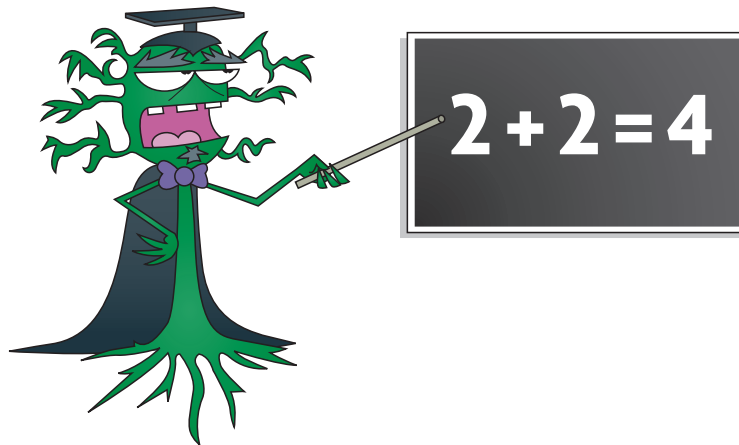


NEURONAL MIGRATION

Putting 2 and 2 together

DOI:

10.1038/nrn2102



Mutations affecting neuronal migration result in abnormal brain development. Keays *et al.* have now identified a mutation in $\alpha 1$ tubulin as a cause for abnormal neuronal migration in mice and showed that some patients with lissencephaly, a rare brain formation disorder, carry mutations in this gene.

$\alpha 1$ tubulin binds to β -tubulin, and the resulting heterodimers form the building blocks of microtubules. Microtubule formation is essential for neurite outgrowth and neuronal migration, which is required for the formation of laminar structures of certain brain regions, such as the cortex and the hippocampus. As part of a large-scale mutagenesis screen, Keays *et al.* tested more than 9000 mice carrying random mutations introduced by ethylnitrosourea (ENU) injections for mutations that cause behavioural abnormalities.

One mouse strain, called Jenna, was identified with a semi-dominant

(*Jen*⁺), hyperactive phenotype and the authors characterized these mice on the genetic, molecular, anatomical and behavioural level. They identified a point mutation in the GTP-binding pocket of $\alpha 1$ tubulin (TUBA1) which resulted in less efficient heterodimer formation with β -tubulin in *in vitro* studies; however, heterodimers could still polymerize to form microtubules.

Anatomical studies revealed morphological abnormalities in the hippocampus and cortex of *Jen*⁺ mice, which affected the layered structure of these brain regions. By injecting 5-bromo-2'-deoxyuridine (BrdU) into different mice at three different time points during embryonic development (just before and during neuronal migration) and comparing numbers and locations of the labelled cells in the hippocampus and the cortex at birth, the researchers showed that the abnormal architecture of the hippocampus and cortex is consistent with impaired radial

migration of neurons in *Jen*⁺ mice. In behavioural tests, *Jen*⁺ mice exhibited impaired hippocampal-dependent memory, but their hippocampal-independent memory was not affected. The mutant mice also showed reduced anxiety and abnormal nesting behaviour, two behaviours linked to hippocampal function. Introducing additional copies of TUBA1 into embryos rescued the behavioural phenotype as well as the morphological abnormalities.

Lissencephaly patients show a similar phenotype and brain anatomy as the *Jen*⁺ mice. As 30% of lissencephaly cases have unknown genetic causes, Keays *et al.* screened a group of 40 patients with this disorder, and showed that 2 patients carried a point mutation in the human homolog of $\alpha 1$ tubulin (TUBA3). In another group of patients with cortical abnormalities, but not lissencephaly, 6 patients were identified carrying mutations in TUBA3. All these mutations were non-inherited, *de novo* mutations. Although the TUBA3 mutations in the patients did not affect the GTP-binding pocket, structural analysis predicts that the mutations would affect interaction of the microtubules with other binding partners.

This study elegantly shows that mouse libraries can be used to screen for and identify mutations that cause neurodevelopmental disorders in humans. As mouse libraries are now becoming available, studies like this will reveal the basis of these disorders.

Claudia Wiedemann

ORIGINAL RESEARCH PAPER Keays, D. A. *et al.* Mutations in α -tubulin cause abnormal neuronal migration in mice and lissencephaly in humans. *Cell* **128**, 45–57 (2007)