

# ANGELMAN SYNDROME GENETICS 101

Rebecca D Burdine, PhD and  
mom to Sophie 14yo del+

## Current Disclosures:

ASF Board Member

ASF Scientific Advisory Committee

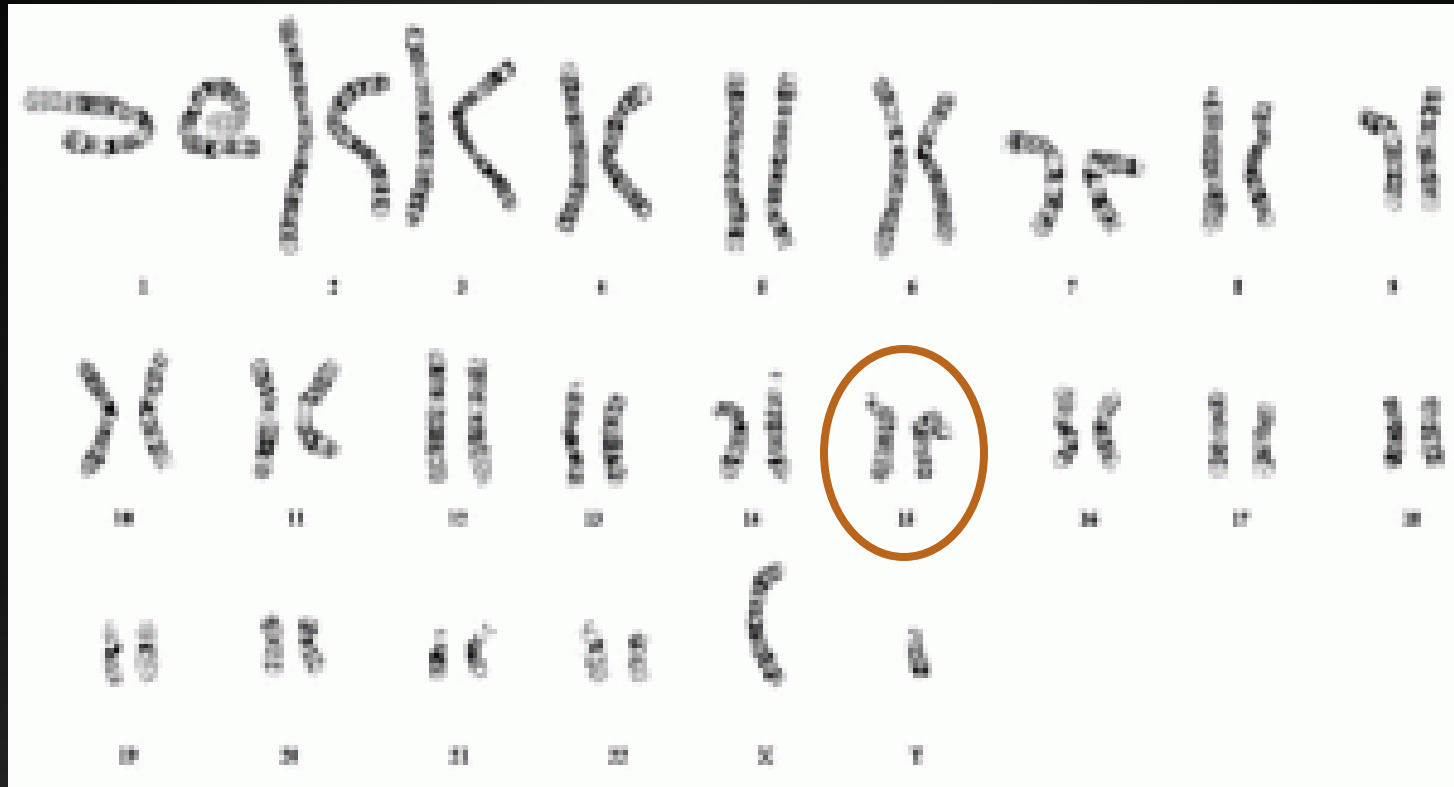
OVID Clinical Trial Steering committee (STARS/ELARA/NEPTUNE)



# TODAY'S PRESENTATION

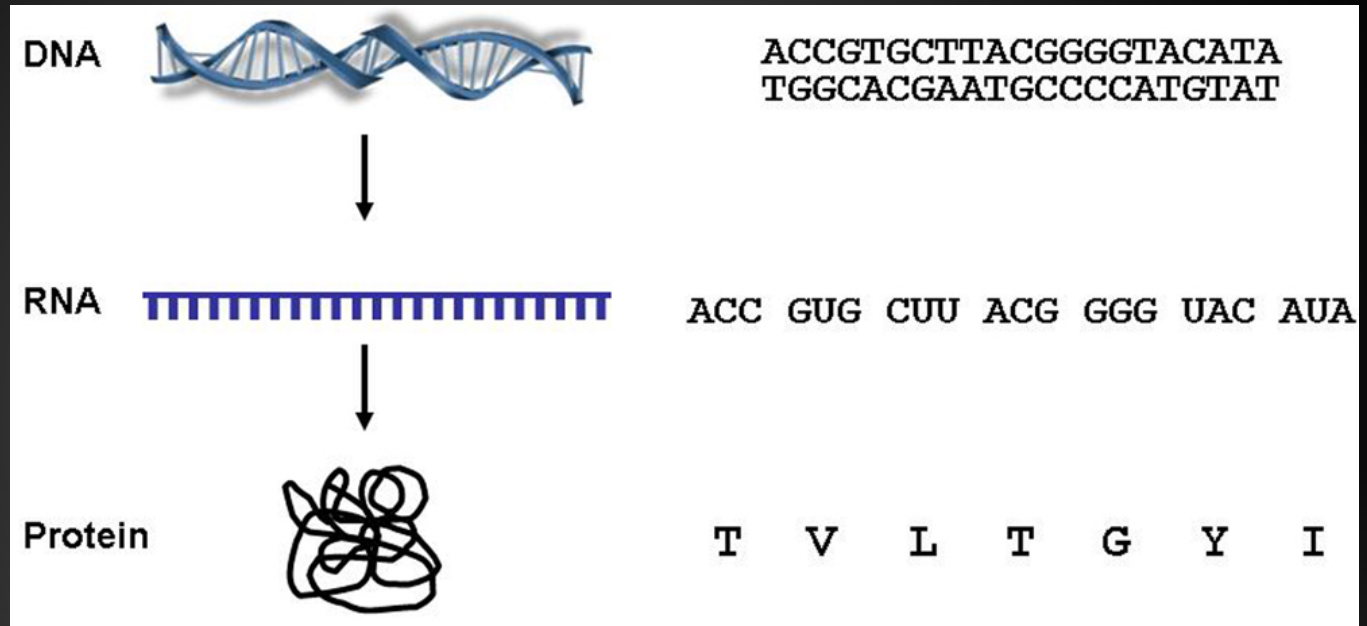
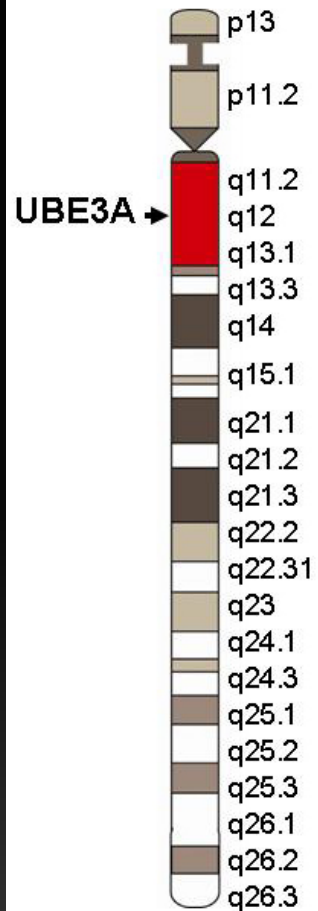
- Overview of genetics behind Angelman Syndrome
- Brief discussion of genotype/phenotypes in AS
- Where should I focus as a beginner?
- Why do we think better therapeutics are possible?
- What do I need to know about clinical trials in general?

