ANGELMAN SYNDROME
GENETICS 101

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Current Disclosures:
ASF Board Member
ASF Scientific Advisory Committee
OVID Clinical Trial Steering committee (STARS/ELARA/NEPTUNE)
TODAY’S PRESENTATION

- Overview of genetics behind Angelman Syndrome
- Brief discussion of genotype/phenotypes in AS
- Where should I focus as a beginner?
- Why do we think better therapeutics are possible?
- What do I need to know about clinical trials in general?
WE HAVE 23 PAIRS OF CHROMOSOMES IN OUR CELLS
GENES ENCODE INSTRUCTIONS FOR MAKING PROTEINS

Proteins can be thought of as machines, signals, and structures.
WE RECEIVE ONE SET OF CHROMOSOMES FROM MOM AND ONE SET FROM DAD

Cells in your body know which chromosome came from mom and which came from dad.
ANGELMAN SYNDROME IS CAUSED BY A LOSS OF FUNCTION UBE3A IN THE BRAIN
**UBE3A** MARKS PROTEINS FOR RECYCLING OR REMOVAL (DEGRADATION)

Ubiquitin activation by **E1**

Transfer to **E2**

**E6-AP** Protein (E3-ligase)

Ubiquitin transfer to target protein (**P**) in Recycling Center

Target protein is polyubiquitinated

Protein degraded by proteasome

Optimal neuron function

\[\text{modified from Dan, 2008}\]
KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME
MICRODELETIONS IN AS

http://www.imprinting-disorders.eu/?page_id=276

Class I deletions are ~6MB

Human Genome is 3235 MB with around 20,000 genes
KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME
GENETICS 201 - MUTATIONS CHANGE GENE INFORMATION AND THE RESULTING PROTEIN PRODUCED

ACC GUG CUU ACG GGG UAC AUA
TVLTVLTVLTVLTVLTVLTVLTVLTVL

The UBE3A gene encodes a protein called a ubiquitin ligase.
KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME
YOUR CELLS KNOW WHICH CHROMOSOME CAME FROM MOM AND WHICH CAME FROM DAD

Chamberlain and Lalande J. Neurosci 2010
UPD = uniparental disomy
KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME

65 - 75%  5 - 11%  3 - 7%  3%
SYMPTOMS OF AS

Consistent
- Predominantly non-verbal
- Movement/Balance Issues
- Skill development is delayed
- EEG Abnormalities

Frequent
- Seizures

Associated
- Anxiety
- Sleep issues
- GI issues – reflux and constipation
- Feeding issues – over eating or lack of appetite
- Drooling/mouthing behaviors
- Aggression – disruptive behaviors
- Myoclonus – tremoring
IN GENERAL....

- Deletion Class I
- Deletion Class II
- Mutation
- UPD
- ICD/Imprinting defect
- Mosaic forms of the above

Decreasing Severity
SO WHAT CAUSES MY LOVED ONES SYMPTOMS?

We know that all of the unique symptoms of AS – impaired verbal communication, motor issues, seizures, generally pleasant demeanor are all from loss of UBE3A.

Remember – there are ~20,000 other genes that contribute to who our loved ones are!
WHAT ARE MY PRIORITIES FOR MY CHILD?

1. Health (seizures, reflux, GI issues)
2. Communication
3. Behaviors (including sleep!)
WHAT ARE MY PRIORITIES FOR ME AS A CAREGIVER?

1. Health (mental, physical – reduce stress and guilt)
2. Sleep
3. Community
WE RECEIVE ONE SET OF CHROMOSOMES FROM MOM AND ONE SET FROM DAD

The egg that developed into your child was created when you/mom was still in utero
Onset of seizures: ~7 months

Sitting up without support: 3-4 years, currently can sit for 30 minutes with protection

Walking: with support only

Number of seizure drugs: Current 2 - tried 6

Bayley’s: lowest possible score

WORDS MATTER

Don’t take it personally – but educate….

Strongly affected by AS VS. Severe, low functioning
Less affected by AS Less severe, higher functioning

• Onset of seizures: ~7 months

• Sitting up without support: 3-4 years, currently can sit for 30 minutes with protection

• Walking: with support only

• Number of seizure drugs: Current 2 - tried 6

• Bayley’s: lowest possible score
INFORMATION BREAK!

WHAT QUESTIONS DO YOU HAVE SO FAR?
WELCOME TO NEW FRONTIER
WHAT THERAPEUTICS ARE CURRENTLY AVAILABLE FOR ANGELMAN SYNDROME?

- Epilepsy (AEDs, diet)
- Sleep (medicine, behavioral therapies)
- Reflux (medications such as Prevacid)
- Behavior (Behavioral Therapies, anxiety medications)
- Motor issues (Physical/Occupational Therapy)
- Communication (IPAD, education, Speech Therapy)
DEVELOPMENT OF THERAPEUTICS IN ANGELMAN SYNDROME

STRATEGIES:

1) Replace UBE3A in neurons
   • Viral delivery of UBE3A gene
   • Activate the silent paternal UBE3A gene using ASOs/LNAs/CRISPR

2) Correct neuronal function in the absence of UBE3A
   • Find drugs/compounds that improve neuronal function

*Please see Industry Updates Video for details!
https://www.angelman.org/events/asf-virtualpalooza/

AS = loss of UBE3A function in neurons
IS IT REASONABLE TO THINK TARGETED THERAPEUTICS ARE POSSIBLE? 3 EXAMPLES

1. Modifications in CamKII rescued the phenotypes of the AS mouse (van Woerden et al. 2007)

CamKII is predominantly expressed in the brain AFTER birth – suggesting AS does not cause defects in brain development.

