Nf1-DEFICIENT MICE DISPLAY SOCIAL LEARNING DEFICITS THAT ARE RESCUED BY THE DELETION OF PAK1 GENE

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Spence, John Paul

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Abstract:

Neurofibromatosis type 1 (NF1) is a neurocutaneous disorder that affects roughly 1 in 3500 individuals. In addition to physical features (e.g., neurofibromas), developmental disorders are also common that can affect cognition, learning, attention and social function. The NF1 gene encodes neurofibromin, a GTPase activating protein (GAP)-like protein that negatively regulates Ras GTPase activation. Mutation at the NF1 locus increases the output of MAPK and PI3K signal transduction from the cellular membrane to the nucleus. Similar to humans, Nf1+/- mice show spatial learning

abnormalities that are potentially correlated with increases in GABA-mediated inhibition and deficits in long-term potentiation in the hippocampus. Here, we demonstrate for the first time that Nf1+/- mice exhibit a selective loss of long-term social learning / memory and increased GABAergic inhibition in the basolateral amygdala, a critical brain region for regulating social behaviors. Next, utilizing a genetic intercross, we show that the co-deletion of p21-activated kinase type 1 (Pak1-/-), which positively regulates MAPK activation, restores Nf1+/--dependent MAPK hyperactivation in neurons cultured from the frontal cortex. We found that the co-deletion of Pak1 in Nf1+/- mice (Nf1+/- / Pak1-/-) also restores the deficits in long-term social learning / memory seen in Nf1+/- mice and normalizes the increases in GABA-mediated inhibition in the BLA, as compared to Nf1+/- mice. Together, these findings establish a role for Nf1 and Pak1 genes in the regulation of social learning in Nf1-deficient mice. Furthermore, proteomic studies identify dysregulation of F-actin and microtubule dynamics in the prefrontal cortex, and implicate proteins associated with vesicular release as well as neurite formation and outgrowth (e.g., LSAMP, STXBP1, DREB). In the BLA, disintegrin and metalloproteinase domain-containing protein 22 (ADAM22) was identified, and ADAM22 may play a role in the regulation of AMPA receptors. Finally, due to the increased co-occurrence of NF1 and autism, these findings may also have important implications for the pathology and treatment of NF1-related social deficits and some forms of autism.

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