the offspring of the chimaeras, as imprinting is reset during gametogenesis.

Imprinting is therefore an epigenetic tumour-suppressing phenomenon. When imprinting is lost, cells are immortalized through the inappropriate regulation of both tumour suppressors and oncogenes. Further genetic alterations are then required for full transformation.

Patrick Goymer

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CANCER GENETICS

History rings true for the dividing cell

A century-old model that links problems in cell division to genome instability and so to the development of cancer has now been validated.

The German biologist Theodor Boveri proposed that the chromosome imbalances that are typical of cancer cells arise because the failure of a cell to divide during mitosis would lead to tetraploid cells; these in turn would be vulnerable to complications during cell division and therefore produce daughter cells that have an abnormal number of chromosomes. Two studies have experimentally shown this to be the case and have provided some mechanistic details.

David Pellman and colleagues chemically blocked cell division in mouse mammary epithelial cells that lacked the tumour suppressor gene *p53*, and showed that the resulting tetraploid cells were more likely to generate cancers in mice and to have unstable genomes.

In the second study, Qinghua Shi and Randall King followed the behaviour of chromosomes in the dividing cells of various human cells lines either by fluorescently tagging histone 2B or by fluorescence *in situ* hybridization. Surprisingly, they found that the spontaneous occurrence of chromosome non-disjunction that occurs at some cell divisions does not necessarily lead to aneuploid cells, as was always assumed. Instead, in cells that undergo non-disjunction, mitosis is halted and the cleavage furrow regresses, giving rise to tetraploid cells. Such tetraploids can then produce further tetraploid daughter cells (if the mitosis is bipolar), but they can also lead to aneuploid progeny (if multiple spindles are formed).

This work explains why the chromosome anomalies that are observed in tumours rarely consist of the occasional missing or extra chromosome but instead seem to have arisen by genome doubling followed by chromosome loss. The results also indicate that changes in ploidy number seen in cancer cells might not be the result of mutational events; genetic changes might in fact occur after the ploidy changes, to promote the formation of multipolar spindles and/or the proliferation of the aneuploid progeny.

Tanita Casci

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ETHICS WATCH

Genetics and social identity after the HapMap

Phase I of the International HapMap Project (HapMap) is now complete, and an analysis of its findings is being published1. Unlike the Human Genome Project's signature message that all individuals have a 99.9% genetic similarity, HapMap will deliver a more mixed message about human genetic variation to scientists as well as the public: that there are common variants that are found across populations, and that there are differences in frequencies of those variants and in genomic structures (such as linkage disequilibrium) between populations.

Although these two messages were evident even in the pre-sequence era, population-specific patterns of variation clearly will become a more significant aspect of genomics in the post-HapMap era, as will the social implications of that enhanced focus. HapMap might fuel the continuing debate about the biological relevance of group identities. Some participants in the debate have argued that differences in frequencies of genetic variants between groups make a relatively small contribution to the health disparities that are associated with social identities, and have been concerned about the adverse implications of designing genetic studies that explicitly make population and ancestral comparisons[2]. Others have argued that population-specific variants make significant contributions to understanding differences in the expression of complex traits, and have been concerned about the adverse scientific implications of ignoring social identities that serve as proxies for ancestry[3].

Each perspective in this debate, which in the United States has focused on the biological meaning of race, emphasizes only one of the above messages.

The prospect of significant investments in infrastructure to support large-scale, population-based association studies (including prospective cohorts) presents the opportunity for a more nuanced framing of genetic variation research, one that could help to reduce potential damage to groups by educating both scientists and the public about the relationship between genetics and social identities.

The question is whether a middle ground can be established in what has become a polarized argument, in which both sides have conflated scientific and social issues. Categorizing individuals by identity, ancestry, locality, lifestyle or genetic markers (among other criteria) can be useful (and sometimes necessary) for biomedical research as well as clinical treatment[4]. However, those who are anxious to argue against the biological basis for race, for example, often make the mistake of denying the potential for racial and other social categories to be biologically informative. At the same time, treating any of these selectively defined categories as natural or fundamental ways of grouping individuals can have obvious adverse implications, both in scientific and social senses. Therefore, those who insist on maintaining racial and ethnic categories in biomedical research, for a contrasting example, often make the mistake of exaggerating claims for their genetic uniqueness and determinism, which only perpetuates practices that advantage one group over another.

We are at the beginning of an era in which genetic variation will become increasingly important in biomedical research and clinical treatment owing to theoretical and technological innovations in genomics. The challenge is to make similar innovations in how we frame that genomic information in the context of contingent social identities.

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IN BRIEF

HUMAN GENETICS

Special Issue: Human Genome Variation

Genome Research **15**, 1463–1600 (2005)

To coincide with the publication of the HapMap paper in *Nature* (see the Highlight on p874) *Genome Research* have devoted their November issue to describing how the data emerging from the project have been applied to understanding human biology, genome structure and disease. As well as research updates on diseases such as prostate cancer, and technical papers on the gene-mapping methods themselves, the issue includes useful resources, such as a guide to using the analysis tools on the International HapMap Project web site.

