A Mouse Model that Recapitulates Cardinal Features of the 15q13.3 Microdeletion Syndrome Including Schizophrenia- and Epilepsy-Related Alterations - DTU Orbit (09/11/2017)

A Mouse Model that Recapitulates Cardinal Features of the 15q13.3 Microdeletion Syndrome Including Schizophrenia- and Epilepsy-Related Alterations

Background: Genome-wide scans have uncovered rare copy number variants conferring high risk of psychiatric disorders. The 15q13.3 microdeletion is associated with a considerably increased risk of idiopathic generalized epilepsy, intellectual disability, and schizophrenia. Methods: A 15q13.3 microdeletion mouse model (Df[h15q13]/) was generated by hemizygous deletion of the orthologous region and characterized with focus on schizophrenia- and epilepsy-relevant parameters. Results: Df(h15q13)/ mice showed marked changes in neuronal excitability in acute seizure assays, with increased propensity to
develop myoclonic and absence-like seizures but decreased propensity for clonic and tonic seizures. Furthermore, they had impaired long-term spatial reference memory and a decreased theta frequency in hippocampus and prefrontal cortex. Electroencephalogram characterization revealed auditory processing deficits similar to those observed in schizophrenia. Gamma band power was increased during active state, but evoked gamma power following auditory stimulus (40 Hz) was dramatically reduced, mirroring observations in patients with schizophrenia. In addition, Df(h15q13)/ mice showed schizophrenia-like decreases in amplitudes of auditory evoked potentials. Although displaying a grossly normal behavior, Df(h15q13)/ mice are more aggressive following exposure to mild stressors, similar to what is described in human deletion carriers. Furthermore, Df(h15q13)/ mice have increased body weight, and a similar increase in body weight was subsequently found in a sample of human subjects with 15q13.3 deletion. Conclusions: The Df(h15q13)/ mouse shows similarities to several alterations related to the 15q13.3 microdeletion syndrome, epilepsy, and schizophrenia, offering a novel tool for addressing the underlying biology of these diseases.

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