# WE HAVE 23 PAIRS OF CHROMOSOMES IN OUR CELLS



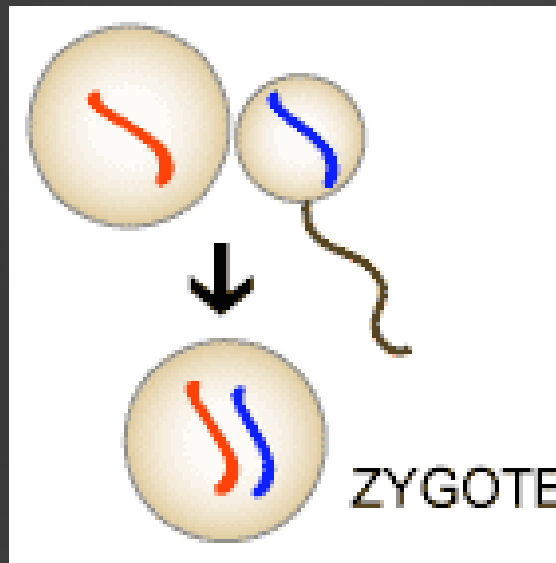
# GENES ENCODE INSTRUCTIONS FOR MAKING PROTEINS

## Chromosome 15



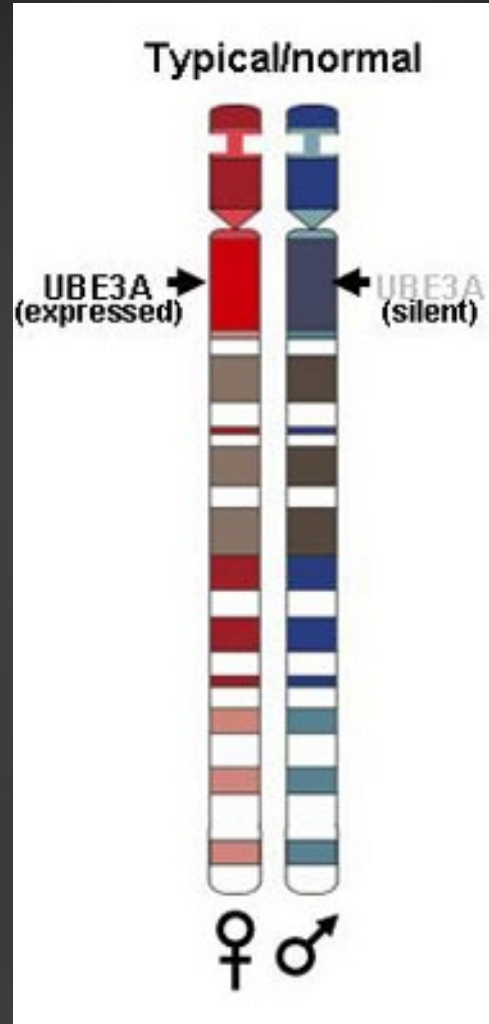
Proteins can be thought of as machines, signals, and structures

# WE RECEIVE ONE SET OF CHROMOSOMES FROM MOM AND ONE SET FROM DAD



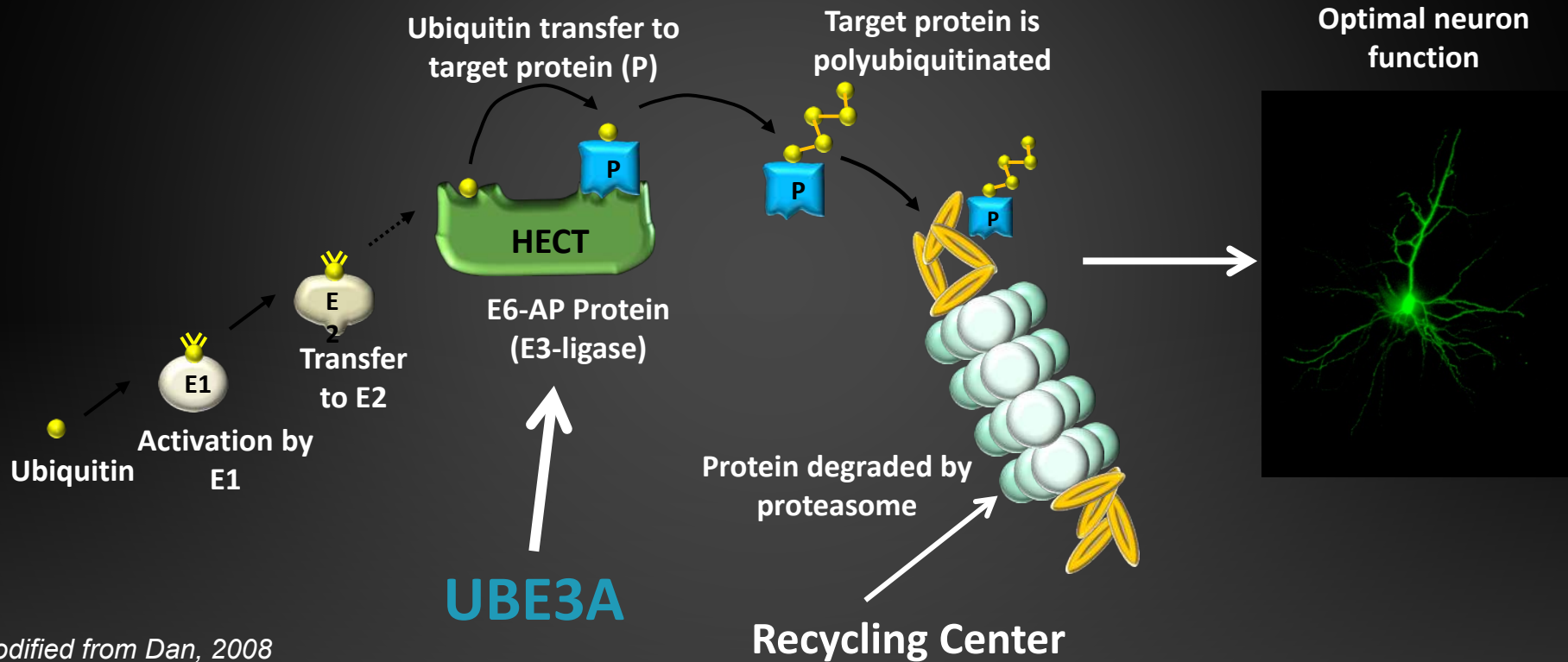
Cells in your body know which chromosome came from mom and which came from dad.

