WEB WATCH

The NHGRI Policy and Legislation Database

• http://www.genome.gov/LegislativeDatabase

A new web-based searchable database for US genetics-related policy and legislative documents promises to be a valuable resource for anyone interested in this ever-expanding and important area.

Francis Collins, director of the US National Human Genome Research Institute (NHGRI), said this tool will be useful for everybody "…from academic researchers seeking to patent genetic technologies to average citizens trying to determine what protections exist in their states against genetic discrimination."

Database users can find legislation and laws from specific states through an interactive US map, as well as doing more specific searches for particular combinations of content type (for example, federal legislative materials), topic (such as genetic testing and counselling) and source (for example, the Department of Health and Human Services). Keyword searching is also possible, but only for words in document titles, not those in their content. Perhaps the most useful 'value-added' feature that the database incorporates is a summary, in layman's terms, of each document: this enables quick identification of relevant documents without the need to trawl through pages of legal jargon.

Of course, one of the biggest limitations of this extremely useful tool is that it only encompasses US policy and legislation. However, this focus is understandable given that the US National Institutes of Health fund this resource. Moreover, the addition of further content categories this autumn, such as foreign statutes and laws and policy material from international organizations, will, at least partially, address this limitation.

Nick Campbell

EPIGENETICS

Family feud

Although relatively few in number, imprinted loci have been of intense interest. The *Gnas* locus on distal mouse chromosome 2 is one of the more complex imprinted regions yet discovered, having an antisense transcript and alternatively spliced isoforms that show biallelic as well as maternal- and paternal-specific expression. The parent-of-origin-specific expression of these and other imprinted genes has yielded insights into the mechanisms of gene regulation, whereas the functional role of imprinting has been one of biology's most intriguing mysteries. Two new studies on the *Gnas* cluster published in *Nature Genetics* advance our understanding on both fronts.

The *Gnas* locus encodes alternative transcripts that arise from 4 different promoters, with different first exons spliced to a common exon 2. Among these, *Gnas* encodes $G_s\alpha$, the α-subunit of the ubiquitous heterotrimeric G protein G_s, which couples receptors to adenylyl cyclase. Although *Gnas* is biallelically expressed in most tissues, it is preferentially maternally expressed in the proximal tubules of the kidney and in brown and white adipose tissue. Williamson *et al.* have now identified a *cis*-acting element that regulates this tissue-specific aspect of *Gnas* imprinting — the first such control region to be identified.

Deletion of a 2.3-Kb differentially methylated region (DMR) that encompasses exon 1A resulted in increased expression of the paternal allele in the kidney and in adipose tissue. The loss of tissue-specific silencing was confirmed by a clever functional assay, in which mice with parathyroid hormone (PTH) resistance were found to have increased $G_s\alpha$-mediated PTH signalling, thanks to increased GNAS production from the paternal allele. The mechanism by which the exon 1A DMR contributes to tissue-specific silencing of the paternal allele remains to be determined.

Plagge *et al.* used a similar gene-targeting approach to examine the function of a paternally expressed *Gnas* transcript, *Gnasxl*, which encodes XLαs. Clues to the function of the various proteins encoded by the *Gnas* locus have come from studies of mice with targeted mutations. Mice that lack $G_s\alpha$ die shortly after birth, with maternal and paternal transmission showing opposing effects on adipose tissue and metabolic rate. As there is no evidence for exclusive paternal expression of $G_s\alpha$ in any tissue, attention turned to the paternally expressed GNASXL as having a distinct functional role.

Plagge and colleagues found that mice in which the XLαs-specific XL domain was deleted also died soon after birth. The pups' growth was retarded, they did not suckle and their lipid stores in adipose tissue were depleted. XLαs sites of expression — nuclei that innervate orofacial and tongue muscles, and the pituitary, pancreas and hypothalamus — are consistent with its role in the postnatal adaptation to feeding and in energy homeostasis.

Notably, the XLαs-deficient phenotype provides compelling support for the parental conflict theory of imprinting, which proposes that paternal genes would increase resource uptake from the mother by offspring, and that maternal genes would restrict nutritional demands. Although this theory has received support from mice with mutations in other imprinted genes, the authors note that this is the first example in which an imprinted locus encodes two proteins that act antagonistically in postnatal physiology — regulating cyclic AMP (cAMP) production in this instance. The *Gnas* locus will no doubt continue to provide a unique window into the role of imprinting in negotiating the competing demands of mothers and fathers.

Alan Packer, Senior Editor, Nature Genetics

References and links

ORIGINAL RESEARCH PAPERS Plagge, A. *et al*. The imprinted signaling protein XLαs is required for postnatal adaptation to feeding. *Nature Genet.* **36**, 818–826 (2004) | Williamson, C.M. *et al.* A *cis*-acting control region is required exclusively for the tissue-specific imprinting of *Gnas*. *Nature Genet*. **36**, 894–899 (2004)

FURTHER READING Wilkins, J. F. & Haig, D. What good is genomic imprinting: the function of parent-specific gene expression. *Nature Rev. Genet*. **4**, 359–368 (2003)