Abstract

Tuberous sclerosis (TS) is an autosomal dominant disorder caused by a mutation in either the TSC1 or TSC2 gene of the tuberous sclerosis complex (TSC). It has been shown that human TSC1 and TSC2 mutations alter neural shape, organization, and complexity (Bassetti et. al, 2021). In addition to TSC1 and TSC2, the TS complex also includes TBC1D7. However, the functions of TBC1D7 and how it affects brain formation remain largely unknown. Here, we examined the effect of TBC1D7 depletion on neuronal migration and organization in the developing brain. *In utero* electroporation was used to electroporate TBC1D7-specific shRNAs into the developing cerebral cortex of control and TSC1/2 mutants at E14.5. Immunohistochemistry was used to determine the spatial arrangement of GFP^+ shRNA expressing neuronal cells in the developing cortical wall. Changes in neuronal migration and distribution were mapped. We found that TBC1D7 knockdown leads to disrupted neuronal migration and distribution of GFP^+/ TBC1D7 deficient neurons in the cortical plate, subventricular zone (SVZ), and intermediate zone (IZ). Our results suggest that TBC1D7 depletion further compounds the TSC1/2 deficient phenotype by disrupting neuronal migration, altering cortical lamination, thus leading to ectopic accumulation of cortical neurons in the SVZ and IZ. These studies highlight the importance of TBC1D7 in the stabilization of the TS complex. By characterizing the functions of TBC1D7, these new observations may help link human brain malformations seen in TSC to disruptions in specific cortical embryonic development events such as neuronal migration and laminar organization.