# ANGELMAN SYNDROME IS CAUSED BY A LOSS OF FUNCTION UBE3A IN THE BRAIN





# UBE3A MARKS PROTEINS FOR RECYCLING OR REMOVAL (DEGRADATION)

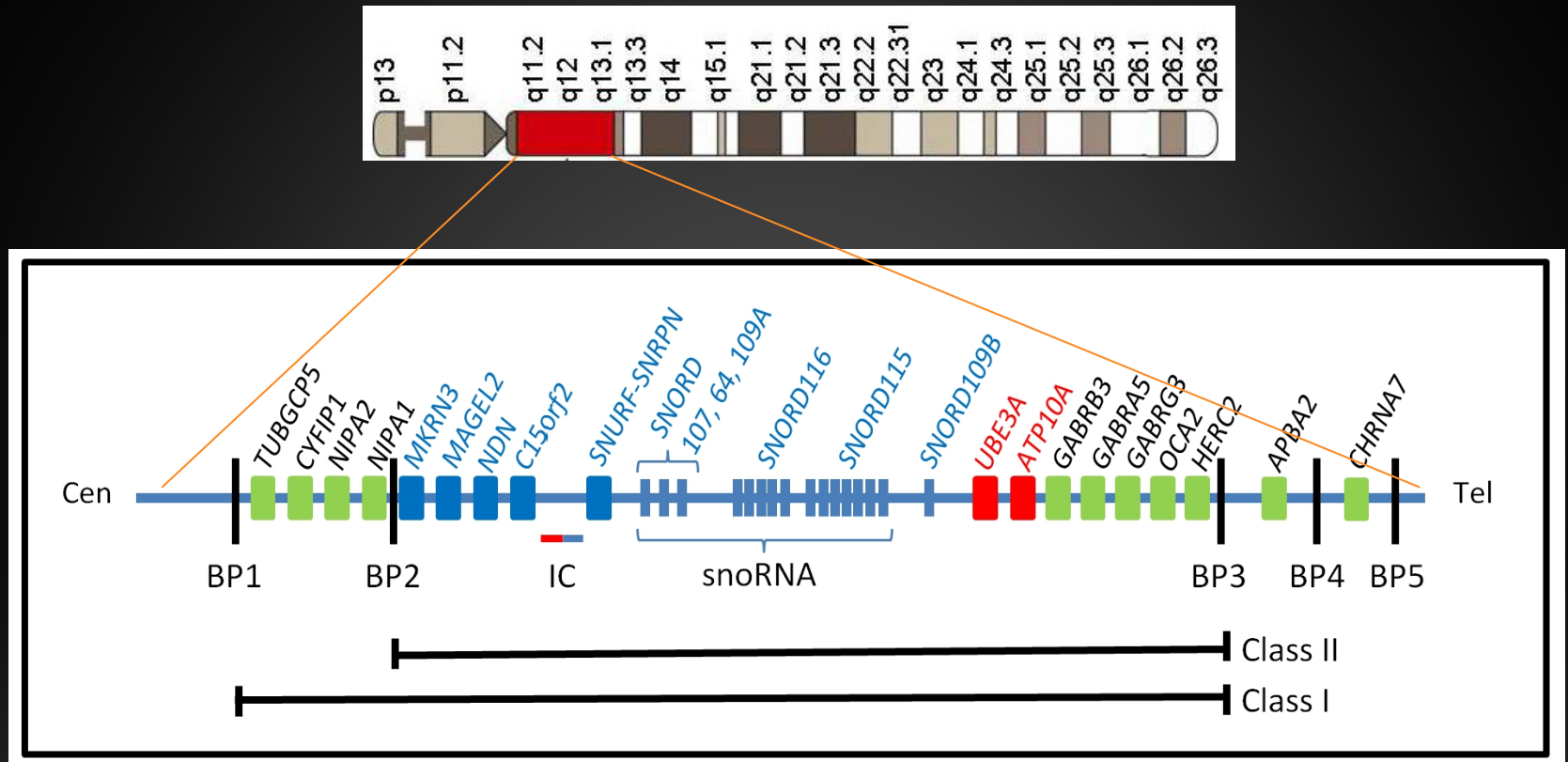


# KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME





# MICRODELETIONS IN AS

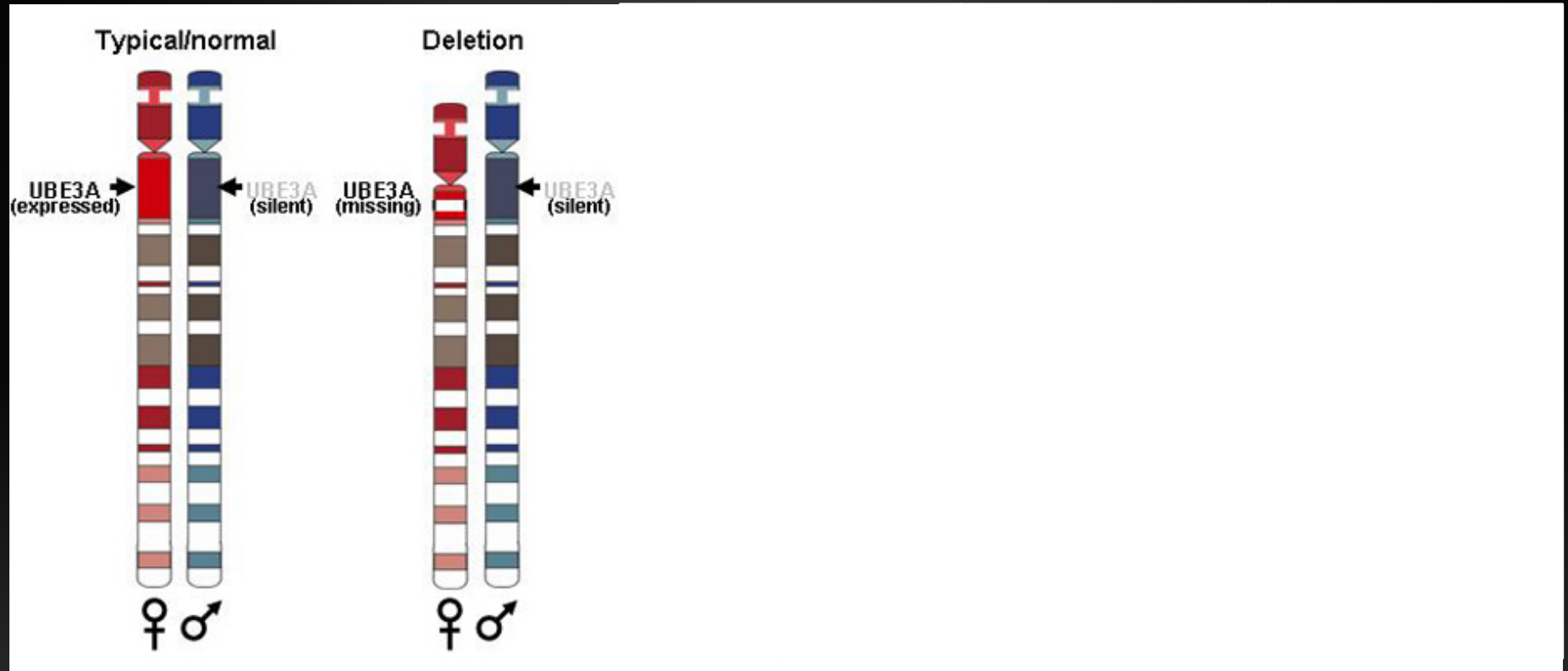


[http://www.imprinting-disorders.eu/?page\\_id=276](http://www.imprinting-disorders.eu/?page_id=276)

