WEB WATCH

Are you policy aware?

• <http://www.humgen.umontreal.ca/en/welcome.cfm>

There is an increasing need for scientists, particularly human geneticists, to consider the social, legal and ethical implications of their work. The HumGen website is an excellent starting point to investigate these areas, as it contains a collection of authoritative policy documents on human genetics. These include legislation, directives and guidelines from international, regional and national bodies, such as the World Health Organization and the Nuffield Council on Bioethics. The website is governed by an international Scientific Advisory Board.

It is possible to compile your personal bibliography at the GenBiblio facility. This allows the browser to search and download relevant articles in a particular area of genetics, such as pharmacogenomics or cancer, and on a particular ethical, legal or social issue — for example, intellectual property or counselling. For more information, it might be necessary to contact one of the 300 organizations that are involved in formulating policy statements on human-genetics research — their contact details can be obtained from GenConnect.

The HumGen team has put together a bimonthly freely-available electronic periodical called GenInfo. This circulates new policy statements and aims to inform lawyers, policy makers, researchers, health professionals and the general public. There is also a new editorial feature — GenEdit. Its first article tackles cloning legislation and provides an overview of the science, discusses the legal, ethical, religious and cultural issues associated with this technology, and has suggestions for future legislation.

This website is a unique source of international genetic policy information and is a must for geneticists that are interested in looking into the wider implications of their work.

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EPIGENETICS

Silent connection

X chromosome inactivation (XCI) — silencing of one of the two female X chromosomes to ensure equal dosage of X-linked genes in XX and XY individuals — and autosomal imprinting — the differential expression of alleles depending on their parent-of-origin — were once considered to be distinct phenomena. Recent data indicate that these regulatory processes have many features in common, and two groups provide evidence in support of this link. Mager *et al.* show, for the first time, that the mouse Eed (embryonic ectoderm development) Polycomb group (PcG) protein is needed for autosomal imprinting, and, building on previous work that demonstrated a role for Eed in imprinted XCI, Silva *et al.* now show that Eed has a central role in random XCI.

The accumulation of *Xist* RNA along the inactive X chromosome (Xi) — the first essential step of XCI — recruits the factors that are needed for silencing, including the

PcG proteins Eed and Enx1. Silva *et al.* used immunofluorescence to show that in differentiating mouse stem-cell lines, and in mouse embryos, these proteins form transient foci on the X that is to be inactivated; this is coincident with *Xist* RNA expression. Transgenic experiments in which *Xist* is ectopically expressed in XY cell lines and mice, and studies of *Xist* mutants, have indicated that *Xist* is both necessary and sufficient for the formation of Eed–Enx1 foci on the X chromosome.

The authors monitored histone H3 modification to find out how the Eed–Enx1 localization generates the histone modifications that are needed for XCI. Strong immunofluorescence staining for methylation of H3-K9 and K27 in the regions of Eed–Enx1 foci support previous data indicating that Eed catalyses histone methylation. Moreover, in *eed*^{−/−} mutant mice, Eed–Enx1 foci no longer form on Xi, and XCI is impaired. The fact that H3-K9 and

K27 methylation is also absent in these mice shows that Eed is necessary for the XCI-associated histone modifications.

Mager *et al.* used the same *eed*^{−/−} mutant line to show that this Polycomb group protein is also required for the silencing of a subset of autosomal imprinted loci. The authors followed specific imprinted loci with different polymorphisms that were associated with maternally

EVOLUTION

No sex please, we're ostracods

Although some species might experiment with alternative methods of reproduction, most eukaryotes — including humans — are hooked on sex. Defying this

trend, a few lineages have avoided early extinction, which is a genetic hazard associated with long-term asexuality. So, how have these ancient asexuals escaped the

deleterious effects of amixis, and what can they tell us about the puzzling prevalence of sex?

Isabelle Schön and Koen Martens have examined the mutational load of the oldest extant asexual species *Darwinula stevensoni* — an ostracod crustacean that has survived without sex for more than 20 million years — to determine the genetic consequences of its unconventional private life.

They sequenced three nuclear regions of *D. stevensoni* — intron and exon regions of the single copy gene *hsp82*, interspersed regions of *ITS1/ITS2* and the calmodulin intron *CadDS* — and estimated the nucleotide divergence within and between individuals and populations, in comparison to the fully sexual ostracod *Cyprideis torosa*.

The authors found that *D. stevensoni* has exceptionally low

Why does loss of *Eed* disrupt imprinting of only a subset of genes? The affected loci do not share a similar chromosomal location, neither do they have common methylation patterns at their imprinting-control loci or differentially methylated regions. The authors speculated that *Eed* function could be restricted to particular genes if the *Eed*–*Enx1* complex associates with a DNA binding protein that recognizes target sequences at the affected loci.

