

EVOLUTION

The advantages of sex

Two new studies using contrasting approaches shed light on why sex evolves, and how it maintains itself.

Sexual reproduction isn't easy. In evolutionary terms it is much less effort to reproduce asexually. However, asexual organisms have genetic loci that are permanently linked and so, theoretically, are more prone to accumulating deleterious mutations — a factor that is often cited to explain the evolutionarily short-lived nature of most asexual species.

Paland and Lynch tested whether the theoretical advantage that sex has in purging deleterious mutations — owing to the meiotic and recombinational reshuffling of genes — is evident in a real system: sexual and asexual forms of the water flea

Daphnia pulex. Their approach was to compare mitochondrial genes of the two forms for ratios of synonymous and non-synonymous nucleotide substitution — if the rate of the former (K_s) is greater than that of the latter (K_n), this indicates that a gene has been subject to the purging effects of purifying selection.

The contrast between the sexual and asexual groups was striking: the K_n/K_s ratio was much higher for asexual branches of the *D. pulex* phylogenetic tree, which indicates an accelerated accumulation of deleterious mutations. The authors estimate that 17.7% of amino-acid substitutions arising in asexual lineages persist despite being deleterious, compared with just 4.4% in sexual lineages. This provides strong empirical evidence that the purging of mildly deleterious mutations is a key advantage of sex.

But does this factor alone account for the prevalence of sex among multicellular organisms? Sex is expected to speed up the purging of deleterious mutations only if mutations in interacting genes are more deleterious in combination than expected from their individual effects, a pattern called negative epistasis. Azevedo and colleagues used a modelling approach to test whether negative epistasis evolves as a consequence of sexual reproduction.

The authors used a model that represents individuals as networks of interacting transcriptional regulators. Under conditions that are known to

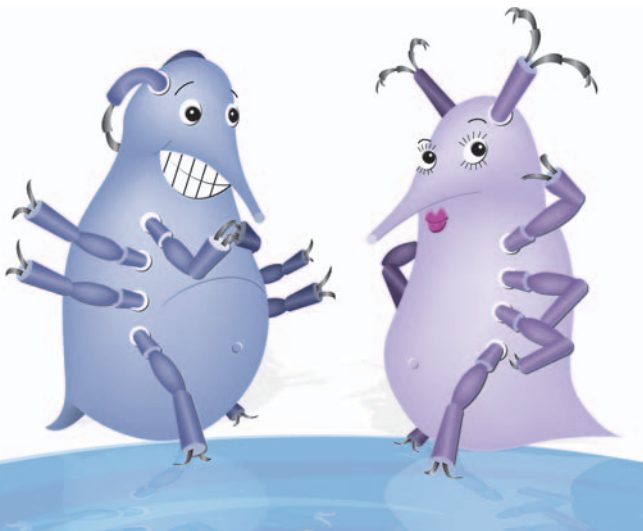
favour genetic robustness (insensitivity of phenotypes to mutations) they compared sexual and asexual populations. As expected, robustness increased in both types of population until it reached an equilibrium, but this equilibrium was reached at a significantly lower value in asexual populations. Moreover, sexual populations at equilibrium showed negative epistasis, whereas asexual populations showed positive epistasis.

This pattern held up under a range of conditions, so it seems that negative epistasis in sexually reproducing organisms is favoured wherever conditions favour genetic robustness (which is likely to be the case in most multicellular organisms). This disproportionate increase of the deleterious effects of interacting mutations in sexual populations obviously favours the maintenance of this reproductive mode, where natural selection can more easily purge deleterious mutations.

Together, these studies suggest that we might be getting close to understanding why most multicellular organisms think that sex is worth bothering with — despite its costs.

Nick Campbell
Assistant Publisher and Executive Editor,
NPG Nature Asia-Pacific

ORIGINAL RESEARCH PAPERS Azevedo, R. B. R. et al. Sexual reproduction selects for robustness and negative epistasis in artificial gene networks. *Nature* **440**, 87–90 (2006) | Paland, S. & Lynch, M. Transitions to asexuality result in excess amino acid substitutions. *Science* **311**, 990–992 (2006)



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Even chromosomes have their weaknesses

The breaking and rejoining of different chromosomes can lead to serious medical conditions, but the cause of these translocations was thought to be largely random. It now emerges that sequence variation is probably responsible for the fracture-prone sites in our DNA.

