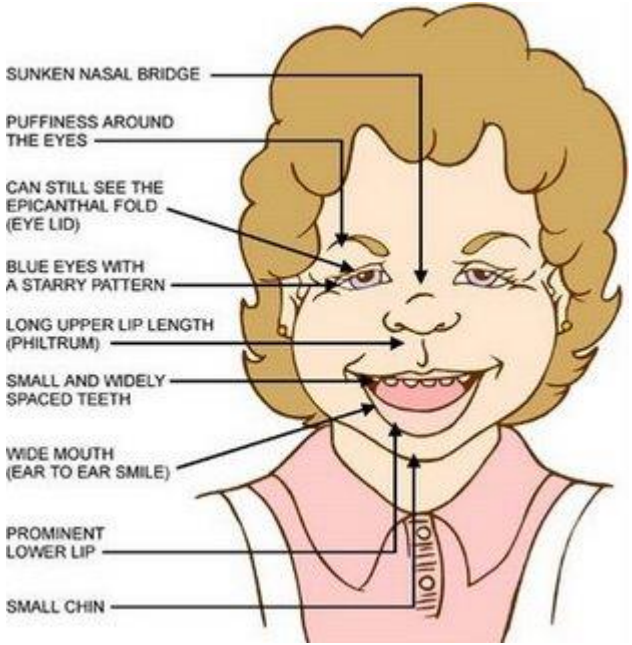
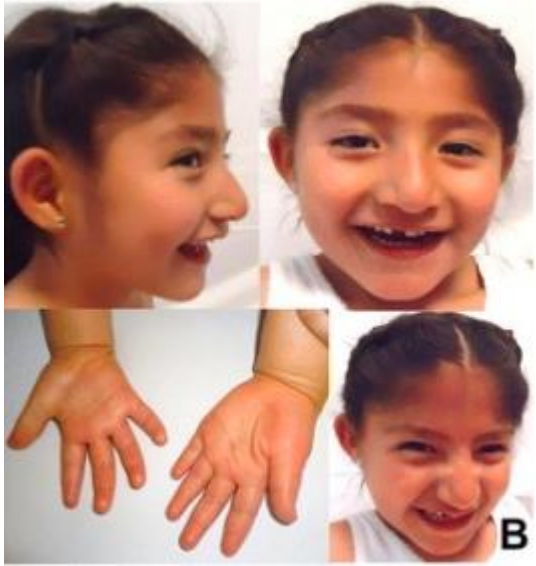
Angelman Syndrome