2. Restoring Ube3a to the adult AS mouse brain rescued many phenotypes (Daly et al. 2011; Silva-Santos et al. 2015)

3. While a one study suggests rescue of some phenotypes may require early interventions, others (neural plasticity) could be rescued at any age. (Silva-Santos et al. 2015)
If you are a mouse with Angelman Syndrome, I have very good news for you! *

Mice aren’t humans. But there is reason to believe targeted therapeutics are possible, and we won’t know until we know. And to know, we need clinical trials.

* Shout out to the late Dr. Judah Folkman for this quip
PHASES OF TESTING

INTERVENTIONS/THERAPEUTICS

- DISCOVERY SCIENCE
  - Studies in the lab
  - Studies in animal models

- CLINICAL TRIALS
  - PHASE 0: first study in a patient to see how the body metabolizes the drug
  - PHASE I: study of a small number of patients to evaluate safety and dosing
  - PHASE II: study of more patients to assess drug’s effectiveness and further evaluate safety
  - PHASE III: study with the largest number of patients to confirm drug is effective and safe; assess side-effects and compare this drug to the current treatments
WHAT ARE OUTCOME MEASURES?

- Tests that accurately assess function at baseline before treatment.
- Can be used during and after treatment to assess change/efficacy.
VERY BASIC TRIAL DESIGN

Population ➔ Randomization ➔ Treatment group ➔ Outcome ➔ Follow-up ➔ Control group ➔ Outcome
WHY DO WE NEED PLACEBO CONTROLLED TRIALS?

AKA: I know myself and I know my child
WHY DO WE NEED PLACEBO CONTROLLED TRIALS?

PHARMACOLOGICAL DRUG TRIAL RESULTS

OUR TRIALS SHOW THAT THE NEW DRUG PERFORMS NO BETTER THAN PLACEBO

MAYBE WE SHOULD INVEST IN PLACEBOS

CHRIS MADDEN
THE FLIP SIDE OF THE PLACEBO

Nocebo:
A harmless thing that causes harm because you believe it's harmful.
SO WHAT DO WE DO?

IN GOD WE TRUST
ALL OTHERS MUST
BRING DATA
WHAT ARE SOME OF THE DIFFICULTIES?

YOUR SAMPLE SIZES ARE SMALL
YOUR STANDARD DEVIATIONS ARE HIGH
YOUR CONCLUSION MEANS NOTHING
AND YOU SHOULD FEEL BAD
What are some of the difficulties?

**Table 2.** 2005: Clinical Features of AS

<table>
<thead>
<tr>
<th>A. Consistent (100%)</th>
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<tbody>
<tr>
<td>• Developmental delay, functionally severe</td>
</tr>
<tr>
<td>• Movement or balance disorder, usually ataxia of gait, and/or tremulous movement of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions</td>
</tr>
<tr>
<td>• Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flap</td>
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<tr>
<td>• Speech impairment</td>
</tr>
<tr>
<td>B. Frequent (more than)</td>
</tr>
<tr>
<td>• Delayed, disproportionate Microcephaly is</td>
</tr>
<tr>
<td>• Seizures, onset usually before age 2 years.</td>
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<tr>
<td>• Abnormal EEG, with EEG changes preceding clinical features</td>
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<tr>
<td>C. Associated (20%–80%)</td>
</tr>
<tr>
<td>• Flat occiput</td>
</tr>
<tr>
<td>• Occipital groove</td>
</tr>
<tr>
<td>• Protruding tongue</td>
</tr>
<tr>
<td>• Tongue thrusting</td>
</tr>
<tr>
<td>• Feeding problem</td>
</tr>
<tr>
<td>• Prognathia</td>
</tr>
<tr>
<td>• Wide mouth, wide lips</td>
</tr>
<tr>
<td>• Frequent drooling</td>
</tr>
<tr>
<td>• Excessive chewing</td>
</tr>
<tr>
<td>• Strabismus</td>
</tr>
<tr>
<td>• Hypopigmented</td>
</tr>
<tr>
<td>• Hypermobility</td>
</tr>
<tr>
<td>• Hyperactive lower limbs</td>
</tr>
<tr>
<td>• Uplifted, flexed arm position especially during ambulation</td>
</tr>
<tr>
<td>• Wide-based gait with pronated or valgus-positioned ankles</td>
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<tr>
<td>• Increased sensitivity to heat</td>
</tr>
<tr>
<td>• Abnormal sleep-wake cycles and diminished need for sleep</td>
</tr>
<tr>
<td>• Attraction/Fascination with water; fascination with crinkly items such as certain papers and plastics</td>
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<tr>
<td>• Abnormal food related behaviors</td>
</tr>
<tr>
<td>• Obesity (in the older child)</td>
</tr>
<tr>
<td>• Scoliosis</td>
</tr>
<tr>
<td>• Constipation</td>
</tr>
</tbody>
</table>

**The Homogeneity of Diversity**
WHAT CAN THE AS COMMUNITY DO?

Get Informed about trials in general

www.fda.gov/forpatients/clinicaltrials

www.angelmanclinicaltrials.com
WHAT CAN THE AS COMMUNITY DO?

PARTICIPATE!

• Save medical records
• Visit AS Clinics
• Participate in Natural History Studies
• Participate in surveys
• Contribute to ongoing studies and trials

• ALWAYS CONSULT YOUR MEDICAL CARE PROVIDER ABOUT STUDIES!
• READ ALL THE PAPERWORK!
WHAT CAN THE AS COMMUNITY DO?

PARTICIPATE! - ClinicalTrials.gov

Signup for newsletters from parent support organizations

Follow companies on social media

Get involved in the Facebook Communities
WHAT CAN THE AS COMMUNITY DO?

Think community-wide

Don’t get in our own way……
THANK YOU!