Translocations are among the most frequent genetic aberration in humans — in fact, many of us carry them around without any noticeable effect on health. Because translocations occur sporadically in so many individuals, the molecular mechanism by which they arise has been difficult to pinpoint. Kato and colleagues have now concentrated on a recurrent translocation between human chromosomes 11 and 22; they noticed that many unrelated translocations occurred within palindromic AT-rich repeats (PATRRs).

The authors then took a closer look at the palindrome on chromosome 11 (PATRR11). In most normal individuals the palindrome is about 450 bp; however, other shorter variants are also present in the healthy population, which probably arise by deletions within the 450-bp allele. But are these size variants functionally important? To find out, the authors looked to see how frequently translocations occurred *de novo* in sperm that carried various combinations of the PATRR11 alleles. What they found was a startling variation of three orders of magnitude in the frequency of translocation, depending on the repeat size — from 1 in 10^4 in the homozygote for the longest PATRR11 variant to 1 in 10^7 in a heterozygote for shorter variants.

This is the first time that sequence variation has been found to underlie human translocations. The fact that PATRR-like sequences have been found at the breakpoints of translocations between other chromosomes reinforces the causal role of palindromes in these aberrations.

Tanita Casci

ORIGINAL RESEARCH PAPER Kato, T. *et al.* Genetic variation affects *de novo* translocation frequency. *Science* **311**, 971 (2006)

FURTHER READING Emanuel, B. S. & Shaikh, T. H. Segmental duplications: an 'expanding' role in genomic instability and disease. *Nature Rev. Genet.* **2**, 791–800 (2001) | van Gent, D. C. *et al.* Chromosomal stability and the DNA double-stranded break connection. *Nature Rev. Genet.* **2**, 196–206 (2001) | Feuk, L. *et al.* Structural variation in the human genome. *Nature Rev. Genet.* **7**, 85–97 (2006)

Ethics watch



CONTROLS OVER PLANT GENETIC RESOURCES — A DOUBLE-EDGED SWORD

In industrialized countries, the proliferation of intellectual property rights (IPRs) that relate to biotechnologies, genes and plants has been dubbed an 'anti-commons' tragedy. Their extension to developing countries presents an even bigger concern, as the IPR models of the industrialized world might not cater for the needs of developing nations. Pressures to adopt IPRs arise primarily from trade instruments, rather than from the desire to support innovation in these countries. Private ownership of genetic resources also conflicts with widely held traditions in farming communities that 'seeds' should be freely shared.

As early as the 1980s, worries about the concentration of power in the seed and pharmaceutical sectors were linked to the control of genetic resources. This resulted in these resources being brought under state sovereignty by the Convention on Biological Diversity (1992), allowing countries to regulate access to these genetic resources within their borders and negotiate a share of the benefits that arise from their use. It also stimulated the recognition of the rights of farmers and traditional healers, who developed and now maintain these resources within these countries.

A dilemma is now arising as countries start to develop and implement legislation on access and benefit sharing. These laws seem to be contributing to an anti-commons situation instead of reversing it; as stakeholders can veto access, transaction costs are skyrocketing, and laws could lead to preferential access by large multinational companies, which can promise the highest benefits. Groups that oppose the legal enclosure of genetic materials through IPRs have, paradoxically, promoted the development of mechanisms that keep even more materials out of the public domain. So far, this has led to a decline in exchange, while the benefits for farmers have been minimal.

The International Treaty on Plant Genetic Resources for Food and Agriculture (2004) attempts to address some of these concerns. Its multilateral system facilitates access and benefit sharing, reducing transaction costs and regaining some aspects of common access and use. A major task at the first session of its governing body in June 2006 will be to design rules for implementation that create significant benefits, while supporting the conservation and sustainable use of genetic resources, as well as farmers' rights.

In addition, strategies from the patent system that keep technologies available to farmers could be adapted and built into biodiversity laws to suit the exchange of genetic resources. These could include broad humanitarian license systems (as pioneered by the Generation Challenge Programme), joint IPR strategies that are followed by public universities (as developed by the Public Intellectual Property Resource for Agriculture), and open-source strategies (as initiated by CAMBIA).

