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Impaired behavioral control and altered processing of spatial information in mice deficient for the X-chromosomal mental retardation gene *Arhgef6*

The *ARHGEF6* gene (also known as alphaPIX or Cool-2), encodes a protein with homology to guanine nucleotide exchange factors (GEF) for Rho GTPases. Mutations in this gene have been recently identified in human patients with X-linked mental retardation (Kutsche et al. Nat Genet 26:247-250, 2000). We report the cognitive and behavioral characterization of male mice carrying a targeted deletion of *Arhgef6*. These mice are healthy and have normal appearance. They were evaluated in a water-maze place navigation task, in a spatial working memory procedure on the 8-arm radial maze, as well as in a set of tests assessing locomotor activity, anxiety, exploratory behavior and their reaction to novel stimuli. In the water maze, they produced navigation errors and showed spatial perseverance when required to adapt to a changed goal position. Their reaction to a novel stimulus within in a familiar environment was clearly disinhibited. Spatial reference and working memory as such, as well as day to day habituation to a novel arena were intact. We found no indication of altered basal activity, anxiety, or abnormal adaptation to stressful situations. Moreover, detailed analysis of locomotion and swim patterns did not reveal neurological deficits. In summary, *Arhgef6* null mice displayed specific behavioral alterations suggesting deficient behavioral control and altered processing of spatial information. The behavioral profile of *Arhgef6* null mice is reminiscent of phenotypic changes observed in other mouse models, with impaired function of the hippocampus and connected cortical regions. Supp. NCCR Neural Plasticity and Repair, Swiss National Science Foundation