Brain Budz

Mary Augustine, Piper Doering, Kristie Trinh, and Colin Twyman

Significance





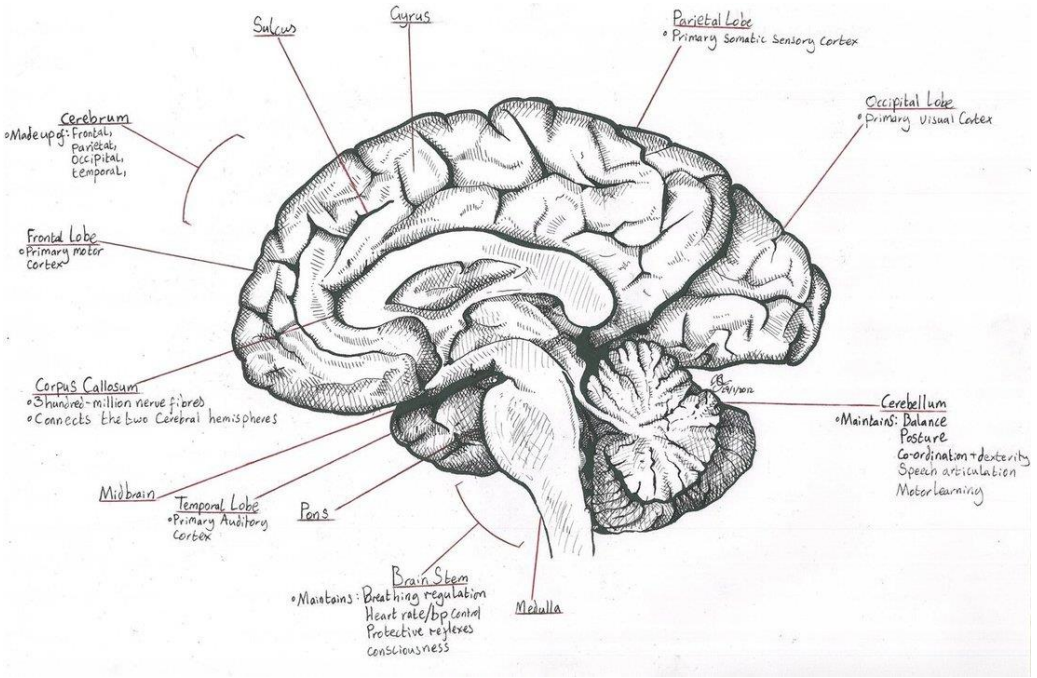
Historical Background

William’s Syndrome

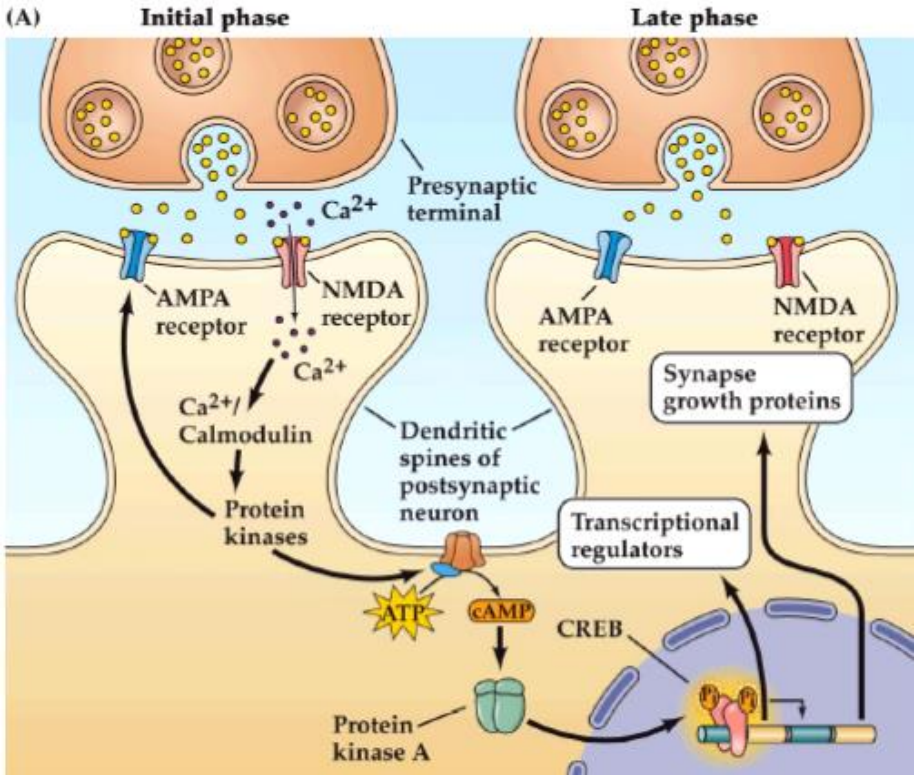
Down Syndrome

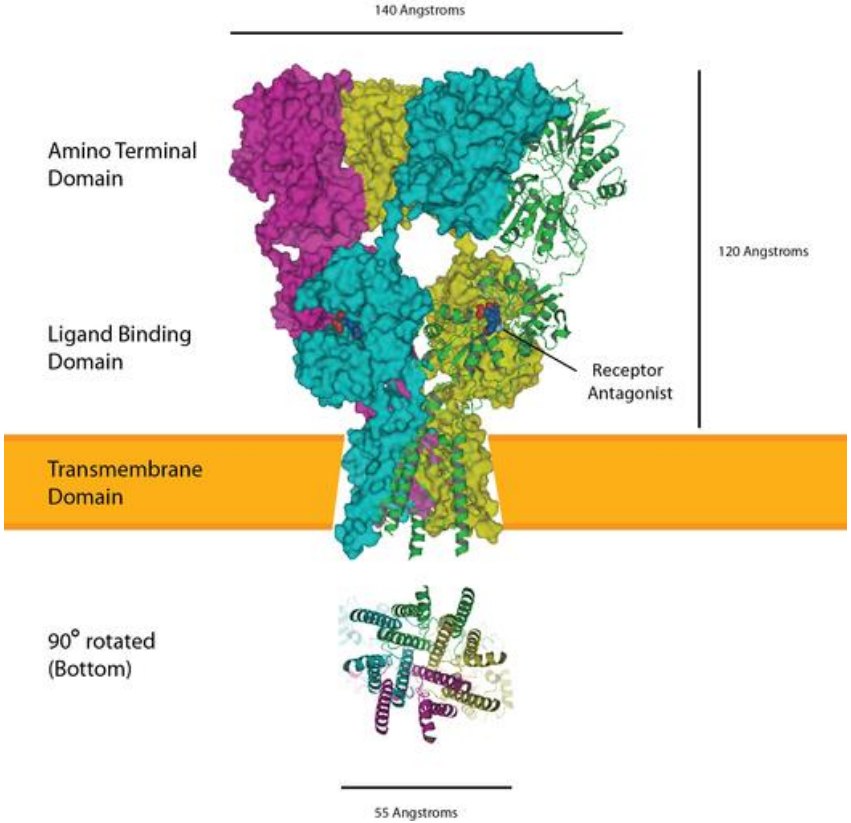
Symptoms and Neuroanatomy

- Seizures
- Stiff or jerky movements
- Tongue thrusting
