

Induced knockouts provide insights into human L1 syndrome

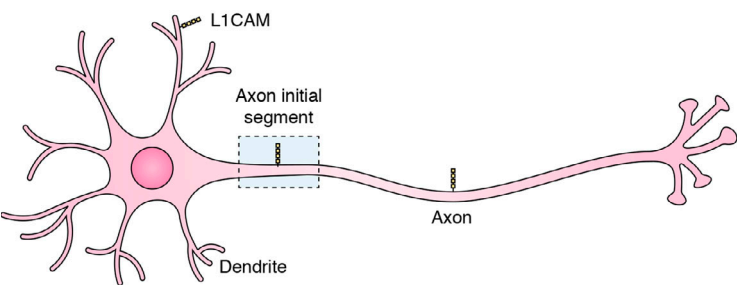
Unraveling the cellular changes elicited by pathogenic mutations is central to the development of novel targeted therapeutics. In this issue, Patzke et al. use advanced stem cell technologies to underscore the role of human L1CAM for neuronal development and function.

Mutations in the cell adhesion molecule L1CAM cause neurological alterations, including severe intellectual disabilities summarized as L1 syndrome. The requirements of L1CAM for neuronal development have been characterized extensively using in vitro, cell culture, and mouse model systems, which have implicated L1CAM in numerous signaling pathways with essential roles for neurite outgrowth, axon guidance, and synaptic transmission. However, distinct differences remain between the phenotypic strength of mouse models and clinical presentations in human patients.

Patzke et al. address the requirements of human L1CAM using embryonic stem (ES) cell-derived neurons and demonstrate that L1CAM is cell-autonomously required for the control of neuronal morphology and excitability, features likely contributing to impaired neurological performances in human patients. The novel approach of generating induced conditional knockout neurons with perfectly matched controls enables precise qualitative and quantitative analyses of disease-associated alterations. Loss of L1CAM not only resulted in reduced axonal outgrowth but also uncovered a requirement for dendritic



Insight from
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	Dendrites	Axon initial segment	Axon
Expression	Temporal, early only	Continuous	Continuous
Cellular	Dendrite elaboration	AIS composition	Axon elongation
Molecular	?	AnkG/ Na ⁺ -channel	AnkB
Physiology	?	Excitability	Connectivity?

The cell adhesion molecule L1CAM is cell-autonomously required for the development of neuronal compartments.

circuits. In combination with in vivo animal models, the ES-based conditional knockout strategy provides an exciting and complementary route to human disease diagnostics and therapeutic development.

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development. In the absence of L1CAM, there is a reduction in the levels of ankyrinG and ankyrinB, two adaptor proteins that are essential organizers of axonal domains. Consequently, mutant neurons exhibited decreased excitability, resulting in impaired action potential generation. Pathogenic mutations in the ankyrin-binding site of L1CAM failed to restore ankyrin distribution, suggesting that L1CAM and ankyrins form interdependent stabilizing complexes controlling the subcellular protein composition of axonal domains.

From a therapeutic point of view, this strategy of matched control and mutant human ES-derived neurons not only enables the identification of human-specific gene functions but also facilitates the testing of potential gene-based or pharmacological interventions to ameliorate disease-associated deficits. However, in the case of adhesion molecules like L1CAM, it is also important to consider that transcellular interactions may alter intrinsic signaling properties and contribute to the establishment of functional neuronal