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## Neuronatin-mediated aberrant calcium signaling and endoplasmic reticulum stress underlie neuropathology in Lafora disease.

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### Abstract

Lafora disease (LD) is a teenage-onset inherited progressive myoclonus epilepsy characterized by the accumulations of intracellular inclusions called Lafora bodies and caused by mutations in protein phosphatase laforin or ubiquitin ligase malin. But how the loss of function of either laforin or malin causes disease pathogenesis is poorly understood. Recently, **neuronatin** was identified as a novel substrate of malin that regulates glycogen synthesis. Here we demonstrate that the level of **neuronatin** is significantly up-regulated in the skin biopsy sample of LD patients having mutations in both malin and laforin. **Neuronatin** is highly expressed in human fetal brain with gradual decrease in expression in developing and adult brain. However, in adult brain, **neuronatin** is predominantly expressed in parvalbumin-positive GABAergic interneurons and localized in their processes. The level of **neuronatin** is increased and accumulated as insoluble aggregates in the cortical area of LD brain biopsy samples, and there is also a dramatic loss of parvalbumin-positive GABAergic interneurons. Ectopic expression of **neuronatin** in cultured neuronal cells results in increased intracellular Ca(2+), endoplasmic reticulum stress, proteasomal dysfunction, and cell death that can be partially rescued by malin. These findings suggest that the **neuronatin**-induced aberrant Ca(2+) signaling and endoplasmic reticulum stress might underlie LD pathogenesis.

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