- Difficulty walking
- Inability to balance
- Hand flapping



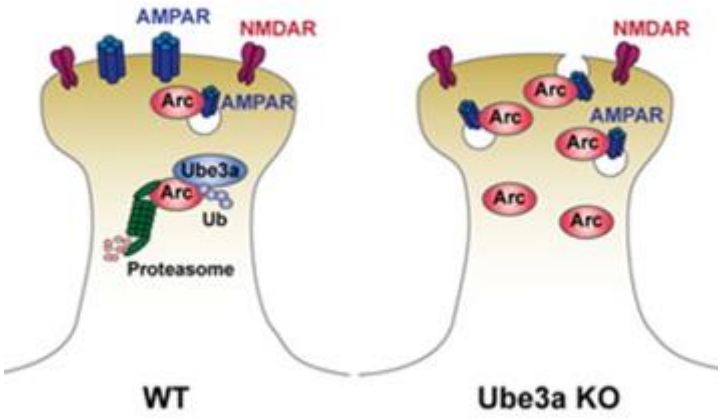
AMPA Receptors





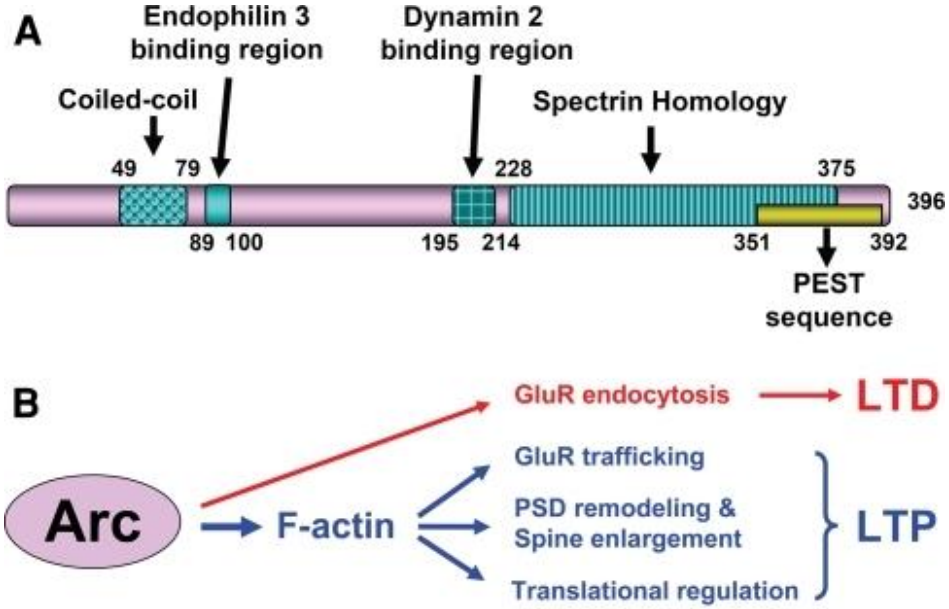
Internalization of AMPA Receptor

- Higher amount of Arc Protein in Angelman Syndrome
- Arc Protein is mediated by Ube3a
- Lower expression of AMPA receptor on synaptic membrane



