An ankyrin-binding motif regulates nuclear levels of L1-type neuroglian and expression of the oncogene *Myc* in Drosophila neurons

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Running title: *Ankyrin-binding motif in regulating nuclear levels of Nrg*

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Keywords: L1-CAM, neuroglian, Myc, nuclear function, ankyrin-binding motif, Drosophila, cancer, oxidative stress, transcriptional regulation

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ABSTRACT

L1 cell adhesion molecule (L1CAM) is well known for its importance in nervous system development and cancer progression. In addition to its role as a plasma membrane protein in cytoskeletal organization, recent *in vitro* studies have revealed that both transmembrane and cytosolic fragments of proteolytically cleaved vertebrate L1CAM translocate to the nucleus. *In vitro* studies indicate that nuclear L1CAM affects genes with functions in DNA post-replication repair, cell cycle control, and cell migration and differentiation, but its *in vivo* role and how its nuclear levels are regulated is less well understood. Here, we report that mutations in the conserved ankyrin-binding domain affect nuclear levels of the sole Drosophila homolog neuroglian (Nrg) and that it also has a noncanonical role in regulating transcript levels of the oncogene *Myc* in the adult nervous system. We further show that altered nuclear levels of Nrg correlate with altered transcript levels of *Myc* in neurons similar to what has been reported for human glioblastoma stem cells. However, whereas previous *in vitro* studies suggest that increased nuclear levels of L1CAM promote tumor cell survival, we found here that elevated levels of nuclear Nrg in neurons are associated with increased sensitivity to oxidative stress and reduced lifespan of adult animals. We therefore conclude that these findings are of potential relevance to the management of neurodegenerative diseases associated with oxidative stress and cancer.

L1-type Cell Adhesion Molecules (CAM) are single pass transmembrane glycoproteins belonging to the immunoglobulin family of receptors that are highly conserved from invertebrates to vertebrates (1). The structure of L1CAM consists of extracellular immunoglobulin- and fibronectin type III (FNIII) domains, a transmembrane domain, and a cytoplasmic tail harboring an ezrin binding FERM domain as well as an ankyrin-binding FIGQY domain (Fig. 1A). In its unphosphorylated state the highly conserved FIGQY domain reversibly binds to Ankyrin (Fig. 1A), which couples L1-type CAMs to actin. This interaction is known to mediate neuritogenesis, synapse growth and stability (2-4). In contrast, phosphorylation of the tyrosine in the FIGQY domain inhibits Ankyrin binding (5,6).

In addition to its function as a cytoskeleton organizing protein at the plasma membrane, vertebrate L1CAM can be proteolytically cleaved with fragments translocating to the nucleus (7-11). The 200 kDa full-length L1CAM is cleaved proximal to the plasma membrane by metalloproteases to a 32 kDa fragment (12,13). The