



## HUMAN GENETICS

## You must remember this...

On the whole, we humans are excellent at remembering our past experiences. This ability — known as episodic memory — mainly depends on the hippocampus, and many studies have addressed the issue of synaptic changes in this part of the brain that accompany memory-associated processes. Brain derived neurotrophic factor (BDNF) is a growth factor that has been implicated in memory-related synaptic transmission — it facilitates long-term potentiation and synaptic vesicle docking. However despite a substantial body of data from animal models, including transgenic mice, the link between BDNF and human memory has only now been established. The evidence comes from Egan and colleagues who use cohort tests of human subjects to show that a particular SNP at the BDNF locus affects human memory and hippocampal function. Using rat neuron tissue culture, the authors also show that these effects are brought about by the abnormal secretion and subcellular localization of BDNF.

Prompted by the association of BDNF with memory and learning in animal models, Egan *et al.* set out to investigate whether the only frequently found amino-acid-altering polymorphism in the human BDNF locus — a valine to methionine substitution at position 66 — would have similar effects. Various memory tests on Val/Val, Val/Met and Met/Met individuals showed that Met/Met individuals performed worse than

other genotype groups in episodic memory tests but that other types of memory were unaffected. As might have been expected, only the Val/Val individuals had normal hippocampal physiology during memory tests. Although the mechanism that underlies this finding remains unknown, Egan *et al.* clearly demonstrated a qualitative difference in hippocampal response between the Val and Met BDNF alleles. Using magnetic resonance scanning, they showed that the Val66Met SNP is associated with reduced neuronal integrity and abnormal physiological activity in the hippocampus. The authors, interested in these underlying mechanisms, turned to *in vitro* experiments. A look inside the cultured hippocampal neurons told them that while Val-containing BDNF localized to cell bodies and distal processes in a punctate manner, the Met version was diffuse and found only in cell bodies. This, together with the result of secretion assays, prompted the authors to suggest that the Val to Met substitution significantly reduces activity-dependent BDNF secretion and prevents the correct synaptic localization of MetBDNF.

Having clearly shown the association between BDNF, memory and hippocampal function, as well as revealing some of the underlying cellular events, the authors end on a speculative note — although present in humans, the relatively deleterious Met allele is absent from lower primates, so, might it confer some as yet unknown compensatory advantage?

Magdalena Skipper

### References and links

**ORIGINAL RESEARCH PAPER** Egan, M. F. *et al.* The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* **112**, 257–269 (2003)

## IN BRIEF

### DEVELOPMENT

Six3 repression of Wnt signaling in the anterior neuroectoderm is essential for vertebrate forebrain development.

Lagutin, O. V. *et al. Genes Dev.* **17**, 368–379 (2003)

From Zebrafish and *Xenopus* data we know that Wnt signalling must be inhibited at the anterior end of the neural plate for normal development of the future forebrain. Using transgenic mice and gene misexpression in chick and zebrafish, Lagutin *et al.* now show that the binding of Six3, a homeobox transcription factor, to the *Wnt1* promoter is required for this inhibition.

### CYTOGENETICS

Reciprocal chromosome painting between human, aardvark, and elephant (superorder Afrotheria) reveals the likely eutherian ancestral karyotype.

Yang, F. *et al. Proc. Natl Acad. Sci. USA* **100**, 1062–1066 (2003)

By painting aardvark and elephant chromosomes with human probes, and *vice versa*, Yang *et al.* were able to infer that the eutherian ancestral diploid karyotype comprised 44 chromosomes. The evolutionary breakpoints identified could be studied in future to identify the motifs promoting chromosome breakage and to investigate the evolution of mammalian genome.

### MOUSE MODELS

Genetics of dark skin in mice.

Fitch, K. *et al. Genes Dev.* **17**, 214–228 (2003)

Programmes to chemically mutagenize the mouse genome are producing many new mutants with which to study molecular pathways that are relevant to human disease. In one of the largest studies of its kind, Fitch *et al.* focus on a new group of dark-skin phenotypes. They map and clone the genes responsible for the increased skin-pigmentation, demonstrating that a phenotype-driven mutagenesis approach that focuses on a specific biological process can be an effective method of identifying new candidate genes and mouse models.

### EVOLUTIONARY GENETICS

Generation of a bacterium with a 21 amino acid genetic code.

Mehl, R. *et al. J. Am. Chem. Soc.* **125**, 935–939 (2003)

Could the genetic code have evolved to specify more than 20 amino acids? Mehl *et al.* engineer an *Escherichia coli* that encodes 21 amino acids: *p*-aminophenylalanine (*pAF*) is the addition to the standard set of 20. This completely autonomous bacterium can synthesize *pAF* from simple carbon sources, and incorporate it into proteins with high fidelity. The *pAF* bacterium will allow intriguing evolutionary experiments and could lead to the production of proteins with enhanced or new abilities.