http://www.cell.com/abstract/S0092-8674(10)00061-9

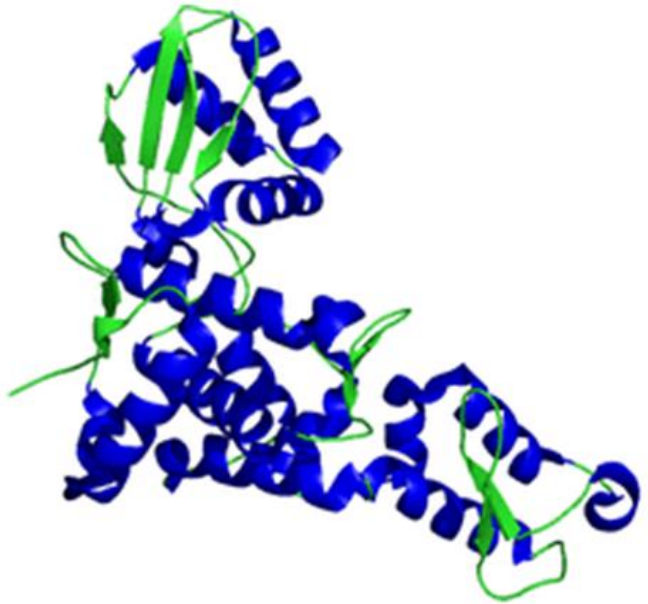
Arc Protein



https://openi.nlm.nih.gov/detailedresult.php?img=PMC2803749_221_2009_1959_Fig2_HTML&req=4

Ubiquitin 3 Ligase

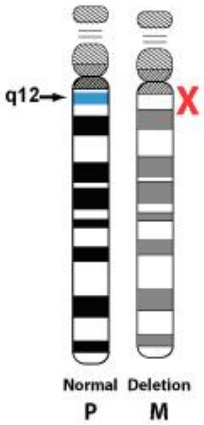
- Catalyze proteins during ubiquitination
- Neuronal activity regulated protein
- Controls synaptic function
- Regulates AMPA receptor internalization



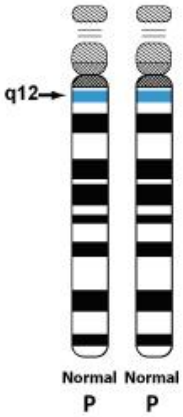
http://pawsonlab.mshri.on.ca/index.html

Genetic Causes

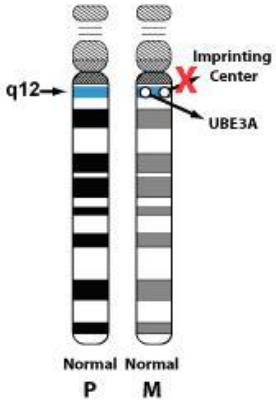
Normal



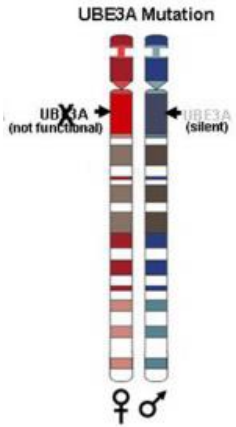
Maternal Deletion



Paternal Uniparental Disomy



Imprinting Defect



UBE3A Mutation

Translocation not shown

15q12 - chromosome 15, long arm, region 1, band 2

15q11.2 - chromosome 15, long arm, region 1, band 1, sub-band 2

Genetic Causes (cont.)

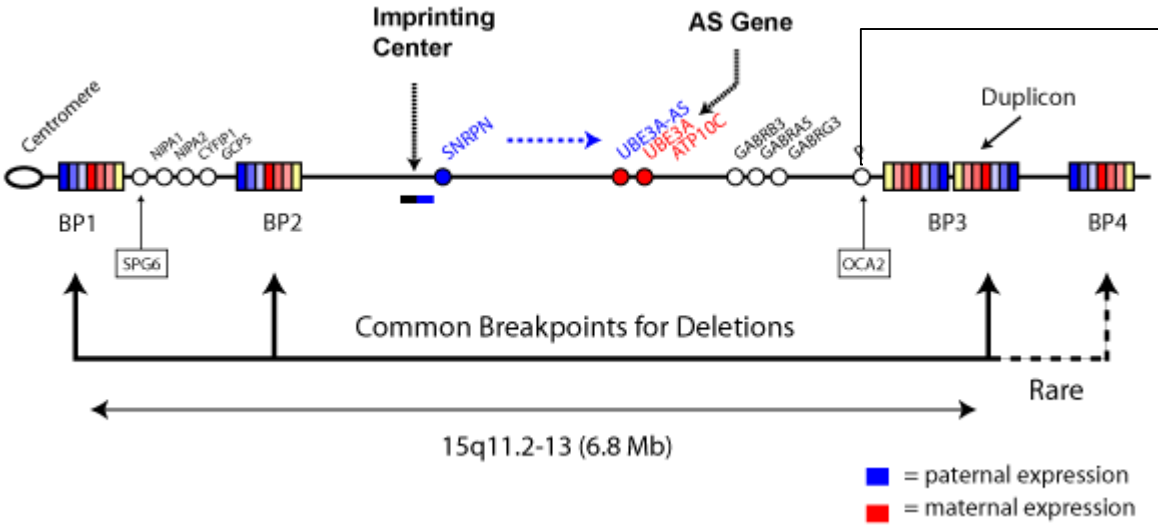
- 5 chromosomal variants lead to Angelman syndrome
- Majority of cases there are no inheritance patterns
  - Occurs in meiosis and early development
- Translocation occurs in rare cases, leading to UBE3A inactivation or lack of TF required for its activation

