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Poster Sessions

Deciphering the role of the histone methyltransferase SETD1A in Schizophrenia

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Schizophrenia (SCZ) is a severe, chronic psychiatric illness characterized by delusions and hallucinations, negative symptoms, and cognitive dysfunction that often lead to a lifetime of impairment and disability. Drug development for cognitive dysfunctions of patients with SCZ remains challenging, given the absence of a unifying pathophysiology, and the highly complex underlying genetic architecture. *SETD1A*, a histone methyltransferase, is a key schizophrenia susceptibility gene. To understand how *SETD1A* deficiency increases disease risk we employed a mouse model carrying a heterozygous loss-of-function mutation of the orthologous gene. We report that mutant mice exhibit alterations in axonal branching and working memory, as well as a molecular pathology pattern that recapitulates SCZ-related alterations. Notably, restoring *Setd1a* expression in adulthood rescues working memory deficits. Moreover, we identify demethylases counteracting the effects of *Setd1a* methyl transferase activity and show that the demethylase antagonism in *Setd1a*-deficient mice results in a full rescue of the behavioral abnormalities and axonal branching deficits. Our findings advance our understanding of how *SETD1A* mutations predispose to SCZ and other neurodevelopmental disorders and point to therapeutic interventions.