Sexually dimorphic phenotypes in mice with neuronal deletion of *Kmt2c*

Sarah Momin, Fisher Simpson, Huda Zoghbi, Lunhui Lin, Kirti Saxena, Jimmy L. Holder Jr.
Texas Children's Hospital, Department of Pediatrics, and Baylor College of Medicine

BACKGROUND

The *KMT2C* gene encodes a protein involved in transcriptional regulation via histone modification. Likely gene disruptive (LGD) *de novo* mutations in *KMT2C* 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.

PURPOSE

In this study, the neurobehavioral effects on *KMT2C* deletion in neurons of mice were determined.

METHODS

- The effect of *Kmt2c* knockdown in mouse primary cortical neurons was determined.
- 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 the deletion of functional *Kmt2c* during neurogenesis.
- Two cohorts of mice will undergo behavioral testing. In the first, we will test rotarod, tail suspension, acoustic startle with prepulse inhibition, and open field tests by individuals blind to genotype of the mice. In the second cohort, we will test elevated plus maze, fear conditioning, marble burying, three chamber, and hot plate tests.

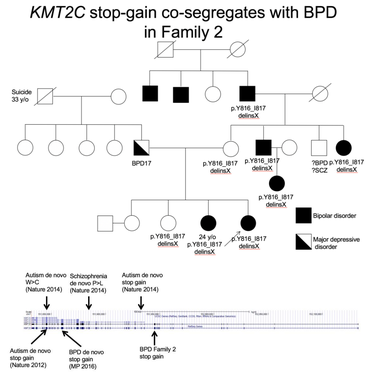

Fig 1: Family pedigree with stop-gain variant segregates with bipolar disorder.

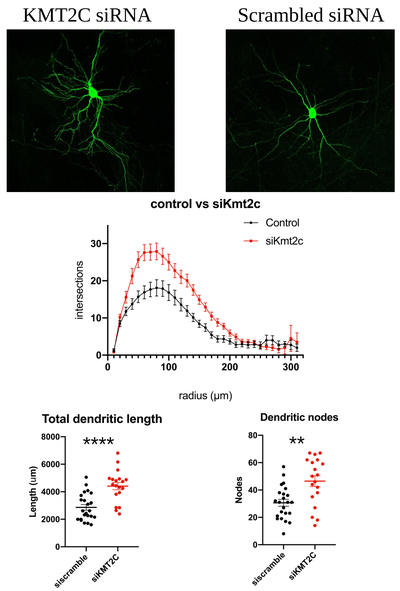

Fig 2: Dendritic complexity increased with *Kmt2c* depletion. **P<0.01, ****P<0.0001, Two-tailed nested ANOVA and unpaired T-test.

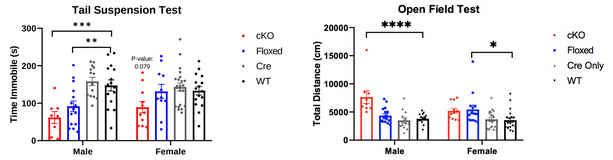

Fig 3: Tail Suspension tests revealed a significant reduction in immobility in male cKO mice over 1 trial. No significant difference was seen for female mice. Open Field tests revealed a significant amount of hyperactivity for male cKO mice over 1 trial. Multiple comparison two-way ANOVA, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 for Dunnett's test. N= 8-22 for TST and N=9-21 for OFA.

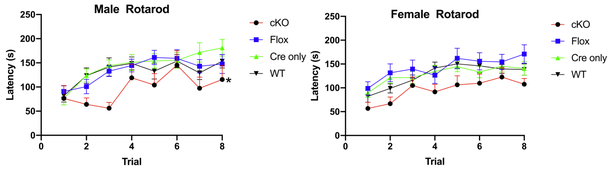

Fig 4: Rotarod tests revealed a significantly short latency to fall in male cKO mice over 8 trials (4 trials per day for 2 days). No significant difference was seen for female mice. Nested one-way ANOVA, *P<0.05 for Dunnett's test. N= 9-24.

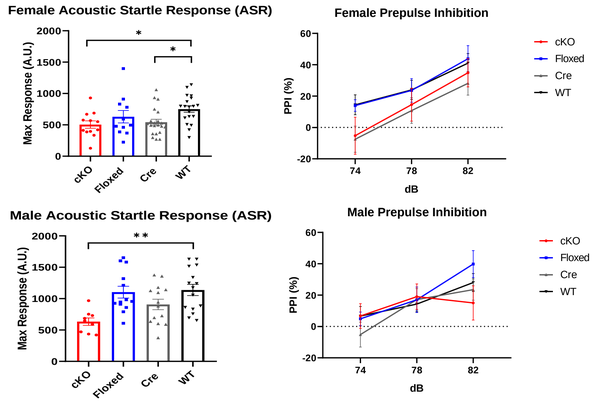

Fig 5: Ordinary one-way ANOVA, *P<0.05, **P<0.01 for Dunnett's multiple comparisons test. N=9-21.

RESULTS

- A loss-of-function variant was found to segregate with bipolar disorder in a large pedigree
- Depletion of *Kmt2c* in mouse cortical neurons causes increased dendritic complexity.
- Male *KMT2C* neuronal conditional knockout mice exhibit behavioral abnormalities including:
  - Decreased immobility by tail suspension testing
  - Hyperactivity by open field assay
  - Reduced acoustic startle response
  - Decreased latency to fall on rotarod

CONCLUSION

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. To better understand this, we created mice in which functional *Kmt2c* was deleted in neurons. Data suggest a sexually dimorphic phenotype with more severe neurobehavioral abnormalities including hyperactivity, motor memory deficits, abnormalities in sensory gating and reduced despair seen in males. These data suggest *Kmt2c* expression in neurons is critical for the normal development and function in male mice. 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.

ACKNOWLEDGEMENTS

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