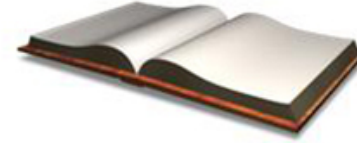
Class I deletions are ~6MB

Human Genome is 3235 MB with around 20,000 genes

# KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME



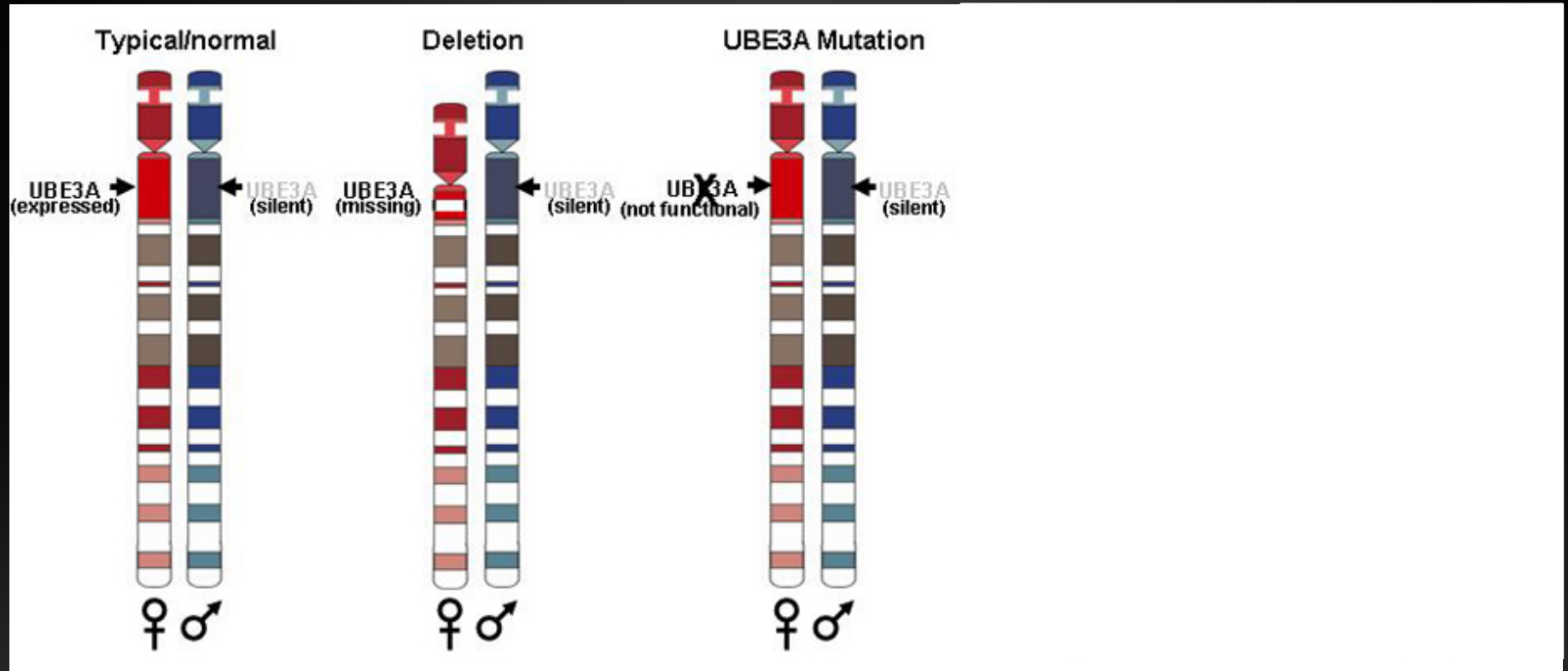
# GENETICS 201 - MUTATIONS CHANGE GENE INFORMATION AND THE RESULTING PROTEIN PRODUCED



ACC GUG CUU ACG GGG UAC AUA  
T V L T G Y I

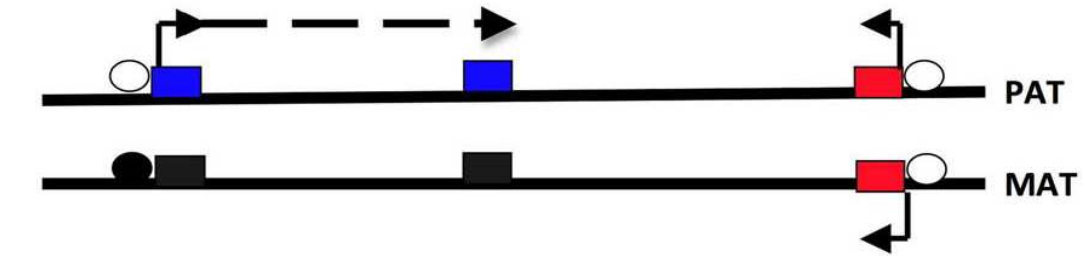
The UBE3A gene encodes a protein called a ubiquitin ligase.

# KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME

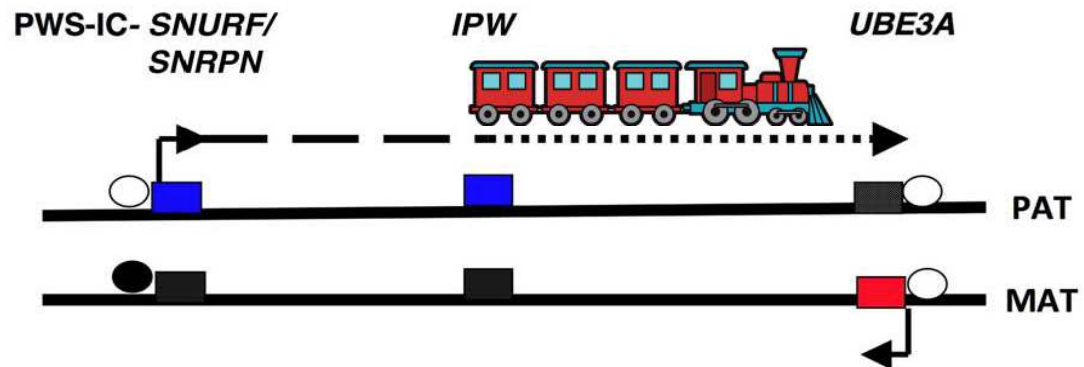


# YOUR CELLS KNOW WHICH CHROMOSOME CAME FROM MOM AND WHICH CAME FROM DAD

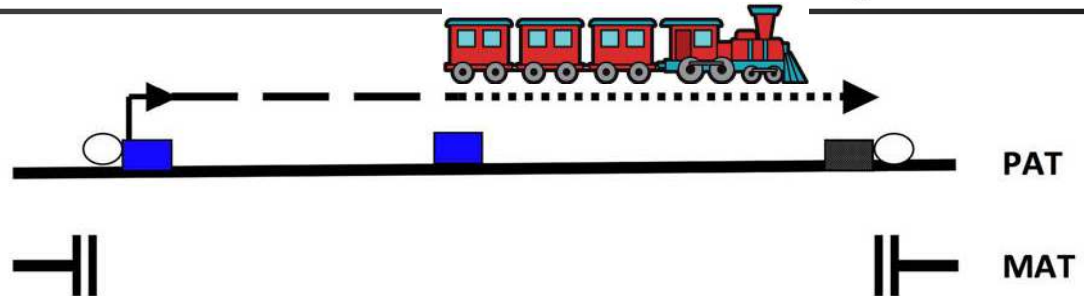
Non-neuron



Neuron



Angelman  
Neuron  
(15q11-q13  
deletion)





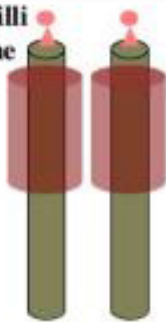
# FIRST IMPLICATIONS OF GENOMIC IMPRINTING IN DISEASE

NATURE • VOL 342 • 16 NOVEMBER 1989

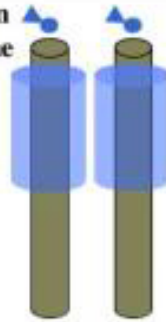
## Genetic imprinting suggested by maternal heterodisomy in non-deletion Prader-Willi syndrome

Robert D. Nicholls<sup>\*†‡</sup>, Joan H. M. Knoll<sup>†</sup>,  
Merlin G. Butler<sup>§</sup>, Susan Karam<sup>||</sup> & Marc Lalonde<sup>\*†¶</sup>

