DELETION OF KMT2C IN NEURONS OF MICE CAUSES MULTIPLE NEUROBEHAVIORAL ABNORMALITIES

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Background: The KMT2C gene encodes a protein involved in transcriptional regulation via histone modification. Studies have shown that likely gene disruptive (LGD) de novo mutations in the KMT2C gene are associated with both neurodevelopmental disorders such as autism spectrum disorder and neuropsychiatric disorders such as bipolar disorder. We have identified an extended pedigree in which a potentially pathogenic variant segregates with bipolar disorder. In this study, the neurobehavioral effects on Kmt2c deletion in neurons of mice were determined.

Materials/Methods: Functional Kmt2c was deleted from neurons of mice by crossing mice harboring a Kmt2c allele in which the SET domain, responsible for methylation, is floxed with mice expressing Cre recombinase driven by the Nestin promoter. This results in deletion of functional Kmt2c during neurogenesis. We then performed a myriad of behavioral tests in adult animals including rotarod, tail suspension, acoustic startle with prepulse inhibition, and open field tests by individuals blind to genotype of the mice.

Results: Our data reveal Kmt2c conditional knockout mice exhibit behavioral abnormalities including reduced immobility by tail suspension testing, suggesting a reduction in despair induced by the test. Open field testing also revealed Kmt2c knockout mice are hyperactive in a novel environment. Abnormal sensory gaiting is present as demonstrated by a reduction in acoustic startle response. Finally, Kmt2c conditional knockout mice have reduced latency to fall by rotarod demonstrating abnormal motor learning.

Conclusions: Loss-of-function mutations in KMT2C have been identified in children with severe neurodevelopmental impairments. Moreover, genomic variants in KMT2C have been associated with neuropsychiatric disorders including bipolar disorder. We have identified an extended pedigree in which a KMT2C variant segregates with bipolar disorder in this family. To better understand how variants in KMT2C cause neurodevelopmental and neuropsychiatric disorders, we created mice in which functional Kmt2c was deleted in neurons. Neurobehavioral abnormalities found included hyperactivity, motor memory deficits, abnormalities in sensory gating and reduced despair. Together these data suggest Kmt2c expression in neurons is critical for their normal development and function. We are currently completing behavioral characterization of these mice and will use them to better understand the molecular and neurophysiologic changes associated with Kmt2c deficiency in neurons.