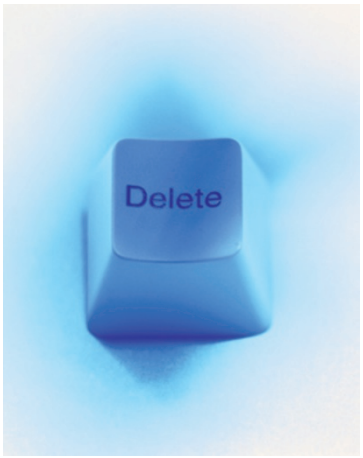
NEUROGENETICS

Understanding deletions



The contributions of microRNAs (miRNAs) to neural function and disease are subject to increasing scrutiny. Building on this growing knowledge, a new paper now indicates that alterations in the production of miRNAs might contribute to the cognitive and behavioural deficits that are associated with a common genetic syndrome.

22q11.2 deletion syndrome, in which a variable region of chromosome 22 is deleted, is linked to learning and social deficits and anxiety. Furthermore, it is the only known *de novo* recurrent copy-number mutation that introduces new cases of schizophrenia into the population. In order to understand the genetic basis of these phenotypes, Stark *et al.* generated mice in which a chromosomal region containing many of the genes that are lost in the human syndrome was disrupted (Df(16)A$^{+/-}$ mice).

Behavioural tests revealed increased anxiety and deficits in sensorimotor gating, associative learning and spatial working memory in Df(16)A$^{+/-}$ mice — a phenotype that closely resembles that of humans that carry 22q11.2 microdeletions. These changes were associated with a decrease in the density and size of dendritic spines and reduced dendritic branch complexity in the hippocampus of the mice.

One gene that is disrupted in Df(16)A$^{+/-}$ mice, *Dgcr8*, encodes a protein that is important for the processing of miRNA precursors into mature miRNAs, suggesting that the mutation might alter miRNA biogenesis. Indeed, the authors observed an increase in the abundance of several miRNA precursors and a decrease in the levels of some mature miRNAs in the hippocampus and prefrontal cortex. Furthermore, mRNA transcripts that were upregulated in these regions in Df(16)A$^{+/-}$ mice were more likely to contain sequences that were complementary to miRNA recognition (seed) sequences than those that were downregulated, indicative of a loss of miRNA-mediated regulation.

To determine the importance of the loss of DGCR8 for the changes that are observed in Df(16)A$^{+/-}$ mice, the authors examined mice that lacked one *Dgcr8* allele. These mice also exhibited altered miRNA biogenesis and a more restricted set of behavioural and morphological alterations that included deficits in spatial working memory and sensorimotor gating and reductions in dendritic spine size and branch complexity.

This study reveals the contribution of abnormal miRNA processing to the phenotypic changes that are seen in a mouse model of human 22q11.2 syndrome, expanding our understanding of both the pathogenesis of this syndrome and the potentially important role of miRNAs in complex genetic disorders.

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ORIGINAL RESEARCH PAPER Stark, K. L. *et al.* Altered brain microRNA biogenesis contributes to phenotypic deficits in a 22q11-deletion mouse model. *Nature Genet.* 11 May 2008 (doi:10.1038/ng.138)