Seeking to maximize benefits for access to agricultural genetic resources by using either IPRs or access laws will not support equity among nations or improve the livelihoods of those in developing countries.

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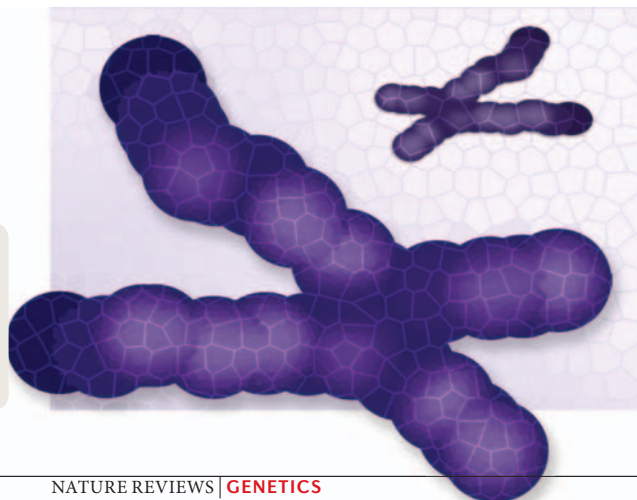
FURTHER READING Esquinas-Alcázar, J. Protecting crop genetic diversity for food security: political, ethical and technical challenges. *Nature Rev. Genet.* **6**, 946–953 (2005)

FURTHER INFORMATION

CAMBIA: www.cambia.org

Generation Challenge Programme: www.generationCP.org

Public Intellectual Property Resource for Agriculture: www.pipra.org



GENETIC VARIATION

When more is more

Much excitement has surrounded the finding of large amounts of structural variation in the human genome. But what contribution does this make to phenotypic variation? A recent study provides evidence that human copy number variants (CNVs) have had a role in the adaptation of humans to their surroundings.

Chris Ponting and colleagues looked at CNVs that were identified in previous studies and used a bioinformatics approach to compare features of CNVs with those of the genome as a whole. Among their findings, the authors showed that CNVs are enriched in genes, and that different gene types are present unevenly within them. Genes that are involved in Mendelian diseases are underrepresented, which could be explained if the extra gene copies provided by CNVs compensate for mutations that might otherwise lead to disease.

By contrast, CNVs are overrepresented in genes that function in innate and acquired immunity and olfaction, and those that encode integral membrane proteins. Interestingly, these classes of gene match those that are predicted to require the ability to evolve particularly rapidly, for example, in response to altered host–pathogen interactions. Consistent with this, the authors found that the genes that contain CNVs have accumulated an unusually large number of substitutions that affect protein sequence, indicating that they have been subject to positive selection. CNVs could contribute to the ability to adapt by providing increased gene dosage, and therefore an adaptive advantage.

The search for structural variants has only recently begun, but many more are likely to be found. The findings from this study indicate that studying these variants closely will be important in understanding how humans have adapted to new environments.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Nguyen, D.-Q., Webber, C. & Ponting, C. P. Bias of selection on human copy-number variants. *PLoS Genet.* **2**, e20 (2006)

FURTHER READING Feuk, L., Carson, A. R. & Scherer, S. W. Structural variation in the human genome. *Nature Rev. Genet.* **7**, 85–97 (2006)



SYNTHETIC BIOLOGY

Building up a picture of gene regulation

Synthetic biologists have been making models of synthetic gene networks that describe the behaviour of these networks *in vivo*.

Guido, Wang and colleagues now show that not only can such models quantitatively describe characteristics of gene expression but also they can be used to predict the *in vivo* behaviour of more complex systems.

The authors engineered the $O_R O_{lac}$ promoter in *Escherichia coli* in a way that allowed them to study, in a controlled way, the effects of repression and/or activation on reporter gene expression. Four modules were constructed — unregulated, repressor-only, activator-only, and repressor and activator — in which the promoter was cloned upstream of a *GFP* ORF, and in which the activator and/or repressor were either present or absent.

