Title

Identification And Functional Characterization Of Zebrafish Gene Technotrousers (tnt)

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Date of Award

9-2010

Document Type

Campus Access

Degree Name

Doctor of Philosophy (PhD)

Degree Program

Molecular and Cellular Biology

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Subject Categories

Cell Biology | Molecular Biology | Neuroscience and Neurobiology

Abstract

Neural networks in the hindbrain and spinal cord require a proper balance between excitation and inhibition. Identification of zebrafish mutants that have defects in motor output mediated by these networks can allow entrée into underlying network mechanisms. *techno trouser* (*tnt*) mutants demonstrate abnormal motor behavior. Two days after fertilization, wild-type larvae perform an escape response consisting of a large-amplitude body bend away from touch stimuli followed by smaller amplitude body bends to swim away. *tnt*mutants perform an initial large amplitude body bend away from touch stimuli, but the following smaller amplitude body bends are interrupted by several, abnormal, large amplitude body bends. Four days after fertilization, wild-type larvae exhibit faster escape behavior, whereas *tnt* mutants are nearly paralyzed and shorter along the rostral-caudal axis. We used meiotic mapping and candidate gene analysis to reveal that the*tnt* mutation disrupts *slc1a2b* , which encodes EAAT2, a glutamate transporter expressed in glial cells. Lesion analysis, *in situ* hybridization, and *in vivo* electrophysiological recordings all support a model in which reduced*slc1a2b* function results in exuberant excitation of neurons, initially in the hindbrain and later in development in the spinal cord, to produce the large-amplitude body bends and subsequent paralysis of *tnt* mutants. Since disruption of human EAAT2 is thought to promote several different neurological diseases, including epilepsy and amyotrophic lateral sclerosis, *tnt* mutants provide a new tool to understand these disorders.

Recommended Citation

McKeown, Kelly Anne, "Identification And Functional Characterization Of Zebrafish Gene Technotrousers (tnt)" (2010). *Doctoral Dissertations 1896 - February 2014*. 204.
https://scholarworks.umass.edu/dissertations_1/204