Table 1. Molecular classes of AS with methylation status

Class	Chromosome/genetic abnormality	~%
I	15q11–13 deletion	70
II	UPD (Uniparental disomy)	5
III	ID (Imprinting defect)	5
IV	UBE3A mutation	10
V	Unknown	10

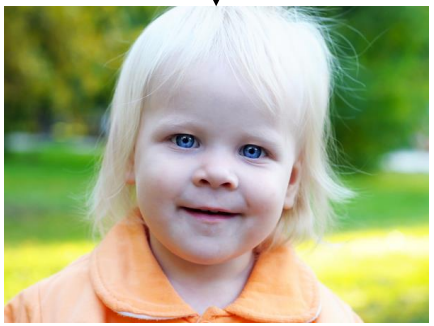
Source: Lalande and Calciano, 2007

15q12

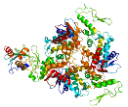


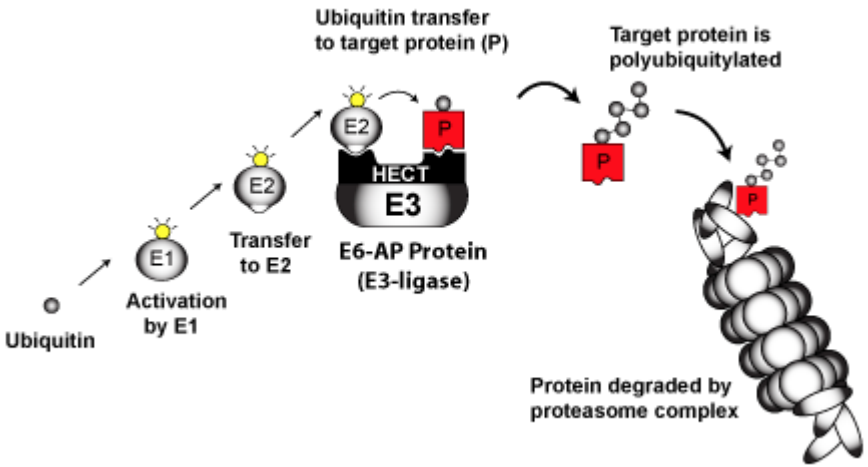
Source: University of Florida Department of Pediatrics Division of Genetics and Metabolism

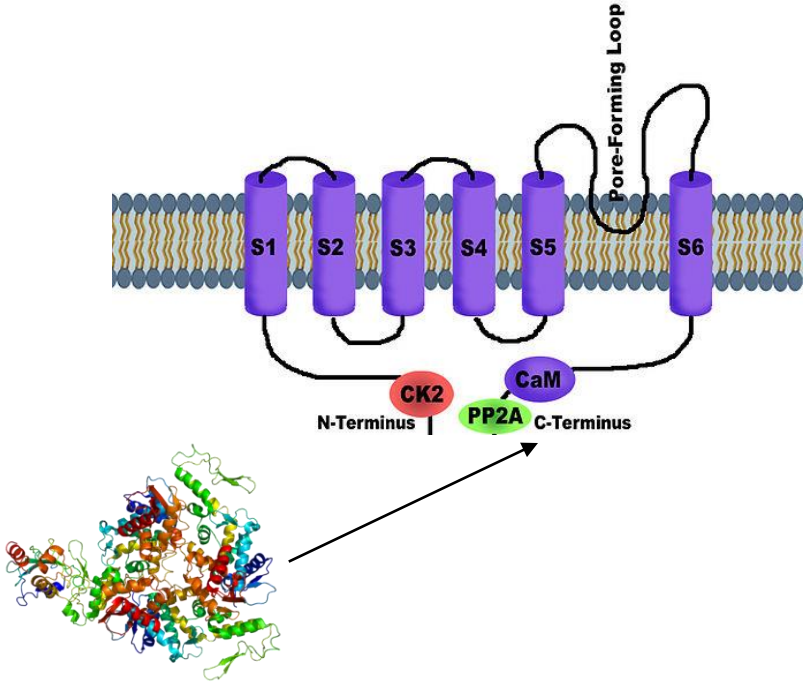
Loss of OCA2 gene leads to distinct phenotypic changes