A stochastic mathematical model that the authors developed

correctly predicted the behaviour of the engineered modules, taking into account factors such as changes in the concentration of transcription factors and cell volume. Moreover, the model was able to make further predictions, for example, that a substantial amount of variability in gene expression in this system was due to fluctuations in the copy number of the plasmid — an expectation that the authors confirmed experimentally by re-cloning their engineered promoters into different plasmids. Strikingly, the model was also able to correctly predict the *in vivo* behaviour of a more complex system, in which a positive-feedback loop was added to the repressor–activator module.

When used to analyse how the different sources of noise contribute to the overall variability in expression, the model returned a surprising result — contrary to expectations, variability between cells seemed to

RNA WORLD

Behind the scenes

In the past decade there has been a surge of interest in microRNAs (miRNAs) — tiny, non-coding molecules of RNA. miRNAs have two functions: they base pair with partially complementary mRNAs to prevent the translation of mRNA into protein, and they reduce the cellular concentration of their mRNA targets. However, despite the significant insights into gene regulation that have been gleaned from the study of miRNAs, their modes of action have remained poorly understood. Two papers now highlight new biological functions and regulatory mechanisms of miRNAs.

Giraldez and colleagues set out to identify the *in vivo* targets of miRNAs, which are largely unknown. Using microarrays and *in vivo* target

validation, the authors identified a large group of mRNAs that had a >85% probability of being direct targets of the miRNA miR-430. They estimated that, during early zebrafish development, there are, in fact, several hundred direct targets of miR-430 regulation. An analysis of the target set showed that most were expressed maternally, which indicated that miR-430 could have a crucial role in the maternal-to-zygotic transition in embryogenesis. Poly(A) tails stabilize mRNAs and enhance translation, and deadenylation can trigger translational silencing and mRNA decay. Giraldez *et al.* tested whether the decay of miRNA targets correlated with changes in the poly(A) tail length of mRNAs. They showed



increase in the absence of cell growth or cell division. The authors explain this prediction, which they also verified experimentally, by saying that: “in a population of cells with varying plasmid copy number, the intercellular variability increases as expression levels increase from new protein synthesis.” Cell division limits the mean and narrows the distribution of protein levels.

By engineering and modelling relatively simple gene expression modules the authors elegantly show

that quantitative models of such modules can predict behaviour of more complex systems. Such bottom-up approaches could help us to build up a detailed picture of how gene regulation is brought about.

Magdalena Skipper

ORIGINAL RESEARCH PAPER Guido, N. J. & Wang, X. *et al.* A bottom-up approach to gene regulation. *Nature* **439**, 856–860 (2006)
FURTHER READING Kaerns, M. *et al.* Stochasticity in gene expression: from theories to phenotypes. *Nature Rev. Genet.* **5**, 451–464 (2005)
 | Wall, M. E. *et al.* Design of gene circuits: lessons from bacteria. *Nature Rev. Genet.* **6**, 34–42 (2004)

that miR-430 does indeed accelerate the deadenylation of target mRNAs. Moreover, the group showed that impaired translation is not sufficient on its own to significantly increase deadenylation, nor is translation required for miR-430 to increase the rate of poly(A) tail removal.

In the second paper, Wu *et al.* examined two different miRNAs, miR-125b and let-7, in mammalian cells, and found that both miRNAs accelerate the decay of mRNA by a mechanism that is distinct from that of small interfering RNAs, which target mRNAs that are perfectly complementary. They showed that the miRNAs interact with the 3′ untranslated region of target mRNA and, similar to miR-430 in the *Science* study, induced accelerated mRNA degradation by expediting poly(A) tail removal. Interestingly, these miRNAs can induce this process for many mRNAs that bear various elements to which the miRNAs are

partially complementary. Wu *et al.* also showed that the reduced translation and increased deadenylation are distinct. These findings indicate that miRNAs downregulate gene expression by two independent mechanisms: reduced translation efficiency and accelerated mRNA deadenylation and decay.

These two papers have identified possible mechanisms for miRNA function and have provided a fascinating behind-the-scenes look at the workings of miRNAs, which should continue to stoke the fire of interest in this ‘tiny RNA world’.

