Srgap3-/- mice present a neurodevelopmental disorder with schizophrenia-related intermediate phenotypes.

Abstract:
Mutations in the SRGAP3 gene residing on chromosome 3p25 have previously been associated with intellectual disability. Genome-wide association studies have also revealed SRGAP3, together with genes from the same cellular network, as risk genes for schizophrenia. SRGAP3 regulates cytoskeletal dynamics through the RHO protein RAC1. RHO proteins are known to be involved in cytoskeletal reorganization during brain development to control processes such as synaptic plasticity. To elucidate the importance of SRGAP3 in brain development, we generated Srgap3-knockout mice. Ten percent of these mice developed a hydrocephalus and died before adulthood. Surviving mice showed various neuroanatomical changes, including enlarged lateral ventricles, white matter tracts, and dendritic spines together with molecular changes, including an increased basal activity of RAC1. Srgap3(-/-) mice additionally exhibited a complex behavioral phenotype. Behavioral studies revealed an impaired spontaneous alternation and social behavior, while long-term memory was unchanged. The animals also had tics.
Lower locomotor activity was observed in male Srgap3(-/-) only. Srgap3(-/-) mice showed increased methylphenidate stimulation in males and an impaired prepulse inhibition in females. Together, the results show neurodevelopmental aberration in Srgap3(-/-) mice, with many of the observed phenotypes matching several schizophrenia-related intermediate phenotypes. Mutations of SRGAP3 may thus contribute to various neurodevelopmental disorders. Waltereit, R., Leimer, U., von Bohlen und Halbach, O., Panke, J., Höltter, S. M., Garrett, L., Wittig, K., Schneider, M., Schmitt, C., Calzada-Wack, J., Neff, F., Becker, L., Prehn, C., Kutscherjawy, S., Endris, V., Bacon, C., Fuchs, H., Gailus-Durner, V., Berger, S., Schönig, K., Adamski, J., Klopstock, T., Esposito, I., Wurst, W., Hrab? de Angelis, M., Rappold, G., Wieland, T., Bartsch, D. Srgap3(-/-) mice present a neurodevelopmental disorder with schizophrenia-related intermediate phenotypes.