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THE XLMR GENE *ACSL4* PLAYS A ROLE IN DENDRITIC SPINE ARCHITECTURE

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ACSL4 is a gene involved in non-syndromic X-linked mental retardation. It encodes for a ubiquitous protein that adds Coenzyme-A to long-chain fatty acids, with a high substrate preference for arachidonic acid; in addition to the ubiquitous variant, a brain-specific isoform deriving from alternative splicing and containing 41 additional N-terminal aminoacids is also present. To unravel the link between *ACSL4* and mental retardation, we have characterized the protein and analyzed the consequences of its absence in cultured rat primary hippocampal neurons. By immunofluorescence microscopy we demonstrated that *ACSL4* is mainly located to the cell soma where it is preferentially associated to endoplasmic reticulum tubules; a significant staining along the dendritic shaft is also observed. Moreover, in some cells, *Acsl4*-rich spots located in close proximity to or co-localizing with actin-rich protrusions emerging from the dendritic shaft are also present. To characterize *ACSL4* function in neurons we silenced the gene by siRNA technology. Our data suggest that *ACSL4* is not necessary for neurons gross architectural features (i.e. axonal and dendritic formation and final length) but it is required for the presence of normal spines. In fact, reduced levels of *ACSL4* led to a significant reduction in dendritic spine density and an alteration in spine/filopodia distribution, in addition, spine distribution among different morphological categories seems to be also affected, suggesting the possibility of an alteration in spine maturation processes. It has been reported that arachidonic acid, *ACSL4* substrate, is involved in the regulation of actin cytoskeleton. These data suggests that *ACSL4* might directly or indirectly influence actin cytoskeleton organization; the observed spine anomalies might thus be a secondary effect of an abnormal actin organization due to *ACSL4* absence.