CLTC-related ID

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De novo CLTC

mutations underlie a spectrum of early-onset neurodevelopmental phenotypes having developmental delay/intellectual disability (ID), epilepsy, and movement disorders (MD) as major clinical features.

CLTC

encodes the widely expressed heavy polypeptide of clathrin, a major component of the coated vesicles mediating endocytosis, intracellular trafficking, and synaptic vesicle recycling. The underlying pathogenic mechanism is largely unknown. Here, we assessed the functional impact of the recurrent c.2669C > T (p.P890L) substitution, which is associated with a relatively mild ID/MD phenotype. Primary fibroblasts endogenously expressing the mutated protein show reduced transferrin uptake compared to fibroblast lines obtained from three unrelated healthy donors, suggesting defective clathrin-mediated endocytosis.

In vitro

studies also reveal a block in cell cycle transition from G0/G1 to the S phase in patient's cells compared to control cells. To demonstrate the causative role of the p.P890L substitution, the pathogenic missense change was introduced at the orthologous position of the

Caenorhabditis elegans

gene,

chc-1

(p.P892L), via CRISPR/Cas9. The resulting homozygous gene-edited strain displays resistance to aldicarb and hypersensitivity to PTZ, indicating defective release of acetylcholine and GABA by ventral cord motor neurons. Consistently, mutant animals show synaptic vesicle depletion at the sublateral nerve cords, and slightly defective dopamine signaling, highlighting a generalized deficit in synaptic transmission. This defective release of neurotransmitters is associated with their secondary

accumulation at the presynaptic membrane. Automated analysis of

C. elegans

locomotion indicates that

chc-1

mutants move slower than their isogenic controls and display defective synaptic plasticity. Phenotypic profiling of

chc-1

(+/P892L) heterozygous animals and transgenic overexpression experiments document a mild dominant-negative behavior for the mutant allele. Finally, a more severe phenotype resembling that of

chc-1

null mutants is observed in animals harboring the c.3146 T > C substitution (p.L1049P), homologs of the pathogenic c.3140 T > C (p.L1047P) change associated with a severe epileptic phenotype. Overall, our findings provide novel insights into disease mechanisms and genotype-phenotype correlations of

CLTC

-related disorders.