Silva *et al.* confirmed that *Eed*–*Enx1* is involved in histone modification in XCI. It will be interesting to see if the same also occurs in autosomal silencing, in which case, the CpG methylation pattern differences at affected loci in *eed*^{−/−} mice might be a secondary consequence of altered histone states — a proposition that is made by Mager *et al.*

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and paternally derived alleles. They looked at 14 imprinted loci and detected biallelic transcription in half of the paternally imprinted loci in *eed*^{−/−} mutants; none of the maternally-repressed loci were affected. Bisulphite sequencing — used to compare the methylation status of DNA — showed that in *eed*^{−/−} mice the pattern of CpG methylation at genes with a loss of imprinting is different from the wild type.

References and links

ORIGINAL RESEARCH PAPERS Silva, J *et al.* Establishment of Histone H3 methylation on the inactive X chromosome requires transient recruitment of *Eed*–*Enx1* polycomb group complexes. *Dev. Cell* (10.1016/S1534580703000686) | Mager, J. *et al.* Genome imprinting regulated by the mouse Polycomb group protein *Eed*. *Nature Genet.* **33**, 502–507 (2003)

genetic divergence in all the regions tested. This was unexpected, as exclusively asexual lineages cannot remove mutations from their genome through recombination, which is predicted to lead to the irreversible build up of deleterious mutations.

In the asexual bdelloid rotifers, the non-homologous accumulation of mutations has led to large allelic divergences at the DNA sequence level. Schön and Martens found that rates of allelic divergence in *hsp82* for the rotifer *Pholidina roseola* are significantly higher than those of *D. stevensoni*. To cope with this high mutational load, asexual rotifers have developed specialized ecological adaptations, such as an extremely short life cycle and large population sizes.

Using powerful new likelihood permutation tests, based on the

Fisher–Wright population model, Schön and Martens show that in the absence of recombination, homogenizing mechanisms have prevented the build up of mutations in *D. stevensoni*. Gene conversion has affected the multiple-copy ITS region, and highly efficient DNA repair might have conserved single copy genes.

So, these data support hypotheses that predict that special mechanisms are necessary to compensate for the genetic consequences of a lack of sex. Although *D. stevensoni* has used a different evolutionary strategy to that of the bdelloid rotifers, both groups have had to go to great lengths to break free from the domination of the dating game.

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References and links

ORIGINAL RESEARCH PAPER Schön, I. & Martens, K. No slave to sex. *Proc. R. Soc. Lond. B* 12 March 2003 (10.1098/rspb.2002.2314)

IN BRIEF

TECHNOLOGY

A directional strategy for monitoring Cre-mediated recombination at the cellular level in the mouse.

Schnütgen, F. *et al.* *Nature Biotech.* (10.1038/nbt811)

Site-specific recombinases, such as the *Cre-loxP* system, have made it possible to generate mice in which gene function can be ablated in a temporally controlled and cell-type restricted manner. Now, Schnütgen *et al.* have developed a reporter system that allows the accurate identification of cells in which gene function has been lost. They designed a new *Cre*-dependent genetic switch in which the target gene is switched off at the same time as a reporter is activated.

TECHNOLOGY

Sequence information can be obtained from single DNA molecules.

Braslavsky, I. *et al.* *PNAS* **100**, 3960–3964 (2003)

With the recent trend for genome sequencing, much attention has focused on improving the cost and efficiency of sequencing methods. Obtaining sequences from single DNA molecules is one potential solution. Braslavsky *et al.* now use DNA polymerase and fluorescence microscopy to show that it is possible to monitor the incorporation of fluorescently labelled nucleotides with single-base resolution for stretches of up to 5 bp at a time.

CANCER GENETICS

Disruption of the Fanconi anemia–BRCA pathway in cisplatin-sensitive ovarian tumors.

Taniguchi, T. *et al.* *Nature Medicine* (10.1038/nm852)

Ovarian tumours that are initially susceptible to chemotherapeutic drugs (such as cisplatin) become resistant to them over time. The Fanconi anemia–BRCA (FANC–BRACA) pathway is involved in cisplatin response, so the authors looked at this pathway and found that it was disrupted in some ovarian tumours. Initial methylation at a CpG island of *FANCF* — a gene that lies upstream in this pathway — inactivates the gene; however, subsequent methylation loss during tumour progression correlates with cisplatin resistance.

HUMAN GENETICS

Use of multivariate linkage analysis for dissection of a complex cognitive trait.

Marlow, A. J. *et al.* *Am J. Hum. Genet.* **72**, 561–570 (2003)

Small sample size, imprecise phenotype definition, genetic heterogeneity and the limitations of statistical methods have all contributed to the fact that the linkage results of complex traits are seldom reproducible. Although multiple correlated traits have been collected in many studies they have been analysed independently. Now, for the first time, the authors use QTLs that influence reading- and language-related measures in families with a history of dyslexia to show the superiority of genome-wide multivariate analysis of complex traits.