Prader-Willi Syndrome



Angelman Syndrome



Patient images: Medical Genetics, 2nd ed., Jorde L.B. et al. ©2000

UPD = uniparental disomy



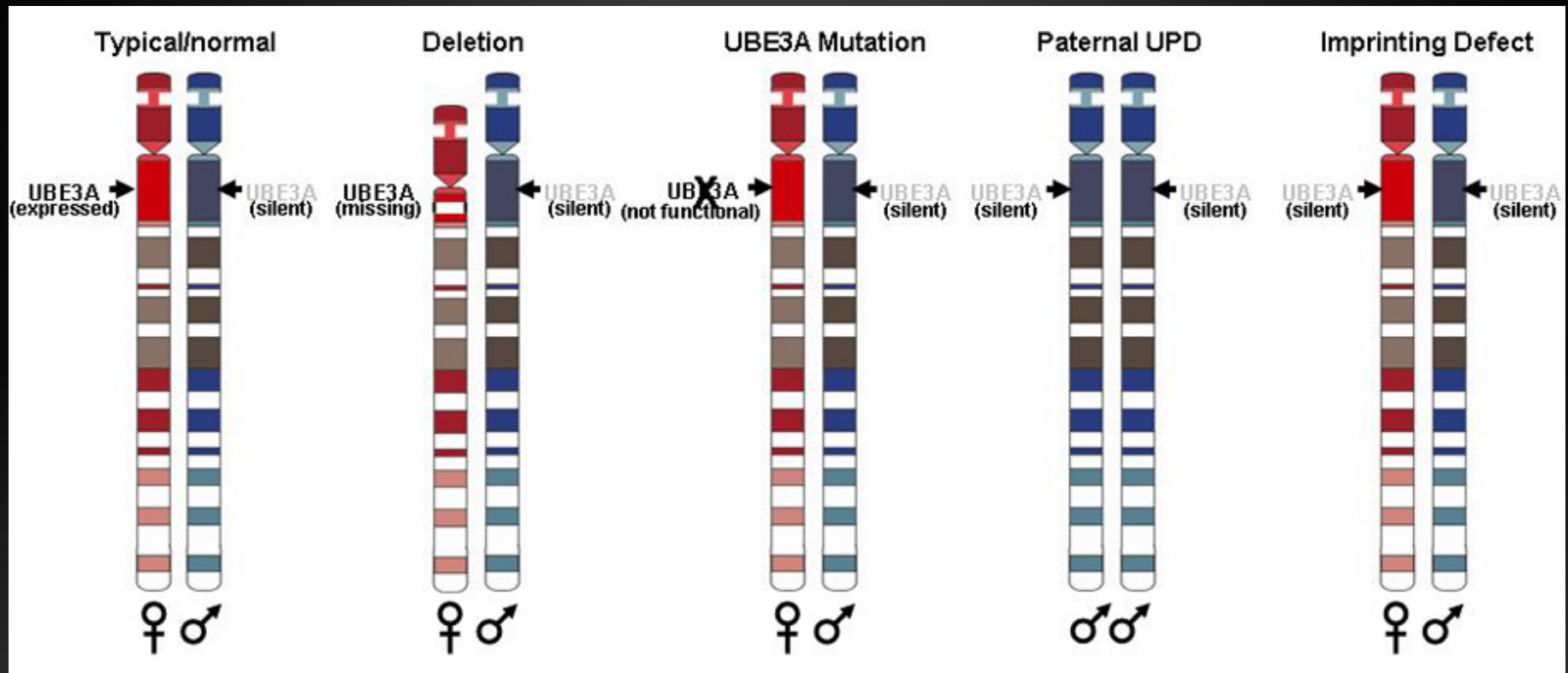
# KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME

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

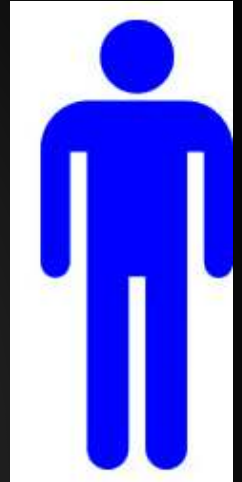
Grandmom



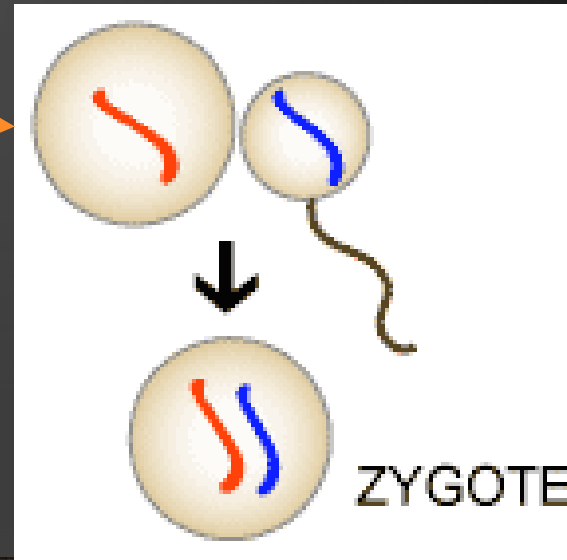
Mom



Dad



The egg that developed into your child was created when you/mom was still in utero



# WORDS MATTER

Don't take it personally – but educate....

Strongly affected by AS  
Less affected by AS

vs.

Severe, low functioning  
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**

