Angelmann Syndrome

Brain Budz

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

- Sunken nasal bridge
- Puffiness around the eyes
- Can still see the epicanthal fold (eye lid)
- Blue eyes with a starry pattern
- Long upper lip length (philtrum)
- Small and widely spaced teeth
- Wide mouth (ear to ear smile)
- Prominent lower lip
- Small chin
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

(A) Initial phase

- AMPA receptor
- NMDA receptor
- 

Ca\(^{2+}\) influx

- Presynaptic terminal

Ca\(^{2+}\) entry

- AMPA receptor
- NMDA receptor

Ca\(^{2+}\) entry

Ca\(^{2+}/\) Calmodulin

- Protein kinases

Ca\(^{2+}\) entry

- Synapse growth proteins

- Transcriptional regulators

- ATP

- CAMP

- CREB

- Protein kinase A

Late phase

140 Angstroms

Amino Terminal Domain

Ligand Binding Domain

Receptor Antagonist

Transmembrane Domain

90° rotated (Bottom)

120 Angstroms

55 Angstroms
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

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Chromosome/genetic abnormality</th>
<th>~%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15q11–13 deletion</td>
<td>70</td>
</tr>
<tr>
<td>II</td>
<td>UPD (Uniparental disomy)</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>ID (Imprinting defect)</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>UBE3A mutation</td>
<td>10</td>
</tr>
<tr>
<td>V</td>
<td>Unknown</td>
<td>10</td>
</tr>
</tbody>
</table>

Source: Lalande and Calciano, 2007
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<sub>A</sub> Receptor**
- β3-α5-γ3 GABA<sub>A</sub> 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<sub>A</sub> receptor

Decrease or loss of inhibition
Williams Syndrome

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

Source: Francke 1999
**Treatments**

**Drugs:** Mainly focuses on treating epilepsy related symptoms

**Communication Therapy:** Early intervention is critical and focuses on visual aides
Clinical Trials: Restoring GABA\textsubscript{A} Receptor Activity

OV101 - gaboxadol

- Extrasynaptic δ - selective GABA\textsubscript{A} receptor agonist
- Still recruiting, in Phase II
Clinical Trials: Restoring Synaptic Development

**Minocycline**: antibiotic being tested to restore synaptic dysfunction

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

Source: STITCH Database

Clinical Trials: Unsilencing the Paternal *UBE3A* Gene

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

Allen, Blake, et al. (2012)
References


