dismorphology is associated with changes in the orientation of cell division.

This work might have uncovered a general mechanism of organ morphogenesis: there is a correlation between the orientation of cell division and the shape of different organs and, importantly, planar cell-polarity genes are well-conserved throughout evolution. We now need specifically targeted experiments to confirm this possibility.

Magdalena Skipper

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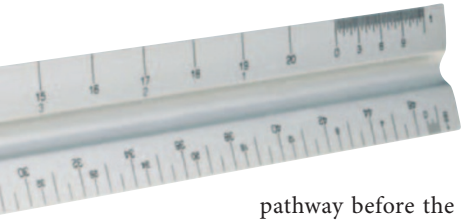

pathway before the critical size is reached extends total development time, but has no effect on the final size of the fly. The opposite was true when INR signalling was blocked after the critical size had been attained.

These studies represent important steps in understanding how body size is regulated in the fly. They might also have implications for understanding the coordination of nutrient availability and developmental transitions in mammals, where steroid hormones and insulin signalling also have key roles in regulating growth.

Louisa Flintoft

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HUMAN EVOLUTION

Brains under pressure

It has taken us many millions of years to evolve the big sophisticated brains that we are so proud of. But it's unlikely to be the best we will ever have. New work shows that two genes that are involved in brain development arose at culturally crucial times during human history and indeed might still be evolving.

It makes sense that genes involved in brain morphology, like so many other developmental genes, are subject to natural selection. Bruce Lahn's initial investigation into the subject was reported last year, when he and his colleagues found that two genes that regulate brain size — microcephalin (*MCPH1*) and abnormal spindle-like microcephaly associated (*ASPM*) — have been under strong selective pressure in the human evolutionary lineage since we split off from the chimpanzee lineage. New work has looked more closely at these two genes to see whether there are signs of more recent selection.

To do this, the distribution of haplotypes for the two genes was studied in a panel of ~90 cell lines that are representative of human diversity. In both cases, one haplotype stood out as being present in a large proportion of cell lines — a frequency that could not be explained by random or demographic factors and therefore might have been driven up in abundance by positive selection. The population distribution of polymorphisms at the two loci and the extent of linkage disequilibrium around each candidate positively selected region support this idea and also point to the occurrence of a recent selective sweep that still continues.

A statistical analysis that is based on estimating the past mutation rate of the genes placed the emergence of the high-frequency alleles at ~37,000 years ago for *MCPH1* and ~5,800 years ago for *ASPM*. These dates coincide with significant periods in recent human history: the first to the emergence of cultural traits such as music, art and symbolism, and the second to the building of the first cities in Mesopotamia.

The young age of the frequent *ASPM* variant makes it likely that brain evolution is still continuing. As the authors themselves point out, however, the results should not be overinterpreted. For example, as we cannot tell what force is driving the positive evolution of gene variants, we cannot ascribe it to variation in cognitive function (both genes are also expressed outside the brain). For the same reasons, we should be wary of reading any adaptive significance into the current geographical distribution of *MCPH1* and *ASPM* alleles.

Tanita Casci

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WEB SITE

Bruce Lahn's home page: http://www.genes.uchicago.edu/fri/lahnres.html

DISEASE MODELS

Of mice and men

For the first time, researchers have generated a mouse strain that also carries a single copy of human chromosome 21. O'Doherty *et al.* have overcome technical obstacles to create this new trans-species model of human Down syndrome, which is the result of chromosome 21 trisomy.

Previous attempts to model Down syndrome in mice have involved either introducing individual human transgenes or creating trisomies of mouse chromosomes. The one-gene-at-a-time approach does not correctly model the 3:2 gene dosage that is found in trisomy, and the mouse trisomies are only approximations to the human condition because genes that lie on human chromosome 21 lie on several mouse chromosomes.

Using injection into female mouse embryonic stem cells, the authors created an aneuploid strain that contains 92% of the gene content of human chromosome 21. The strain had several characteristics of Down syndrome such as heart defects and decreases in long-term synaptic potentiation and memory, neuronal density and T-lymphocyte activation, but only minor facial defects.

The model is a starting point for the study of the specific dosage effects of individual genes, although the precise consequences of heterologous interactions between human and mouse proteins need to be investigated.

Patrick Goymer

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