Sharon Ahmad, Assistant Editor,
Nature Reviews Molecular Cell Biology

ORIGINAL RESEARCH PAPERS Giraldez A. J. *et al.* Zebrafish miR-430 promotes deadenylation and clearance of maternal mRNAs. *Science* 16 February 2006 (doi:10.1126/science.1122689)
 | Wu, L. *et al.* MicroRNAs direct rapid deadenylation of mRNA. *Proc. Natl Acad. Sci. USA* 22 February 2006 (doi:10.1073/pnas.0510928103)

IN BRIEF

EVOLUTION

DNA sequences shaped by selection for stability.

Ackermann, M. & Chao, L. *PLoS Genet.* **2**, e22 (2006)

The nucleotide composition of a DNA stretch influences the probability that it will accumulate mutations during replication and expression. Selective forces might therefore exist that make coding sequences avoid the most unstable nucleotide sequences, namely mononucleotide stretches. On the other hand, mutations are also a source of sequence variation, and therefore have adaptive potential. Sampling the genomes of several organisms showed that there is indeed selection against mononucleotide stretches. This means that selection for sequence stability against mutations is a stronger force than selection for sequence variation.

EVO-DEVO

Dorso/ventral genes are asymmetrically expressed and involved in germ-layer demarcation during cnidarian gastrulation.

Matus, D. Q. *et al. Curr. Biol.* **16**, 499–505 (2006)

In bilaterally symmetrical animals, the TGFB signalling pathway has a well-documented role in establishing the dorsal–ventral axis. A series of experiments in *Nematostella vectensis*, which is radially symmetrical, shows that the orthologues of some TGFB pathway members and interactors are expressed asymmetrically at the onset of gastrulation, and segregate into different germ layers. This work suggests that the original function of the TGFB pathway might have been in germ-layer formation or epithelial patterning rather than in axis patterning.

HUMAN DISEASE

Lamin A/C and emerin are critical for skeletal muscle satellite cell differentiation.

Frock, R. L. *et al. Genes Dev.* **20**, 486–500 (2006)

Mutations in lamin A cause several forms of human muscular dystrophy; now, a mouse model of Emery–Dreifuss muscular dystrophy reveals that this component of the nuclear envelope causes muscle wastage by interfering with myoblast differentiation. Cells in which the expression of *Lmna* (which codes for lamins A and C) was reduced by *Lmna* deficiency or siRNA-mediated knockdown showed altered expression of muscle differentiation genes and arrested muscle differentiation, effects that were reversed by expressing *Lmna* or *MyoD*.

EPIGENETICS

RNAi components are required for nuclear clustering of Polycomb group response elements.

Grimaud, C. *et al. Cell* **124**, 957–971 (2006)

Polycomb group (PcG) genes maintain homeotic genes in a silent chromatin state. Grimaud *et al.* show that components of the RNAi machinery are required for the maintenance of long-range silencing at *Fab-7*, a Polycomb response element from *Abdominal B*, a fly homeotic gene. Mutant analysis revealed an unexpected role for the RNAi machinery in spatial gene regulation — Dicer 2, PIWI and Argonaute 1 co-localize with PcG proteins and might be required to stabilize gene clustering at specific nuclear bodies, which might be important for cosuppression.

In the news

KEEPING UP WITH THE GREWCOCKS

Men who share the same surname have a 25% chance of being related, a British study reveals. The rarer the surname, the greater the chance of random pairs of surnames being related (*The Scotsman*, 22 February 2006). So there is little hope of building a large family tree for the Smiths, Joneses and Taylors, but there are much improved chances for the Attenboroughs and Grewcocks, for example.

For the study, which was published in *Current Biology* on 21 February 2006, researchers recruited 150 pairs of English men that shared the same surname but were not knowingly related. About a quarter of these men were genetically connected through their Y chromosome, meaning that they must have shared an ancestor more recently than 20 generations ago, or about AD 1300, when surnames were first used in the United Kingdom (*New Scientist*, 22 February 2006).

Y chromosomes are inherited from father to son, and surnames are inherited from father to children, so men who share surnames are also related. Has this work merely told us what we know already? Yes and no. Complicating factors such as illegitimacy, adoption and multiple originators would increase the chances that two people with the same surname would not be related (*Seed Magazine*, 27 February 2006).