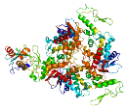
UBE3A - encoded in 15q12



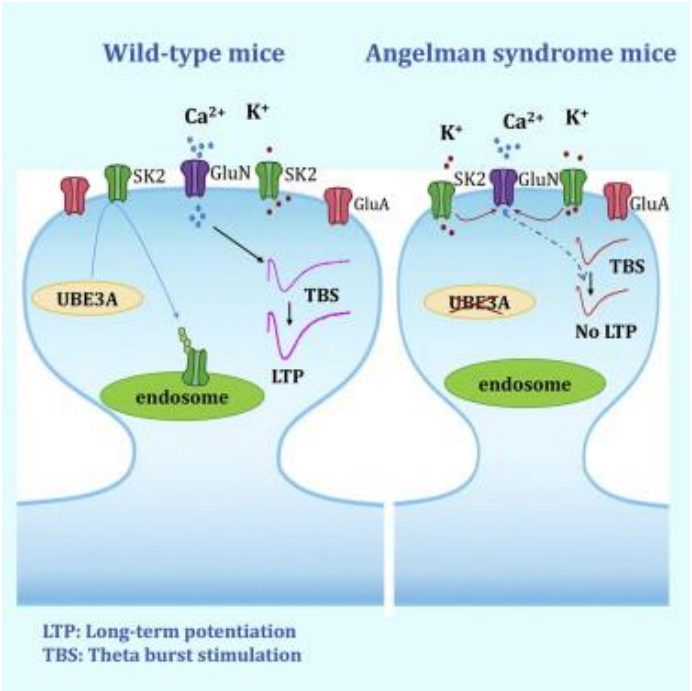




UBE3A Regulates SK2 Channel Endocytosis

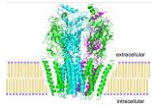


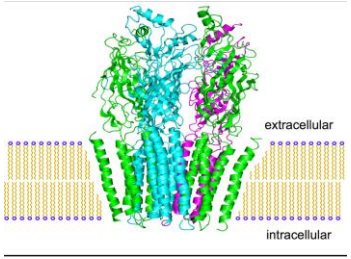
- SK channels are critical for learning, memory, rhythmic activity, and sleep
- Therefore, UBE3A regulates learning and memory by controlling SK2 channel endocytosis

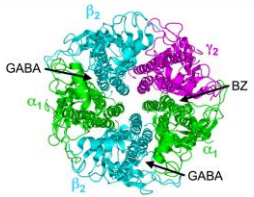


Source: Jiandong et al., 2015

$GABA_A$ Receptor - encoded in 15q12







$GABA_A$ Receptor

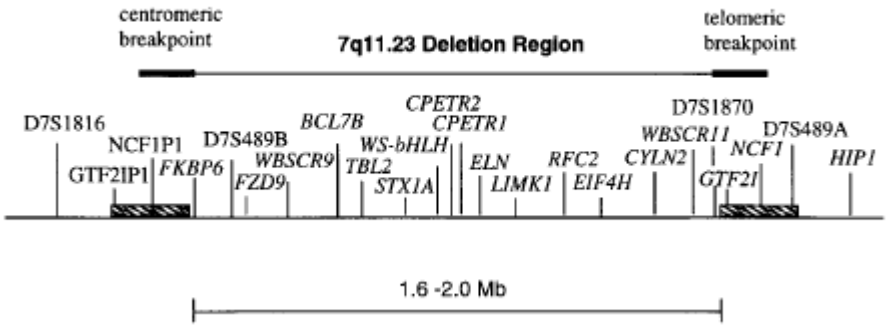
- β3-α5-γ3 $GABA_A$ receptor subunit gene cluster is located in 15q11-q13 region and can be deleted along with UBE3A

GAT1

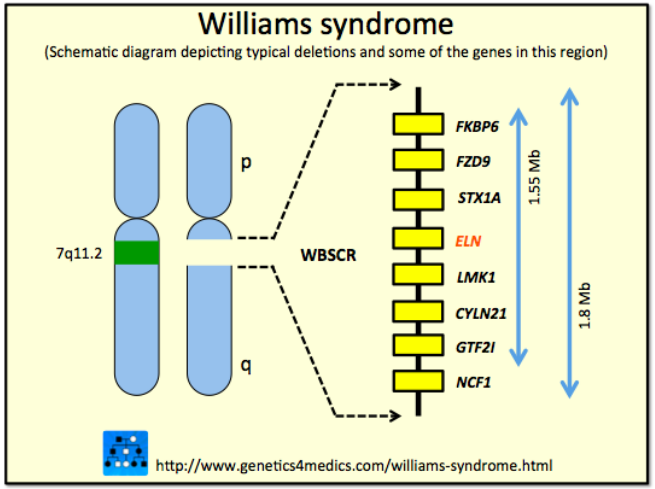
- GAT1 removes GABA from synaptic cleft
- UBE3A targets GAT1 for degradation and recycling
- Without UBE3A, there is an increase of GAT1, which leads to GABA deficiency

