Angelman Syndrome-associated mutations reveal the mechanism and importance of UBE3A nuclear targeting

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Mutations affecting ubiquitin-ligase UBE3A cause Angelman Syndrome (AS). Although most studies focus on the synaptic function of UBE3A, UBE3A is highly enriched in the nucleus of mouse and human neurons. We found that the two major isoforms of UBE3A exhibit a highly distinct nuclear versus cytoplasmic subcellular localization. We found that both isoforms undergo nuclear import through direct binding to PSMD4/RPN10, but the amino-terminus of the cytoplasmic isoform prevents nuclear retention. We identified AS-associated UBE3A missense mutations that interfere with either nuclear targeting or retention of UBE3A.

Mice lacking the nuclear UBE3A isoform recapitulate the behavioural and electrophysiological phenotypes of AS mice, whereas mice harbouring a targeted deletion of the cytosolic isoform are unaffected. Taken together, our findings elucidate the mechanisms underlying the subcellular localization of UBE3A, and point to a critical function of nuclear UBE3A in neurodevelopment.