That striking strong signal immediately suggests a practical application. Forensic scientists could use DNA retrieved from a crime scene to predict the surname of the suspect (*BBC News*, 21 February 2006) when used in combination with other intelligence. Indeed, Brian Sykes, from the University of Oxford, recommends that we create a Y-chromosome database (*The Scotsman*).

The bottom line is, if you think you've got criminal tendencies, you could do worse than change your name to Smith.

Tanita Casci

NEUROGENETICS

A male gene for a male brain

Male and female brains are different in important ways — not just in generating distinct sexual behaviours, but also in terms of cognition and other key functions. Until recently, these differences were thought to arise from the effects of sex hormones during brain development, but there have been several hints lately that genes in the adult brain have a role in maintaining this male–female divide. Work from Eric Vilain and colleagues now shows that the Y-chromosome gene *Sry*

directly influences the function of the brain in adult males.

Sry is a transcriptional regulator and is best known as the master controller of male sexual development. However, previous studies have shown that, intriguingly, this gene is also expressed in the adult male brain. Vilain and colleagues confirmed this, showing that *Sry* mRNA is present at a low level throughout the brain cortex in male mice, and at higher levels in two regions: the mammillary bodies and the substantia nigra (SN). Focusing



CANCER GENETICS

From expression signatures to their regulators

Analyses of global gene-expression patterns have yielded molecular signatures that predict progression, prognosis and response to therapy for many tumour types. Adler and Lin *et al.* now take this approach a step farther — they have developed a genetic linkage-based method to identify key molecular players that regulate cancer-associated changes in transcriptional signatures.

With the aim of understanding the genetic determinants that underlie the characteristic and at times predictive changes in gene expression that occur in tumours, the authors developed a genome-wide genetic linkage method. In a procedure that the authors call SLAMS (stepwise linkage analysis of microarray signatures), the linkage of prospective regulator genes is first mapped to large chromosomal regions. This is achieved by looking for correlation between a specific expression signature and copy-number changes within particular genomic regions. This

“...a general method that ... can be adapted to identify linkage between expression signatures and other types of data, such as SNPs or DNA methylation.”

linkage is subsequently validated and refined by determining whether increased expression of candidate genes from within these regions is correlated with the signature, as would be expected if increased copy number of a gene had a regulatory effect. To improve the robustness of their analysis, Adler and Lin *et al.* considered the coordinated behaviour of many genes in an expression signature.

The authors previously identified a ‘wound response signature’, which is a powerful predictor of metastasis and poor prognosis in many tumour types. SLAMS was used to identify genetic regulators of this signature in breast cancer tissue. Using 37 samples, they identified a region on 8q that strongly associated with the wound signature. Further refinement indicated that within this region it is the *MYC* oncogene and *CSN5* (a catalytic subunit of the COP9 signalosome) that cooperate to generate the expression signature. Consistent with this prediction,

on the SN, which controls voluntary movement, the authors showed that the SRY protein colocalizes with tyrosine hydroxylase (TH), an enzyme that is involved in the synthesis of the neurotransmitter dopamine, which is essential for the functioning of this region.

To investigate the functions of SRY in TH-expressing cells, male rat SNs were microinfused with antisense oligonucleotides targeted against *Sry*. This led to reduced TH expression in the SN and in regions that are usually innervated by TH-expressing neurons, showing that SRY directly regulates the expression of this enzyme. The authors were also able to show that SRY expression in the SN has a functional consequence. Microinfusion of *Sry* antisense oligonucleotides into the SN on one side of the brain reduced the stepping activity of

rats using the forelimb on the corresponding side of the body.

The fact that SRY functions in the adult male brain in a way that doesn't rely on hormones indicates that we should think differently about sexual dimorphisms in the brain, taking direct genetic effects into account. This will be important for many reasons, not least for understanding the differing susceptibilities of men and women to psychiatric disorders and other neurological diseases.