Decrease or loss of activation of $GABA_A$ receptor → Decrease or loss of inhibition

Williams Syndrome



Source: Francke 1999

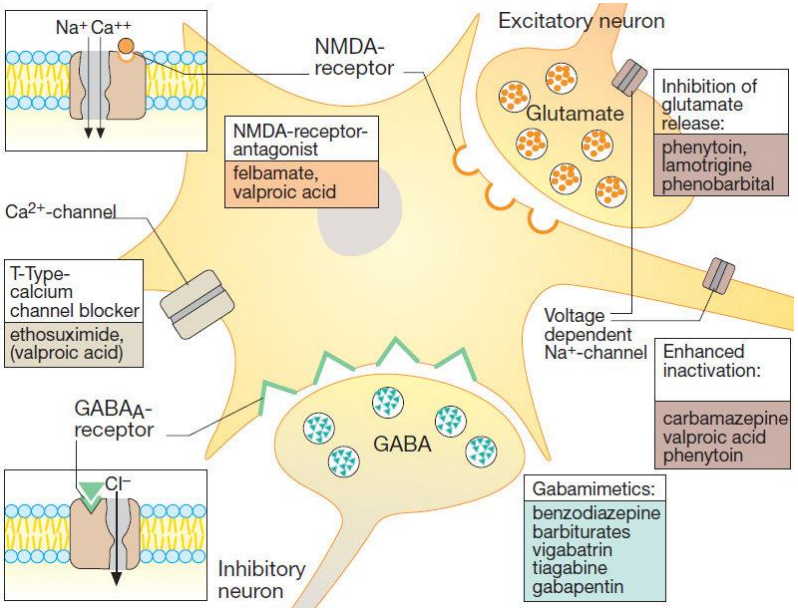


- Deletion of tropoelastin (ELN) leads to cardiovascular problems
- GTF2IRD1 regulates gene expression in the brain and skeletal muscles
- LIMK1 regulates neuronal development

Treatments

Drugs: Mainly focuses on treating epilepsy related symptoms

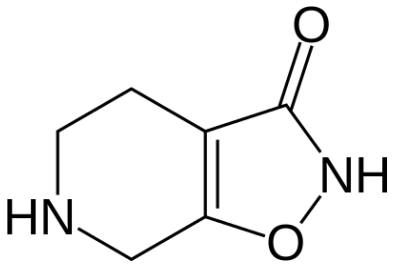
Communication Therapy: Early intervention is critical and focuses on visual aides



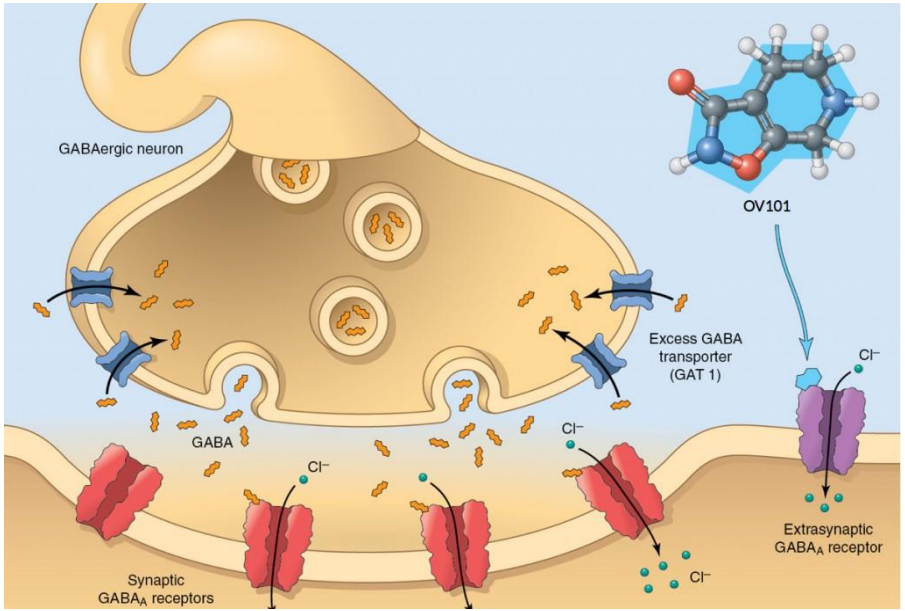
Clinical Trials: Restoring $GABA_A$ Receptor Activity

