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NEURODEGENERATIVE DISEASE

A social role for microRNA

> an intraperitoneal injection of an AMPAR antagonist increased sociability in 8-month-old *CHMP2B*^{Intron5} transgenic mice

Frontotemporal dementia (FTD) is characterized by changes in social behaviour, among other symptoms. The molecular and cellular mechanisms underlying these changes are not known, but a new study shows that they may involve altered AMPA receptor (AMPAR) subunit composition caused by reduced microRNA 124 (miR-124) levels in the frontal cortex.

Mutations in the gene encoding charged multivesicular body protein 2B (*CHMP2B*) have been implicated in FTD. Gascon *et al.* generated transgenic mice in which a mutated form of the human *CHMP2B* gene was expressed in forebrain neurons. Although these *CHMP2B*^{Intron5} transgenic mice showed similar social recognition and social memory to wild-type controls, they spent less time interacting with other mice at 4 and 8 months of age, but not at earlier ages.

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Investigating the molecular basis of this impairment in sociability, the authors found that gene and protein expression of the AMPAR subunits GRIA2, GRIA3 and GRIA4 were increased in the cortex of 4- and 8-month-old *CHMP2B*^{Intron5} transgenic mice compared with wild-type controls. In addition, electrophysiology data were suggestive of an increased proportion of GRIA2-containing, Ca^{2+}-impermeable AMPARs over non-GRIA2-containing AMPARs in the frontal cortex of 4-month-old transgenic mice.

These findings indicated a possible link between changes in cortical AMPAR function and impairments in sociability. Indeed, an intraperitoneal injection of an AMPAR antagonist increased sociability in 8-month-old *CHMP2B*^{Intron5} transgenic mice but had no effect in wild-type controls.

The authors next examined whether miRNAs play a part in the upregulation of the AMPAR subunits. They found that levels of miR-124 — one of the most abundant microRNAs in the brain — were reduced in the cortex of *CHMP2B*^{Intron5} transgenic mice relative to wild-type controls and that preventing the expression of the mutant gene normalized miR-124 levels. Computer models and *in vitro* data indicated that *Gria2*, *Gria3* and *Gria4* mRNAs are potential targets for suppression by miR-124. Furthermore, miR-124 expression decreased with age in the cortex of *CHMP2B*^{Intron5} transgenic mice, coinciding with the increase in cortical GRIA2, GRIA3 and GRIA4 levels and the appearance of impaired sociability.

The findings suggested that decreased suppression of AMPAR subunits — and GRIA2 in particular — by miR-124, which results in altered AMPAR function, can contribute to impairments in sociability. Supporting this notion, cortical expression of miR-124 was reduced and expression of *GRIA2* and *GRIA4* was increased in post-mortem cortex samples from patients with FTD who had deficits in social behaviour. Moreover, in 8-week-old neurons (but not in 2-week-old neurons) obtained from induced pluripotent stem cell lines derived from such patients, miR-124 expression was lower and *GRIA2* and *GRIA4* mRNA expression was higher than expression levels in neurons from control lines. In addition, viral expression of miR-124 in the frontal cortex of 7-month-old *CHMP2B*^{Intron5} transgenic mice reduced *Gria2* and *Gria4* mRNA levels in this brain area and increased sociability from 1 month post-injection onwards. Similarly, silencing cortical *Gria2* expression using RNA interference partially reversed the impairment in sociability in *CHMP2B*^{Intron5} transgenic mice.

Together, these findings suggest that altered social behaviour in FTD may be due, at least in part, to a reduction in miR-124 levels — which could itself be caused by mutations in *CHMP2B* — resulting in altered AMPAR composition and function in the frontal cortex.

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ORIGINAL RESEARCH PAPER Gascon, E. *et al.* Alterations in microRNA-124 and AMPA receptors contribute to social behavioral deficits in frontotemporal dementia. *Nature Med.* http://dx.doi.org/10.1038/nm.3717 (2014)