Louisa Flintoft

ORIGINAL RESEARCH PAPER

Dewing, P. *et al.* Direct regulation of adult brain function by the male-specific factor SRY. *Curr. Biol.* **16**, 415–420 (2006)

WEB SITE

Eric Vilain's web page: <http://dgsom.healthsciences.ucla.edu/research/institution/personnel?personnel%5fid=9435>

the region that contains CSN5 and MYC tends to be significantly amplified in tumours with the wound signature. Moreover, expressing MYC and CSN5 in non-transformed breast epithelium is sufficient to activate the wound signature. These cells become invasive but remain untransformed, indicating that wound signature and MYC and CSN5 expression are early markers of metastatic potential. The authors also showed that CSN5 controls the ubiquitylation and activity of MYC, providing a biochemical basis for their genetic interaction.

The utility of this elegant research is twofold. First, the authors provide

a general method that, although prone to some bias because it requires human interpretation, can be adapted to identify linkage between expression signatures and other types of data, such as SNPs or DNA methylation. Second, they provide new insights into the genetic circuitry of breast cancer, therefore identifying targets for potential new approaches to treatment.

Magdalena Skipper

ORIGINAL RESEARCH PAPER

Adler, A. S. & Lin, M. *et al.* Genetic regulation of large-scale transcriptional signatures in cancer. *Nature Genet.* **05** March 2006 (doi:10.1038/ng1752)

WEB SITE

Howard Chang's web site: <http://changlab.stanford.edu>

IN BRIEF

TECHNOLOGY

Genome-wide detection of polymorphisms at nucleotide resolution with a single DNA microarray.

Gresham, D. *et al.* *Science* **9** March 2006 (doi:10.1126/science.1123726)

This paper describes a simple, inexpensive method for the genome-wide detection of intraspecific mutation and variation using a single microarray. The authors used a tiling array that provides roughly fivefold coverage of the *Saccharomyces cerevisiae* reference genome. Using known SNPs as a training set, they devised an algorithm that predicts the presence of single-nucleotide differences across the genome on hybridization to the array. In several scenarios, this approach provided sensitive, high-resolution detection of SNPs and also identified insertions and deletions, highlighting its potential for a range of applications.

NETWORK BIOLOGY

Genome-wide prediction of *C. elegans* genetic interactions.

Zhong, W. & Sternberg, P. W. *Science* **311**, 1481–1484 (2006)

Genetic interactions can be revealed by modifier screens but their success depends on easily scorable phenotypes and they are not feasible on a global scale in metazoans owing to their genome complexity. These authors used a computational approach to integrate interactome, gene-expression, phenotype and functional annotation data from baker's yeast, the fly and the worm. Pooling information from different species overcomes incompleteness of the data for any one organism. The result was a network of 18,183 functional genetic interactions in the worm, which is publicly available and serves as a cross-species genetic data search engine for genetic interactions.

LIFESPAN

Germ-cell loss extends *C. elegans* life span through regulation of DAF-16 by *kri-1* and lipophilic-hormone signalling.

Berman, J. R. & Kenyon, C. *Cell* **124**, 1055–1068 (2006)

SMK-1, an essential regulator of DAF-16-mediated longevity.

Wolff, S. *et al.* *Cell* **124**, 1039–1053 (2006)

These studies provide new insights into the specificity and integration of pathways that control lifespan. Berman and Kenyon showed that the *Caenorhabditis elegans* gene *smk-1* is essential for the control of longevity by the transcription factor DAF-16, which is the effector of the insulin signalling pathway. Furthermore, *smk-1* is needed specifically for DAF-16 to regulate stress responses that are involved in lifespan extension, but not for other physiological effects of the insulin signalling pathway. This indicates that lifespan regulation can be uncoupled from other potentially harmful functions of this pathway. As well as insulin signalling, reproductive status also affects longevity, and Wolff and colleagues showed how these two factors might be integrated. In a screen for new genes that are required for increased lifespan due to loss of germ cells, they identified *kri-1*, and showed that hormone signalling from the reproductive system to the intestine promotes DAF-16 function through the activity of this gene.

Following the signposts of selection

Despite our fascination with the evolutionary processes that have led to the unique characteristics of humans, insights into the genetic basis of these changes have been limited. Only a handful of genes have been pinpointed as strong candidates for having undergone adaptive changes in the human lineage, and our knowledge of the underlying mechanisms is also sparse. However, as illustrated by two recent papers that use different strategies to identify regions and genes that have experienced selection during human evolution, the tools are now becoming available to make greater progress in this area.