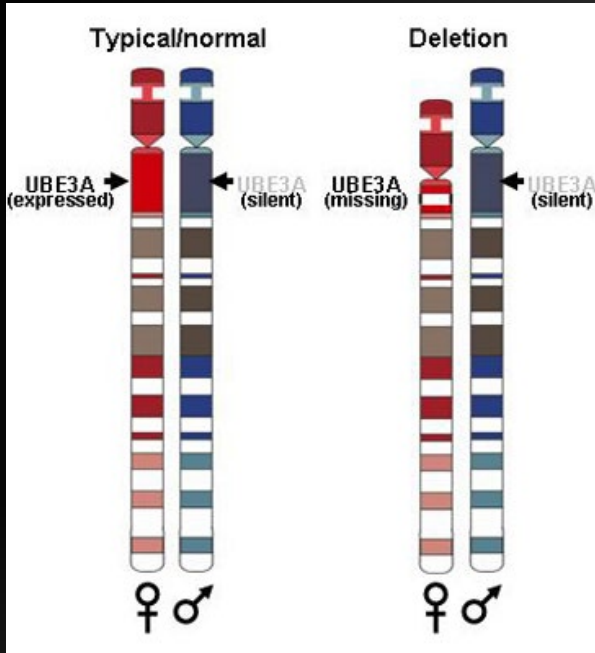


# WHAT THERAPEUTICS ARE CURRENTLY AVAILABLE FOR ANGELMAN SYNDROME?

- ❖ 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



**AS = loss of **UBE3A** function in neurons**

## 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/>

# 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)

## BOTTOM LINE

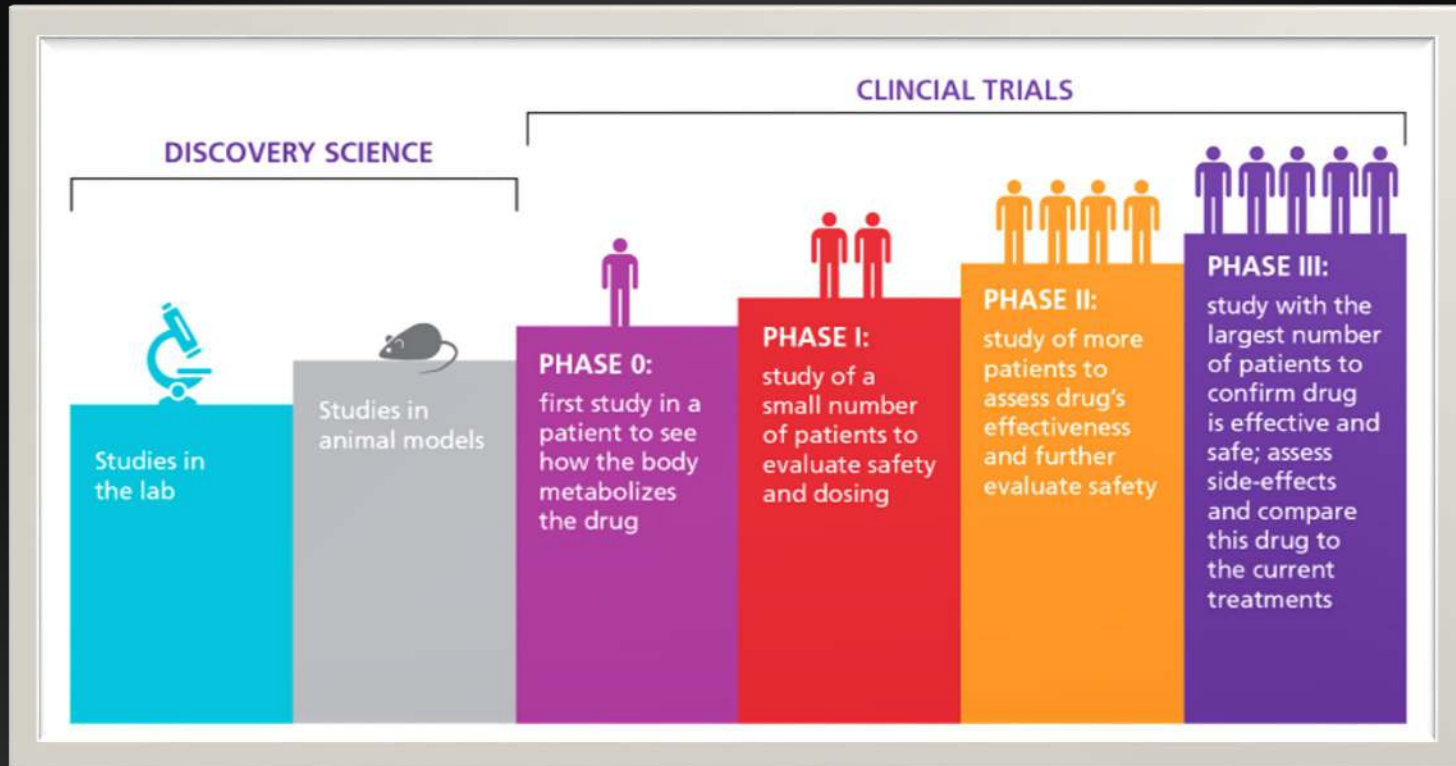


If you are a mouse with Angelman Syndrome,  
I have very good news for you! \*

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



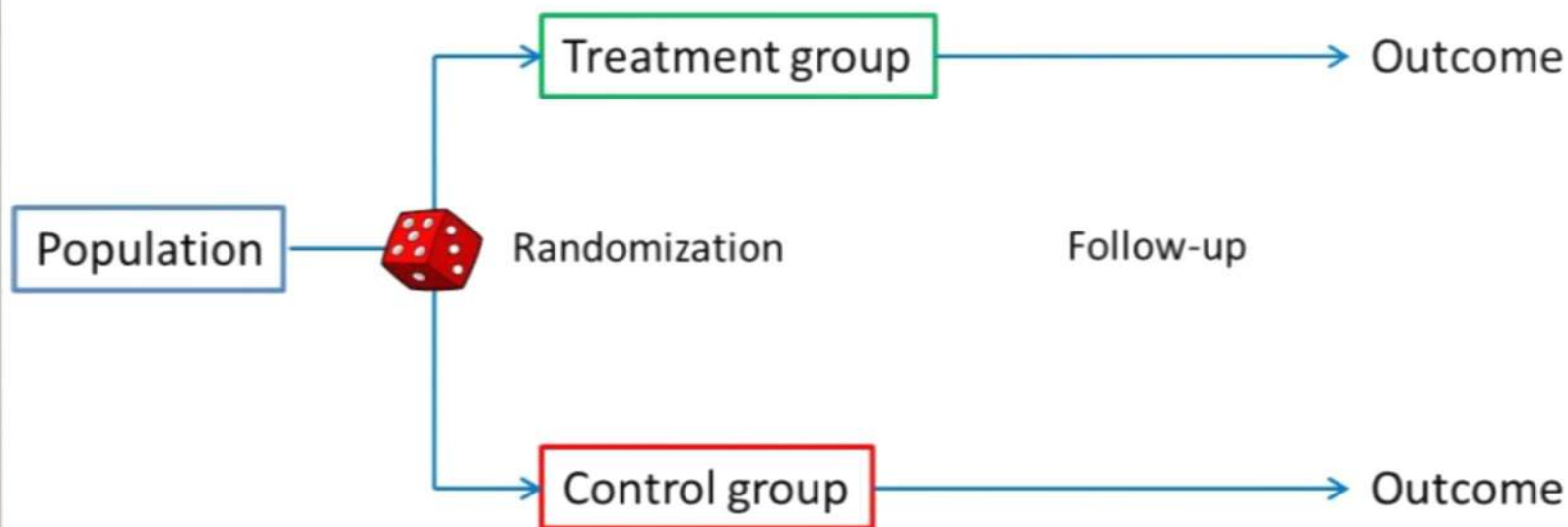
# WHAT ARE OUTCOME MEASURES?