OV101 - gaboxadol

- Extrasynaptic δ - selective $GABA_A$ receptor agonist
- Still recruiting, in Phase II



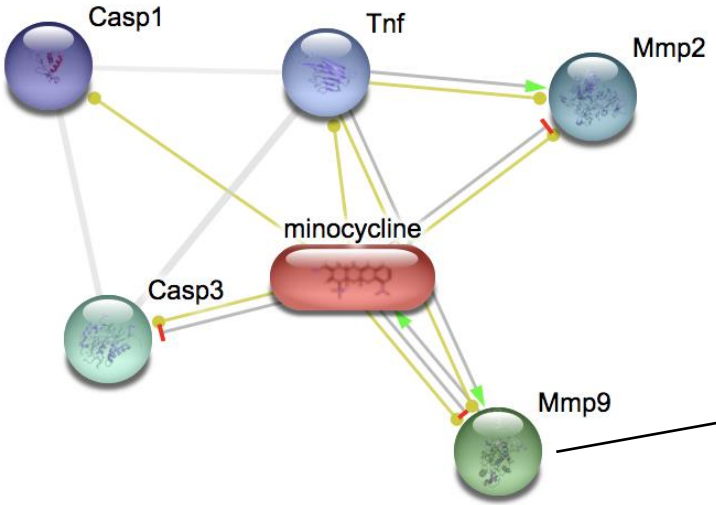
Source: Wikipedia



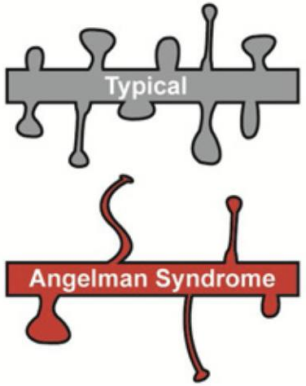
Source: Foundation for Angelman Syndrome Therapeutics

Clinical Trials: Restoring Synaptic Development

Minocycline: antibiotic being tested to restore synaptic dysfunction



Source: STITCH Database

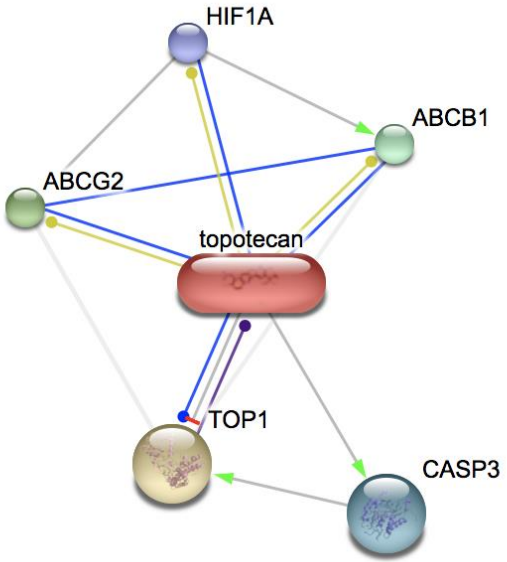


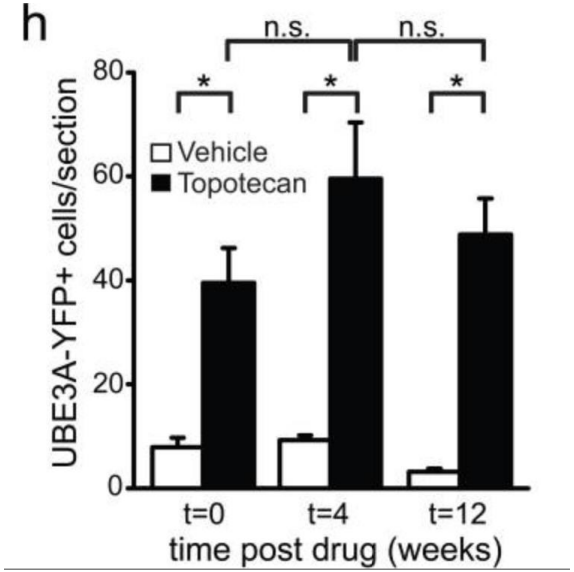
Source: Miller and Phillips (2015)

Mmp9: enzyme that degrades the extracellular matrix of cells. Believed to be involved in synaptic plasticity

Clinical Trials: Unsilencing the Paternal *UBE3A* Gene

Topotecan: topoisomerase inhibitor that results in increased levels of paternal UBE3A levels





Allen, Blake, et al. (2012)

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