Targeted deletion of RIC8A in mouse neural precursor cells interferes with the development of the brain, eyes and muscles.

Kask K¹, Tikker L², Ruisu K¹, Lulla S¹, Oja EM¹, Meier R¹, Raid R¹, Velling T¹, Tönissoo T¹, Pooga M¹,³

Abstract

Autosomal recessive disorders like Fukuyama Congenital Muscular Dystrophy, Walker-Warburg syndrome and the Muscle-Eye-Brain disease are characterised by defects in the development of patient's brain, eyes and skeletal muscles. These syndromes are accompanied by brain malformations like type II lissencephaly in the cerebral cortex with characteristic over-migrations of neurons through the breaches of the pial basement membrane. The signalling pathways activated by laminin receptors, dystroglycan and integrins, control the integrity of the basement membrane, and their malfunctioning may underlie the pathologies found in the rise of defects reminiscent of these syndromes. Similar defects in corticogenesis and neuromuscular disorders were found in mice when RIC8A was specifically removed from neural precursor cells. RIC8A regulates a subset of G-protein α subunits and in several model organisms, it has been reported to participate in the control of cell division, signalling and migration. Here, we studied the role of RIC8A in the development of the brain, muscles and eyes of the neural precursor-specific conditional Ric8a knockout mice. The absence of RIC8A severely affected the attachment and positioning of radial glial processes, Cajal-Retzius' cells and the arachnoid trabeculae, and these mice displayed additional defects in the lens, skeletal muscles and heart development. All of the discovered defects might be linked to aberrancies in cell adhesion and migration, suggesting that RIC8A has a crucial role in the regulation of cell-extracellular matrix interactions and that its removal leads to the phenotype characteristic to type II lissencephaly associated diseases. This article is protected by copyright. All rights reserved.

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