Mutations in PRC2 histone methyltransferase *EZH1* disrupt neuronal differentiation and lead to neurodevelopmental disorders

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The disruption of chromatin modifiers during cortical neurogenesis is one of the underlying causes of neurodevelopmental and intellectual disability disorders. One such chromatin modifier is Enhancer of Zeste Homologue 1 (*EZH1*), which is one of the two histone H3 lysine 27 (H3K27) mammalian methyltransferases, and part of the Polycomb Repressive Complex 2 (PRC2). Its parologue, *EZH2*, has an essential role in maintaining transcriptional repression of non-lineage specific genes during development. However, the contribution of *EZH1* to transcriptional silencing during development is poorly understood. In a neurodevelopmental context, *EZH2* is highly expressed in dividing cells, and its dysfunction leads to defects in neural progenitor proliferation and fate specification. In contrast, *EZH1* is expressed in both the developing and adult nervous system, suggesting an unknown epigenetic role in this context. Here we uncover patients with a novel neurodevelopmental delay syndrome caused by *de novo* missense or biallelic truncating mutations in *EZH1*. We show that biallelic mutations lead to loss of *EZH1* expression and delayed neuronal differentiation using cortical brain organoids. In contrast, using in vitro histone methyltransferase assays and overexpression in neural stem cells, we show that *de novo* missense variants change the catalytic activity of *EZH1* resulting in increased H3K27 methylation. Opposite to *EZH1* loss-of-function (LOF), brain organoids expressing hyperactive gain-of-function (GOF) *EZH1* led to a premature neuronal differentiation, suggesting that *EZH1* contributes to the regulation of neurodevelopmental timing by controlling neuronal differentiation transcriptional programming. This newly identified developmental syndrome is the first evidence of a genetic association of *EZH1* with a human disorder. And in addition to our preliminary data, it strongly suggests that *EZH1* has important and unexplored functions in humans, especially during neurodevelopment.