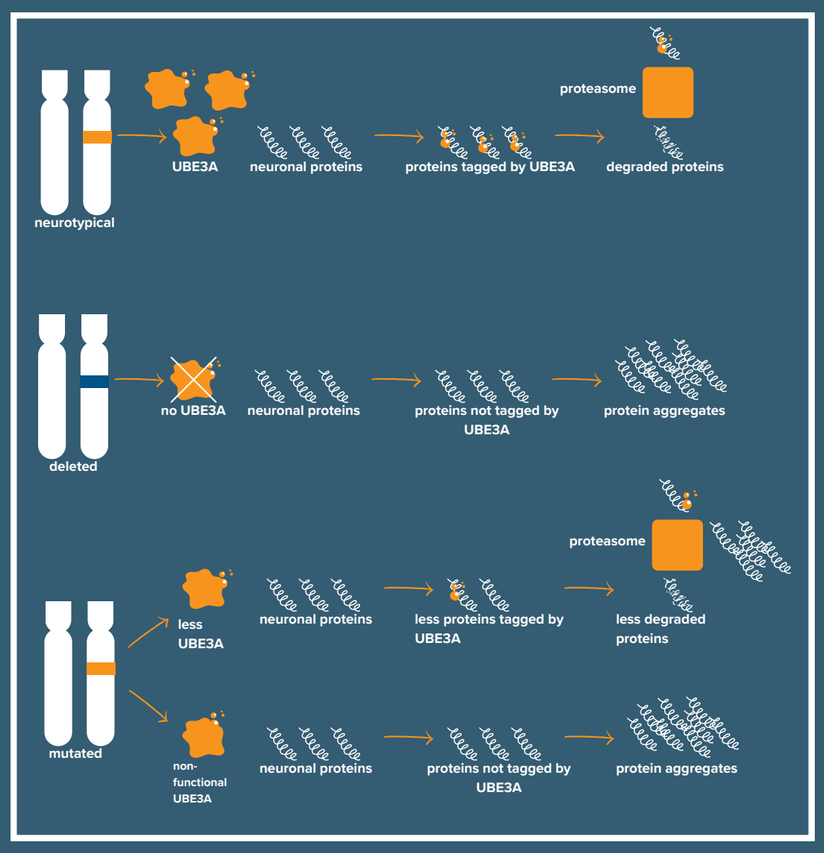
Research Progress Update 2024

Contribution of hemizygous HERC2 deletion to Angelman syndrome pathophysiology

Eric Levine, Ph.D. Dept. of Neuroscience University of Connecticut Health Center

angelman SYNDROME FOUNDATION | FAMILIES. RESEARCH. CLINICS. COMMUNITY. WITH YOU FOR THE JOURNEY.

BACKGROUND



In neurotypical individuals, the UBE3A gene on chromosome 15 allows the proper breakdown of proteins in the brain. In Angelman Syndrome (AS) the breakdown of these proteins is impaired because the UBE3A gene is either deleted completely or it's mutated to a nonfunctional form. This can mean that the mutated gene variants can cause either less of the functional UBE3A or a completely nonfunctional version of the UBE3A.

Furthermore, the cells that are affected, are usually neurons, the cells in our brains! These cells have a standard way of sending signals, using ions (sodium, potassium, calcium) that give the cell a net positive or net negative cell compared to its environment. These processes, termed depolarization and repolarization, help cells send those signals. When there is enough of a negative charge (from depolarization) the cell reaches what is called a "threshold" that acts like permission for that neuron to speak to the next neuron. The messages spread and spread. We measure this through electrophysiology and can describe it as a cell's biochemical characterization.

Another gene of interest is HERC2. This gene is typically not affected in individuals with mutation-AS. However, because deletions occur randomly, not every deletion is at the same starting and ending point. Sometimes, this means HERC2 (among other genes) can get cut out in addition to UBE3A. Much like UBE3A, HERC2 encodes a protein that tags the neuron proteins for breakdown.

GABA-A receptors, which may be implicated in altering neuron communication in AS, typically functions by inhibiting communication between neurons.

AIMS

1. Establish and compare the biochemical and electrophysiological responses of the neurons in individuals with a. deletion of UBE3A-AS and b. UBE3A-deficient-AS (mutated).
2. Explore the role of HERC2 when it is deleted in individuals with a. a deleted UBE3A gene and b. those do not have it deleted along with the UBE3A gene.

PROGRESS

AIM 1:

- further characterized the biochemical differences between cells with UBE3A mutations (nonfunctional) compared to control cells
  - indicating a better functional understanding of what is happening differently in the neuron cells of people with AS
- identified cellular characterizations that demonstrate less severity compared to cells with UBE3A deletions
  - indicating that the deletions that take more than just the UBE3A gene could play a role in AS
- comparison between cells with UBE3A deletions versus UBE3A mutations (nonfunctional)
  - cells with deletions demonstrate more excitability and altered communication between neuron cells
- some of the neurons with altered communication are also lacking three subunit receptors, called GABA-A

AIM 2:

- HER2C cell lines are being compared to each other; the belief is that a neuron cell line that has UBE3A mutated, and then gets HER2C knocked out, will function and develop the same way neurons in AS deletion lines do (increased excitability and altered communication)
- current studies have confirmed the ability to knock-out 50% of HER2C (like would happen in an AS deletion or mutation making it nonfunctional on one chromosome) and are being continued to ensure stability over a 10-15 week time period

NEXT steps

- use 3 new precursor cell lines (that can be differentiated into wild-type (neurotypical), UBE3A-mutation, and large AS deletion to further characterize the differences in their characterizations, or phenotypes.
- use a new isogenic GABA-A deficient cell line to determine it's role in AS neurons with altered transmission
- quantify how many neurons are increased excitability or altered communication by cell line and determine if it's functional or structural changes
- determine if HER2C will be a good therapeutic target and if so, developing a method to determine best drug therapy for individuals by their cellular characterizations