One theory is that changes in gene regulation have been key to human evolution, a hypothesis that can be tested by examining gene-expression differences between humans and other primates. Gilad and colleagues used a multi-species microarray to assess differences in expression in the liver between over 1,000 human genes and their orthologues from three other primates. They identified 19 genes that are expressed at the same levels in the three non-human primates, but at higher or lower levels in humans compared with these other species. This is strong evidence that changes in the expression of these genes have been selected for specifically in the human lineage.

Notably, the genes that show increased expression in humans were particularly enriched for transcription-factor genes. This is consistent with previous findings that such genes have evolved rapidly at the level of coding sequence in humans, and ties in with how gene-expression changes might have evolved, with transcription-factor modifications affecting the regulation of their target genes.

In a second study, Voight and colleagues used a different strategy to identify regions containing alleles that have been under very recent selection and have not yet reached fixation in the human genome. They took advantage of SNP data from the International HapMap Project for three

different populations to locate genomic regions that contain unusual patterns of linkage disequilibrium that are indicative of an ongoing selective sweep — a process that alters linkage disequilibrium patterns and ultimately drives down genomic diversity in the region surrounding a positively selected allele. This analysis revealed many such regions throughout the genome, some of which contain genes that have been shown to have undergone positive selection in previous studies.

The authors also picked out the genes within their regions of interest that are the best candidates for having experienced selection. Several functional categories were enriched within these genes, including those such as olfaction and reproduction that have previously been highlighted as targets of selection. However, a number of new categories also stood out, including genes that are involved in metabolism. Intriguingly, this might correspond to changes in the human diet during the expansion of agriculture, which fits in with the authors' estimates of the timing of the selection that is captured in their study.

Much remains to be learned from the approaches that were used in both of these studies: for example, the expression-based method has so far been used only for genes that are expressed in the liver, and the authors of the second study stress that much uncertainty remains about the actual genetic targets of selection and the nature of the adaptation. Clearly, exploring the genetic basis of human evolution is a challenge that has only just begun.

Louisa Flintoft

ORIGINAL RESEARCH PAPERS Gilad, Y. *et al.* Expression profiling in primates reveals a rapid evolution of human transcription factors. *Nature* 9 March 2006 (doi:10.1038/nature04559) | Voight, B. F. *et al.* A map of recent positive selection in the human genome. *PLoS Biol.* 4, e72 (2006)

A small leap for adaptation

How does a trait evolve from A to B? Does it take many small steps, or one big one, or does it take one largish step followed by a few small ones? These questions are difficult to answer, mainly because adaptive events are only observed after they have taken place. An experimental evolution study in *Pseudomonas* spp. has captured the first adaptive event as it happens — the fitness advantage of such mutations is high, and so that first step to adaptation is more of a jump.

The view that evolution is a gradual process has been challenged by evidence that large-effect mutations can also underlie adaptive changes. But developing a general rule of adaptation is not easy, especially because beneficial mutations occur rarely. Experimental evolution presents a unique advantage: many beneficial mutations can be recovered, and their adaptive fitness can be compared to that of the ancestral population.

In this study, populations of the bacterium *Pseudomonas fluorescens* were grown in a harsh, carbon-limited medium for approximately 100 generations. The selection coefficients of the 68 fixed beneficial mutations that were recovered followed a bell-curve distribution; they also occurred at a higher rate than expected (3.8×10^{-8} per cell division) and had a much greater selective advantage (2.1).

The fact that the first beneficial steps in evolution are larger than previously supposed has theoretical importance, but it also has a direct bearing on modelling the evolutionary trajectory of microbes that are harmful to human health.

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ORIGINAL RESEARCH PAPER Barrett, R. D. H. *et al.* Mutations of intermediate effect are responsible for adaptation in evolving *Pseudomonas fluorescens* populations. *Biol. Lett.* 14 February 2006 (doi:10.1098/rsbl.2006.0439) | **FURTHER READING** Orr, H. A. The genetic theory of adaptation: a brief history. *Nature Rev. Genet.* 6, 119–127 (2005)