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



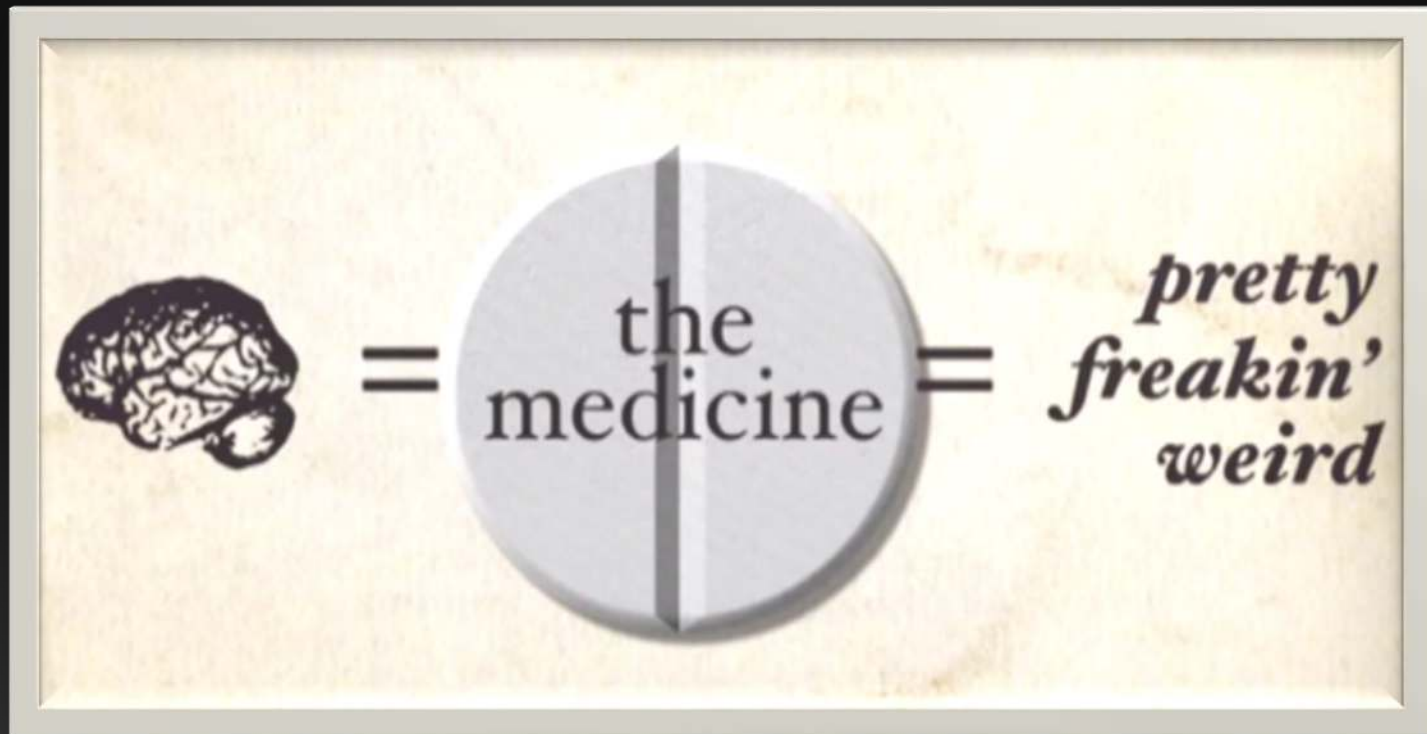
# VERY BASIC TRIAL DESIGN





# WHY DO WE NEED PLACEBO CONTROLLED TRIALS?

AKA: I know myself and I know my child



# WHY DO WE NEED PLACEBO CONTROLLED TRIALS?



# THE FLIP SIDE OF THE PLACEBO



## **Nocebo:**

**A harmless thing  
that causes harm  
because you believe it's harmful**

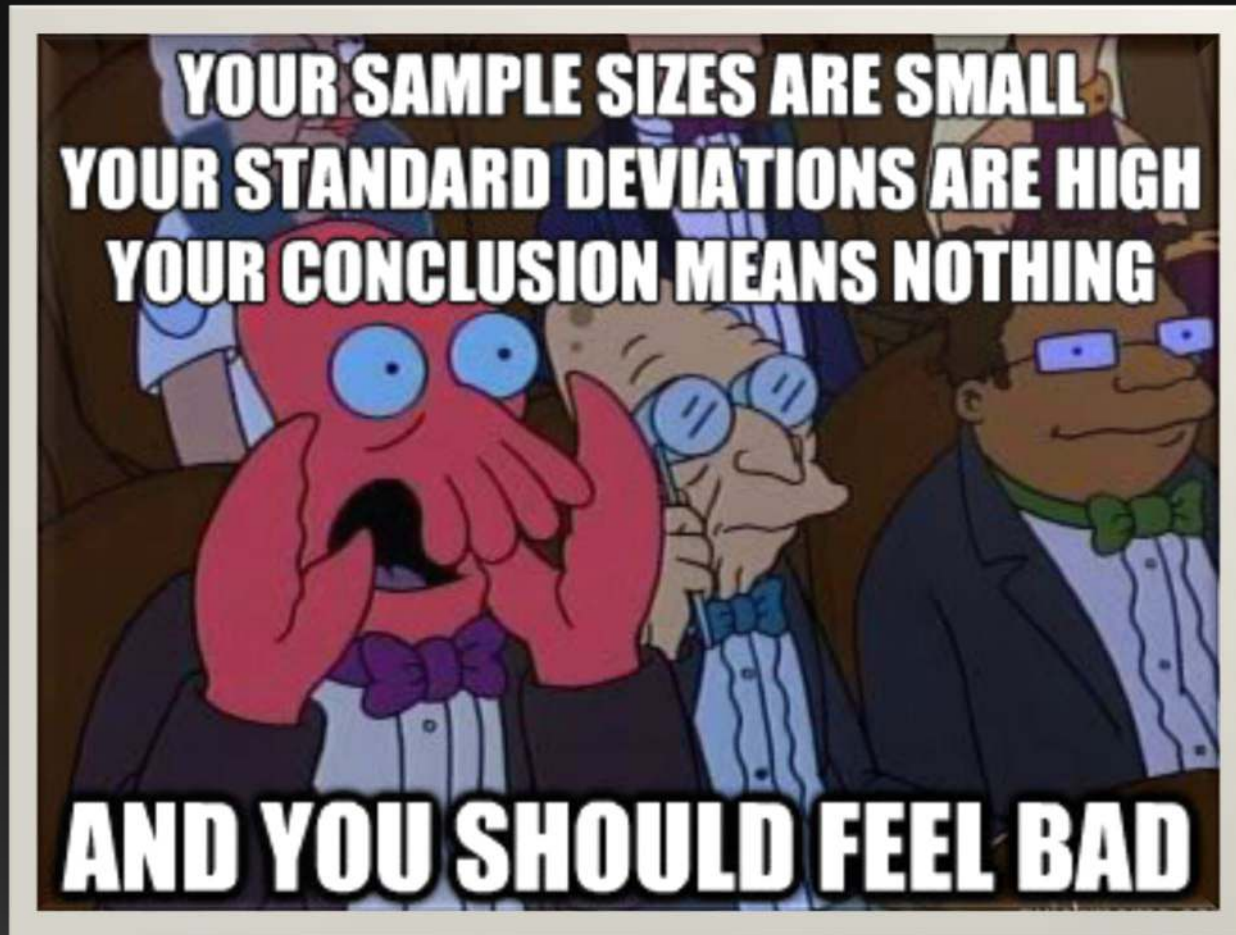
SO WHAT DO WE DO?



IN GOD  
WE TRUST  
ALL OTHERS MUST  
BRING  
DATA



# WHAT ARE SOME OF THE DIFFICULTIES?





# WHAT ARE SOME OF THE DIFFICULTIES?

TABLE II. 2005: Clinical Features of AS

## A. Consistent (100%)

- Developmental delay, functionally severe
- 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
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping
- Speech impairment

## B. Frequent (more than 75%)

- Delayed, disprop
- Microcephaly is r
- Seizures, onset u
- Abnormal EEG, v
- precede clinical f

## C. Associated (20%–80%)

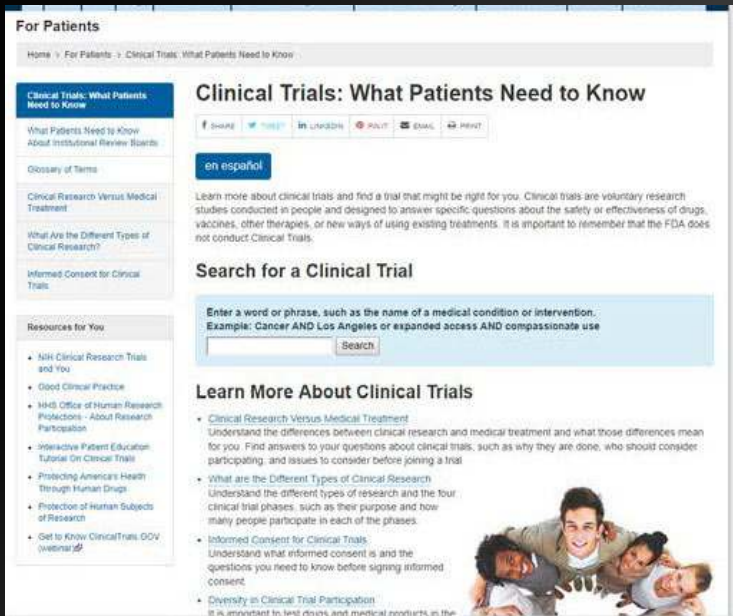
- Flat occiput
- Occipital groove
- Protruding tongue
- Tongue thrusting
- Feeding problem
- Prognathia
- Wide mouth, wide
- Frequent drooling
- Excessive chewing
- Strabismus
- Hypopigmented
- Hyperactive lower
- Uplifted, flexed arm position especially during ambulation
- Wide-based gait with pronated or valgus-positioned ankles
- Increased sensitivity to heat
- Abnormal sleep-wake cycles and diminished need for sleep
- Attraction to/fascination with water; fascination with crinkly items such as certain papers and plastics
- Abnormal food related behaviors
- Obesity (in the older child)
- Scoliosis
- Constipation

