



'It's a Knockout!' provides an update of some of the latest mouse knockouts in TBASE (Refs 1, 2). The column provides a concise phenotypic profile of novel mutants, and renders their complete characterization directly accessible to Web users via unique and unchanging accession numbers (TG-nnn-nn-nnn). Where possible, interesting knockouts will be grouped according to gene families, application or phenotypic similarities.

It's a Knockout!

Targeted mutagenesis frequently results in functional loss of genes that are critically involved in development. Numerous knockout models have recently emerged elucidating the role of their respective genes in developmental processes. As a putative model of non-insulin-dependent diabetes mellitus, *Slc2a2* (previously *Glut2*) homozygous null mice lacking solute carrier family 2 (TG-000-04-633) have aberrations in postnatal pancreatic islet formation and early diabetes³. Inactivation of *Gad1*, encoding glutamic acid decarboxylase 1, causes a highly penetrant, cleft, secondary palate and neonatal demise (TG-000-04-594), suggesting a role for γ -aminobutyric acid in palate development⁴. Follow-up analysis of *Pdgfra* knockouts (TG-000-03-747, TG-000-04-643) lacking platelet-derived growth factor α demonstrates that failure of alveogenesis is associated with the absence of distal spreading of alveolar smooth muscle progenitor cells during lung development^{5,6}. Loss of plectin unveils its crucial involvement in the reinforcement of mechanically stressed cells: in fact, plectin-deficient mutants (TG-000-04-676) provide a paradigm of human epidermolysis bullosa simplex and myopathies involving cardiac and skeletal muscle⁷. Furthermore, remodeling of the cardiovascular system, specifically closure of the ductus arteriosus, is shown to fail in neonatally lethal *Ptgerep4* knockouts lacking prostaglandin F₂ receptor EP4 subtype (TG-000-04-637), highlighting its role as a sensor that responds to perinatal reduction of prostaglandin E2 (Ref. 8). Reduced inflammatory responses and pain perception are noted in *Ptgir*-null mice (TG-000-04-646) lacking prostaglandin I receptor, which are nevertheless viable, fertile and normotensive, but have increased susceptibility to thrombosis⁹. In contrast, *Pkcc*-null mutants, deficient in protein kinase C γ (TG-000-04-650), respond normally to acute pain stimuli, but are unable to develop a persistent, neuropathic pain syndrome following partial sciatic nerve injury¹⁰.

Interestingly, *Dab1* murine knockouts (TG-000-04-608), deficient in disabled

homolog 1 (*Drosophila*), show perturbed neuronal layering in the cerebral cortex, hippocampus and cerebellum¹¹, partly phenocopying the *reeler* mouse with respect to neuroanatomy and neuronal birth-dates^{12,13}. Severe malformations of the nervous system and other anomalies associated with mutations in the L1 cell adhesion molecule gene (collectively known as 'CRASH', corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia, and hydrocephalus) are reported for *Llcam* knockouts (TG-000-04-642)¹⁴. Moreover, adult *Tlx* knockouts (TG-000-04-671), lacking the *tailless* homolog (*Drosophila*) exhibit impaired development of the rhinencephalic and limbic structures¹⁵, while *Arnt*-null mice (TG-000-04-674) display defects in neural tube closure and forebrain hypoplasia, as well as failure of the placenta to vascularize and form the labyrinthine spongiotrophoblast¹⁶. Marked neuropathies, encompassing embryonic degeneration of the peripheral nervous system, are also noted in *ErbB3*-null mutants (TG-000-04-604, TG-000-04-605), deficient in a high-affinity neuregulin receptor; the ensuing phenotype emphasizes the significance of neuregulins and their receptors in Schwann cell development¹⁷. Lastly, *Gsh2*-null mice (TG-000-04-678) lacking genomic screened homeobox 2, are neonatally lethal and manifest severe fore- and hind-brain malformations as well as altered distributions of markers specific for serotonergic and cholinergic neurons¹⁸.

Finally, a novel mouse autosomal recessive mutant, named *klotho* after the mythological Greek goddess spinning the thread of life, has risen as a result of an insertional mutation of a transgene previously described by Kuro-o *et al.*¹⁹ Mice homozygous for the transgene (TG-000-04-624) display variable but fully penetrant phenotypes reminiscent of premature ageing syndromes. These include arteriosclerosis, skin atrophy, osteoporosis, ectopic calcifications, infertility, short lifespan and emphysema²⁰. All phenotypic alterations noted in *kl/kl* mutants are ameliorated by

exogenous *kl* gene expression, confirming that the *klotho* mouse is the first animal model recapitulating human ageing phenotypes caused by a single gene mutation²⁰.

References

- 1 <http://www.bis.med.jhmi.edu/Dan/tbase/tbase.html>
- 2 Jacobson, D. and Anagnostopoulos, A. (1996) *Trends Genet.* 12, 117-118
- 3 Guillam, M-T. *et al.* (1997) *Nat. Genet.* 17, 327-330
- 4 Condie, B.G., Bain, G., Gottlieb, D.I. and Capecchi, M.R. (1997) *Proc. Natl. Acad. Sci. U. S. A.* 94, 11451-11455
- 5 Boström, H. *et al.* (1996) *Cell* 85, 863-873
- 6 Lindahl, P. *et al.* (1997) *Development* 124, 3943-3953
- 7 Andri, K. *et al.* (1997) *Genes Dev.* 11, 3143-3156
- 8 Nguyen, M-T. *et al.* (1997) *Nature* 390, 78-81
- 9 Murata, T. *et al.* (1997) *Nature* 388, 678-682
- 10 Malmberg, A.B., Chen, C., Tonegawa, S. and Basbaum, A.I. (1997) *Science* 278, 279-283
- 11 Howell, B.W., Hawkes, R., Soriano, P. and Cooper J.A. (1997) *Nature* 389, 733-737
- 12 Caviness, V.S., Jr (1982) *Brain Res.* 256, 293-302
- 13 Hoffarth, R.M., Johnston, J.G., Krushel, L.A. and Van Der Kooy, D. (1995) *J. Neurosci.* 15, 4838-4850
- 14 Dahme, M. *et al.* (1997) *Nat. Genet.* 17, 346-349
- 15 Monaghan, A.P. *et al.* (1997) *Nature* 390, 515-517
- 16 Kozak, K.R., Abbott, B. and Hankinson, O. (1997) *Dev. Biol.* 191, 297-305
- 17 Riethmacher, D. *et al.* (1997) *Nature* 389, 725-730
- 18 Szucsik, J.C. *et al.* (1997) *Dev. Biol.* 191, 230-242
- 19 Kuro-o, M. *et al.* (1995) *Circ. Res.* 76, 148-153
- 20 Kuro-o, M. *et al.* (1997) *Nature* 390, 45-51

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