Tbr1 and Fezf2 regulate alternate corticofugal neuronal identities during neocortical development.

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Public Summary:
The corticothalamic neurons are essential for normal brain function and have been implicated in many neurological diseases. We aim to understand what genes regulate the neural stem cells in the cerebral cortex to generate the corticothalamic neurons during development. We have found that a transcription factor, named TBR1, is essential for the normal development of these neurons. In mice that carry mutations in Tbr1 gene, the corticothalamic neurons are not generated, but instead are replaced by the subcerebral neurons. The knowledge gained from this study can be used to facilitate the generation of different types of cortical neurons from stem cells for future cell replacement therapy.

Scientific Abstract:
The molecular mechanisms regulating fate divergence of closely related, but distinct, layer 6 corticothalamic and layer 5 subcerebral projection neurons are largely unknown. We present evidence for central transcriptional mechanisms that regulate fate specification of corticothalamic (layer 6) and subcerebral (layer 5) projection neurons. We found that TBR1 promotes the identity of corticothalamic neurons and represses subcerebral fates through reducing expression of Fezf2 and CTIP2. These conclusions are based on the following: (1) In Tbr1(-/-) mice, the number of cells expressing layer 6 markers was reduced, and the number of cells expressing layer 5 markers was increased. Early-born (birthdated on E11.5) neurons ectopically expressed subcerebral neuronal markers, and extended their axons into subcerebral targets. (2) Ectopic Tbr1 expression in layer 5 neurons prevented them from extending axons into the brainstem and the spinal cord. (3) Chromatin immunoprecipitation analysis using TBR1 antibodies showed that TBR1 bound to a conserved region in the Fezf2 gene. (4) Analysis of Fezf2 mutants and Tbr1(-/-); Fezf2(-/-) compound mutants provided evidence that Fezf2 blocks corticothalamic fate in layer 5 by reducing Tbr1 expression in subcerebral neurons. All neocortical regions appear to use this core transcriptional program to specify corticothalamic (layer 6) and subcerebral (layer 5) projection neurons.