## THE HOMOGENEITY OF DIVERSITY



# WHAT CAN THE AS COMMUNITY DO?

## Get Informed about trials in general



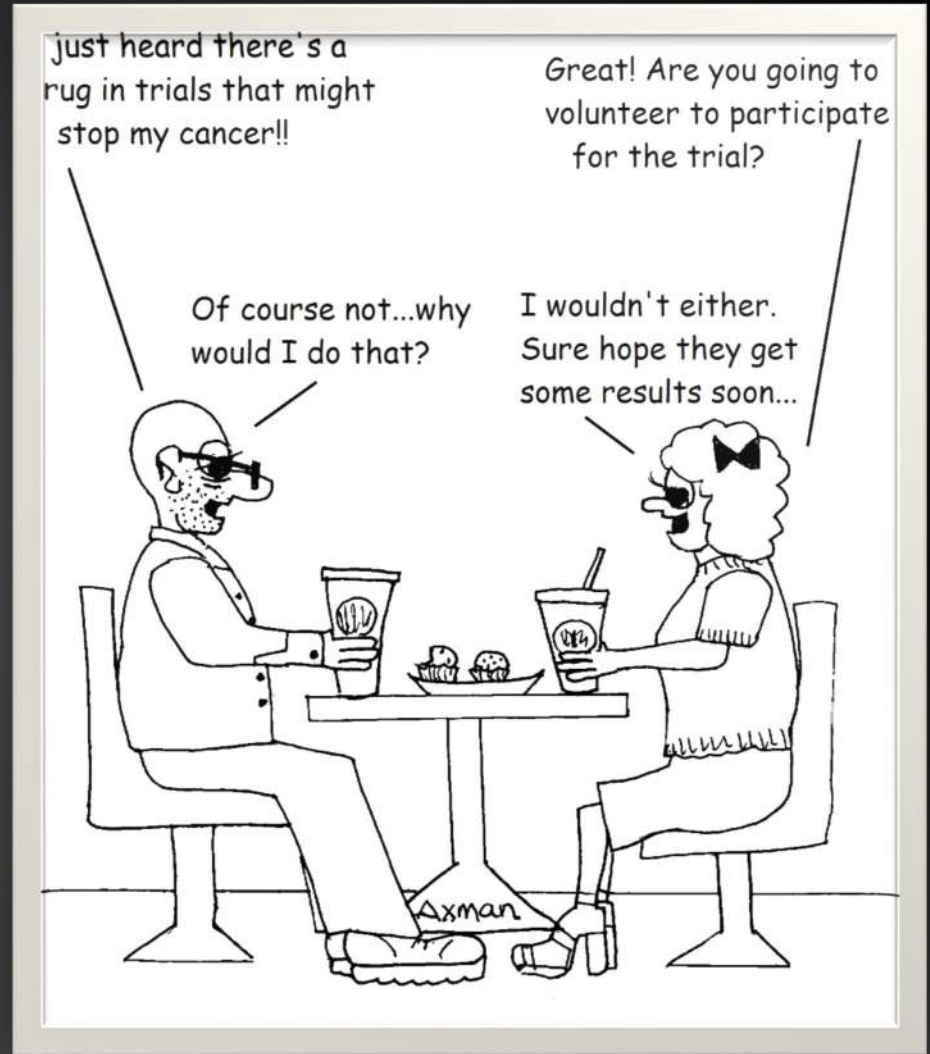
[www.fda.gov/forpatients/clinicaltrials](http://www.fda.gov/forpatients/clinicaltrials)

[www.angelmanclinicaltrials.com](http://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

The screenshot shows the ClinicalTrials.gov website interface. At the top, there's a navigation bar with links like 'Find Studies', 'About Studies', 'Submit Studies', 'Resources', and 'About Site'. Below this, a search box is visible with the following fields: 'Condition / Disease' (Angelman Syndrome), 'Other Terms', and 'Country'. There are buttons for 'Search' and 'Advanced Search'. Below the search box, it says '8 Studies found for: Recruiting Studies | Angelman Syndrome'. On the left side, there's a 'Filters' section with a 'Status' filter set to 'Recruiting'. The main content area displays a table of studies. The table has columns for 'Row', 'Sponsor', 'Status', 'Study Title', 'Conditions', and 'Interventions'. The table lists 8 studies, all with a status of 'Recruiting'. The first study is 'A Study in Adults With Angelman Syndrome' by 'Angelman Syndrome'. The second study is 'Single-Dose Pharmacokinetics (PK) Study' by 'Angelman Syndrome, Fragile X Syndrome'. The third study is 'Single-Dose Pharmacokinetics and Neurocognitive Response (SNDP)' by '22q11 Deletion Syndrome, DiGeorge Syndrome, Treacy 21, Treacy 18, Treacy 13, Monosomy X, Sex Chromosome Abnormalities, Cri-du-Chat Syndrome, Angelman Syndrome, Prader-Willi Syndrome, 16p11 Deletion Syndrome'. The fourth study is 'Development of Neurocognitive Phenotypic Test for Microdeletion and Other Deletions' by 'Microdeletion Syndromes: Treacy 21, Treacy 18, Treacy 13, Sex Chromosome Abnormalities'. The fifth study is 'Development of Neurocognitive Phenotypic Test for Microdeletion and Other Deletions' by 'Treacy 21, Treacy 18, Treacy 13, Sex Chromosome Abnormalities, Microdeletion Syndromes'. Below the table, it says 'Your search: (Recruiting Studies | Angelman Syndrome) found only a few studies'.

Row	Sponsor	Status	Study Title	Conditions	Interventions
1	Recruiting	A Study in Adults With Angelman Syndrome	Angelman Syndrome		Drug: OX101 Regimen 1; Drug: OX101 Regimen 2; Other: Placebo
2	Recruiting	Single-Dose Pharmacokinetics (PK) Study	Angelman Syndrome, Fragile X Syndrome		Drug: OX101
3	Recruiting	Single-Dose Pharmacokinetics and Neurocognitive Response (SNDP)	22q11 Deletion Syndrome, DiGeorge Syndrome, Treacy 21, Treacy 18, Treacy 13, Monosomy X, Sex Chromosome Abnormalities, Cri-du-Chat Syndrome, Angelman Syndrome, Prader-Willi Syndrome, 16p11 Deletion Syndrome		
4	Recruiting	Development of Neurocognitive Phenotypic Test for Microdeletion and Other Deletions	Microdeletion Syndromes: Treacy 21, Treacy 18, Treacy 13, Sex Chromosome Abnormalities		
5	Recruiting	Development of Neurocognitive Phenotypic Test for Microdeletion and Other Deletions	Treacy 21, Treacy 18, Treacy 13, Sex Chromosome Abnormalities, Microdeletion Syndromes		

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!