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ENU mutagenesis identifies mice modeling Warburg Micro Syndrome withsensory axon degeneration caused by a deletion in Rab18.

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Abstract

Mutations in the gene of RAB18, a member of Ras superfamily of small G-proteins, cause Warburg Micro Syndrome (WARBM) which is characterized by defective neurodevelopmental and ophthalmological phenotypes. Despite loss of Rab18 had been reported to induce disruption of the endoplasmic reticulum structure and neuronal cytoskeleton organization, parts of the pathogenic mechanism caused by RAB18mutation remain unclear. From the N-ethyl-N-nitrosourea (ENU)-induced mutagenesis library, we identified a mouse line whose Rab18 was knocked out. This Rab18$^{-/-}$ mouse exhibited stomping gait, smaller testis and eyes, mimicking several features of WARBM. Rab18$^{-/-}$ mice were obviously less sensitive to pain and touch than WT mice. Histological examinations on Rab18$^{-/-}$ mice revealed progressive axonal degeneration in the optic nerves, dorsal column of the spinal cord and sensory roots of the spinal nerves while the motor roots were spared. All the behavioral and pathological changes that resulted from abnormalities in the sensory axons were prevented by introducing an extra copy of Rab18transgene in Rab18$^{-/-}$ mice. Our results reveal that sensory axonal degeneration is the primary cause of stomping gait and progressive weakness of the hind limbs in Rab18$^{-/-}$ mice, and optic nerve degeneration should be the major pathology of progressive optic atrophy in children with WARBM. Our results indicate that the sensory nervous system is more vulnerable to Rab18 deficiency and WARBM is not only a neurodevelopmental but also neurodegenerative disease.

KEYWORDS:

Axonal degeneration; Rab18; Sensory; Stomping gait; Warburg Micro Syndrome

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