NEWS

Molecular mechanisms: Autism mutations cause cell stress

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Misplaced mutants: A mutation causes CNTNAP2 (red) to localize at the endoplasmic reticulum (green, bottom) instead of the cell surface (top).

Autism-linked mutations in CNTNAP2 prevent proper localization and folding of the protein and activate a cellular stress response, according to a study published 23 August in *Human Molecular Genetics*[1].

CNTNAP2 helps organize **synapses**, the connections between neurons, by forming a seal with partner proteins. Common variants in the gene are linked to **autism**, **specific language impairment** and **language delay** in the general population.

In the new study, researchers looked at the effect of each of 12 mutations of CNTNAP2 identified in individuals with autism. Six of the mutations prevent proper processing of CNTNAP2, stalling it in the endoplasmic reticulum — the cellular structure in which proteins are synthesized and modified.

One of these mutations, D1129H, has the most significant effect on the production of functional CNTNAP2.

Only a small fraction of this mutant travels to the cell membrane and to synapses. The rest remains in the endoplasmic reticulum, where it is bound by chaperones, which fold proteins and help dispose of faulty ones.

The stalled CNTNAP2 activates a cellular stress response that turns up the production of chaperones, turns down protein synthesis to prevent a backlog, and can ultimately result in cell death.

Another mutation, CNTNAP2-1253, results in a version of the protein lacking the section that adheres it to the cell membrane. This version exits the cell instead of assuming its role at the synapse.

CNTNAP2 typically turns over quickly in the cell, the researchers found. This supports its role in dynamically changing the strength of synapses in response to experience, they say.

References:

1: Falivelli G. *et al. Hum. Mol. Genet.* Epub ahead of print (2012) **PubMed**