CANCER GENETICS

The tumour suppressor HIC1 directly regulates SIRT1 to modulate p53-dependent DNA-damage response.

Chen, W. Y. *et al. Cell* **123**, 437–448 (2005)

HIC1 — hypermethylated in cancer 1 — suppresses age-dependent tumorigenesis in mice by functionally cooperating with p53. The authors show that a HIC1–SIRT1 (sirtuin 1) complex represses transcription of the stress-responsive SIRT1 deacetylase. Cells that lack HIC1 do not apoptose in response to DNA damage because SIRT1 deacetylates and inactivates p53. The authors point out that in ageing cells, in which *HIC1* is more likely to be epigenetically silenced, SIRT1 overexpression promotes cell longevity while increasing cancer risk.

CHROMOSOME BIOLOGY

Telomere-binding protein Taz1 establishes Swi6 heterochromatin independently of RNAi at telomeres.

Kanoh, J. *et al. Curr. Biol.* **15**, 1808–1819 (2005)

Despite much attention, the mechanism of heterochromatin formation at telomeres is far from clear. Working in fission yeast, these authors show that telomeric repeats are required to establish HP1 heterochromatin, and that this process is mediated by Taz1, a telomere binding protein that, as shown here, also mediates subtelomeric heterochromatin formation. Establishment of telomeric heterochromatin also requires a *cis* element that lies in the subtelomeric region and is regulated by RNAi–RITS, which in fission yeast initiates heterochromatin formation at the centromere and the silent *mat* locus.

RNA WORLD

Silencing of microRNAs *in vivo* with 'antagomirs'.

Krützfeldt, J. *et al. Nature* 30 October 2005 (doi:10.1038/nature04303)

This paper reports important progress in our ability to investigate the *in vivo* functions of microRNAs (miRNAs) and to manipulate their levels therapeutically. The authors generated synthetic RNA analogues — antagomirs — that are complementary to miRNAs, chemically modified for stability, and conjugated to cholesterol to enable *in vivo* delivery. As a test, antagomirs that target endogenous miRNAs were administered to mice intravenously. This resulted in the specific downregulation of the miRNAs and allowed the identification of several miRNA target genes through their increased expression.

GENOME EVOLUTION

An adaptive view of non-coding DNA

Increasing evidence indicates that although most DNA in eukaryotic genomes is non-coding it is far from being non-functional. An investigation of evolutionary patterns in the *Drosophila* genome now reinforces this theory by showing that non-coding DNA has been shaped by adaptive evolution — a finding that throws into further doubt the neutral theory of evolution.

By assessing sequence divergence between *Drosophila melanogaster* and its close relative *Drosophila simulans*, Peter Andolfatto examined the evolutionary rate of different types of genomic element. This indicated that non-coding regions have evolved more slowly than synonymous sites — those that lead to amino-acid changes in proteins when they are mutated. Polymorphism levels in *D. melanogaster* are also lower for non-coding sites than for synonymous sites, and together these results provide evidence for selective constraints against mutations in non-coding regions — a sign of functional importance.

Is selective constraint the only force at work in the evolution of non-coding DNA, or might adaptive evolution through positive selection also have a role? Andolfatto tested this on the basis that positive selection leads to increased levels of interspecies sequence divergence relative to levels of polymorphism within species, whereas selective constraint has the opposite effect. In a variation on standard methods, rare polymorphisms were excluded from the analysis, as such variants that have been subject to negative selection can decrease the ability to detect adaptive evolution. Andolfatto found that non-coding sequences showed a higher level of divergence than of polymorphism, with the difference being greater than that seen for synonymous sites — which is evidence that non-coding DNA is subject to adaptive evolution.

The fact that non-coding DNA shows low levels of variation within populations, but has been under positive selection, provides strong support for the theory that such regions have important functional roles. It also suggests that comparative-genomics approaches that are used to identify functional non-coding regions on the basis of sequence conservation are likely to miss many such regions, as they fail to take into account adaptive changes.

Crucially, this study has wider implications for understanding the significance of positive selection, as Andolfatto estimates that many non-coding sites are subject to this evolutionary force. Given the large proportion of eukaryotic DNA that consists of such sites, this presents an important challenge to the widely held theory that it is mainly neutral evolution that shapes eukaryotic genomes.

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References and links

ORIGINAL RESEARCH PAPER Andolfatto, P. Adaptive evolution of non-coding DNA in *Drosophila*. *Nature* **437**, 1149–1152 (2005)
FURTHER READING Kondrashov, A. S. Evolutionary biology: Fruitfly genome is not junk. *Nature* **437**, 1106 (2005)
WEB SITE
Peter Andolfatto's home page: http://www.biology.ucsd.edu/faculty/andolfatto.html