Scientists show extra copies of a gene carry extra risk

February 4 2009

Is more of a good thing better? A gene known as LIS1 is crucial for ensuring the proper placement of neurons in the developing brain. When an LIS1 gene is missing, brains fail to develop the characteristic folds; babies with lissencephaly or 'smooth brain' are born severely mentally retarded. But new research by Prof. Orly Reiner of the Institute's Molecular Genetics Department, which recently appeared in *Nature Genetics,* shows that having extra LIS1 genes can cause problems as well.

Reiner was the first to discover LIS1's tie to lissencephaly, in 1993. Their latest study shows that it works by helping to determine polarity in the cell - how the various organelles are arranged inside the cell as well as where it connects to neighboring cells. Neurons alter their polarity several times during development, especially when they take on an elongated shape and migrate to new locations in the brain.

But what if, rather than too little, the body has too much LIS1? One of the surprises to come out of the recent spate of post-human-genome research is the number of genes that can be repeated or deleted in an individual's genome. Most extra copies of genes may be no more harmful than a computer backup disk, but scientists have been finding that some repeats can cause disease.

Research associate Dr. Tamar Sapir and lab technician Talia Levy, working in Reiner's lab, developed a mouse model in which additional LIS1 protein was produced in the brain. The scientists found that the brains of these mice were a bit smaller than average. On closer

inspection, they discovered a range of subtle changes in cell polarity and movement: Nuclei within the proliferating zone tended to move faster, but with less control; rates of cell death were higher; and various factors in the cell became more disordered.

Reiner then asked whether their findings might apply to humans. Together with Jim Lupski and Drs. Weimin Bi and Oleg A. Shchelochkov of Baylor College of Medicine in Houston, Texas, they searched through blood samples using a technique that matches a patient's DNA with control DNA to identify additions or deletions in its sequence. They identified seven individuals with extra copies of either LIS1 or adjacent genes that are also involved in brain development. All suffered developmental abnormalities. Two of the patients - children with a second LIS1 gene - had previously been diagnosed with failure to thrive and delayed development, and were found to have small brain sizes. A third, who had three copies of the gene, was mentally retarded and suffered from bone deformation as well.

Reiner: 'Several brain diseases, including schizophrenia, epilepsy and autism, have been linked to faulty neuron migration, and recent research has hinted that some of these may involve variations in gene number. Our study is the first to demonstrate the effects of the duplication of a single gene in a mouse model and tie it to a new 'copy number variation' human disease.'

For the scientific paper, please see:
www.nature.com/ng/journal/v41/n2/pdf/ng.302.pdf

Source: Weizmann Institute of Science