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Abstract: The development of the human brain occurs through a tightly regulated series of dynamic and adaptive processes during prenatal and postnatal life. A disruption of this strictly orchestrated series of events can lead to a number of neurodevelopmental conditions, including Autism Spectrum Disorders (ASD). ASDs are a very common, etiologically and phenotypically heterogeneous group of disorders sharing the core symptoms of social interaction and communication deficits and restrictive and repetitive interests and behaviors. They are estimated to affect one in 59 individuals in the U.S. and, over the last three decades, mutations in more than a hundred genetic loci have been convincingly linked to ASD pathogenesis. Yet, for the vast majority of these ASD-risk genes their role during brain development and precise molecular function still remain elusive.

De novo loss of function mutations in the ubiquitin ligase-encoding gene *Cullin3* (*CUL3)* lead to ASD. In the study described here, we used *Cul3* mouse models to evaluate the consequences of *Cul3* mutations *in vivo.* Our results show that *Cul3* haploinsufficient mice exhibit deficits in motor coordination as well as ASD-relevant social and cognitive impairments. *Cul3* mutant brains display cortical lamination abnormalities due to defective neuronal migration and reduced numbers of excitatory and inhibitory neurons. In line with the observed abnormal columnar organization, *Cul3* haploinsufficiency is associated with decreased spontaneous excitatory and inhibitory activity in the cortex. At the molecular level we show that *Cul3* regulates cytoskeletal and adhesion protein abundance in mouse embryos. Abnormal regulation of cytoskeletal proteins in *Cul3* mutant neural cells results in atypical organization of the actin mesh at the cell leading edge. Of note, heterozygous deletion of *Cul3* in adult mice does not induce the majority of the behavioral defects observed in constitutive *Cul3* haploinsufficient animals, pointing to a critical time-window for *Cul3* deficiency.

In conclusion, our data indicate that *Cul3* plays a critical role in the regulation of cytoskeletal proteins and neuronal migration and that ASD-associated defects and behavioral abnormalities are primarily due to *Cul3* functions at early brain developmental stages.