IN BRIEF

EVOLUTION

Evolutionary EST analysis identifies rapidly evolving male reproductive proteins in *Drosophila.*

Swanson, W. J. *et al. Proc. Natl Acad. Sci. USA* **98**, 7375–7379 (2001)

Reproductive proteins are likely candidates for causing the rapid divergence between closely related species, as their modification favours adaptive divergence. To test this hypothesis, Swanson *et al*. compared the sequences of 285 ESTs (expressed sequence tags) isolated from the male accessory glands — which secrete seminal-fluid proteins — of *Drosophila simulans* and *D. melanogaster*. 11% of the 176 genes identified showed evidence of positive selection, and the 57 newly identified accessory gland genes should become candidate genes for further positive selection studies.

CANCER GENETICS

Mitotic recombination effects homozygosity for *NF1* germline mutations in neurofibromas.

Serra, E. *et al. Nature Genet*. **28**, 294–296 (2001)

Neurofibromatosis type 1 (NF1) is an autosomal-dominant disorder caused by mutations in the *NF1* tumour suppressor gene. Of the many cell types seen in NF1 nerve-sheath tumours, only Schwann cells are homozygous for *NF1* mutations. Through molecular and *in situ* hybridization of cultured Schwann cells, this paper shows that loss of heterozygosity for *NF1* occurs by mitotic recombination. As there is inter-individual variability in mitotic recombination rates, genes that control this phenomenon might act as modifier genes for susceptibility to NF1 and other cancers.

HUMAN GENETICS

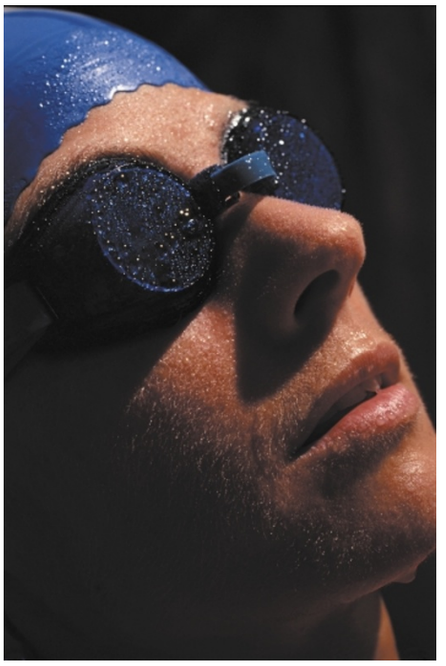
Charcot–Marie–Tooth disease type 2A caused by mutation in a microtubule motor K1F1Bβ.

Zhao, C. *et al. Cell* **105**, 587–597 (2001).

CMT2A is a dominant subtype of Charcot–Marie–Tooth disease (CMT) — the most commonly inherited human peripheral neuropathy — that maps to 1p35–36. When Zhao *et al.* knocked out the mouse β isoform of *K1f1B* — which encodes a motor protein belonging to the kinesin superfamily — null mutants died at birth with multiple neurological abnormalities, and heterozygotes developed progressive muscle weakness and defective synaptic vesicle transport. This CMT-like phenotype and the chromosome-1 map location of *K1f1B* lead the authors to analyse the gene in CMT2A patients, in whom they found loss-of-function mutations in the motor domain of *K1F1B*. As axons lack protein-synthesis machinery, their survival depends on the transport of essential proteins. Haploinsufficiency for *K1f1B* might therefore reduce levels of synaptic vesicle transport of essential factors and receptors, leading to the impairment of nerve endings and to the decreased survival of peripheral neurons.

GENE EXPRESSION

Facing up to antisense



Gene expression is primarily regulated at the levels of transcription, RNA splicing or translation. But evidence is accumulating for another way to regulate gene expression — through the interaction of endogenous antisense RNA with the corresponding sense transcript. In a recent issue of *PNAS*, Blin-Wakkach *et al.* present evidence that *Msx1* — a key transcription factor involved in craniofacial skeleton formation — is regulated by an endogenous antisense transcript, and that this mode of regulation is conserved between rodents and humans.

In tissues such as cartilage and muscle, the downregulation of *Msx1* expression during development is associated with a transition from an undifferentiated, proliferative state to a terminally differentiated one. When Blin-Wakkach and colleagues generated *Msx1*-deficient mice by means of a *lacZ* insertion, they noticed that *lacZ* was not expressed in mice that were heterozygous for the insertion, even though the transcript was detectable by PCR. To test whether the lack of *lacZ* expression was due to regulation by an antisense RNA, the authors identified, by Northern blot analysis, an endogenous transcript the sequence of which was complementary to part of the *Msx1* transcript and had no obvious coding potential. The antisense transcript was ~2.2 kb and overlapped with at least one *Msx1* intron–exon boundary. The authors also mapped the transcription initiation site of the antisense transcript and identified a 66-bp putative promoter region that is conserved in five mammalian species.

The antisense RNA was much more abundant than the sense RNA and its transcription coincided with terminal differentiation in the craniofacial region. Simultaneous disappearance of the Msx1 protein indicates that *Msx1* expression might be regulated by the ratio of its sense and antisense transcripts.

Interaction between the sense and antisense transcripts of *Msx1* seems to be important in the transition from proliferation to terminal differentiation during craniofacial development. Although the exact mechanism is unclear, the authors propose that sense–antisense interactions prevent the correct splicing of the *Msx1* mRNA. More generally, this study highlights an important additional level of gene regulation.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Blin-Wakkach, C. *et al*. Endogenous *Msx1* antisense transcript: *in vivo* and *in vitro* evidences, structure, and potential involvement in skeleton development in mammals. *Proc. Natl Acad. Sci. USA* **98**, 7336–7341 (2001)

FURTHER READING Kumar, M. & Carmichael, G. Antisense RNA: function and fate of duplex RNA in cells of higher eukaryotes. *Microbiol. Mol. Biol. Rev.* **62**, 1415–1434 (1998)