ANGELMAN SYNDROME GENETICS 101

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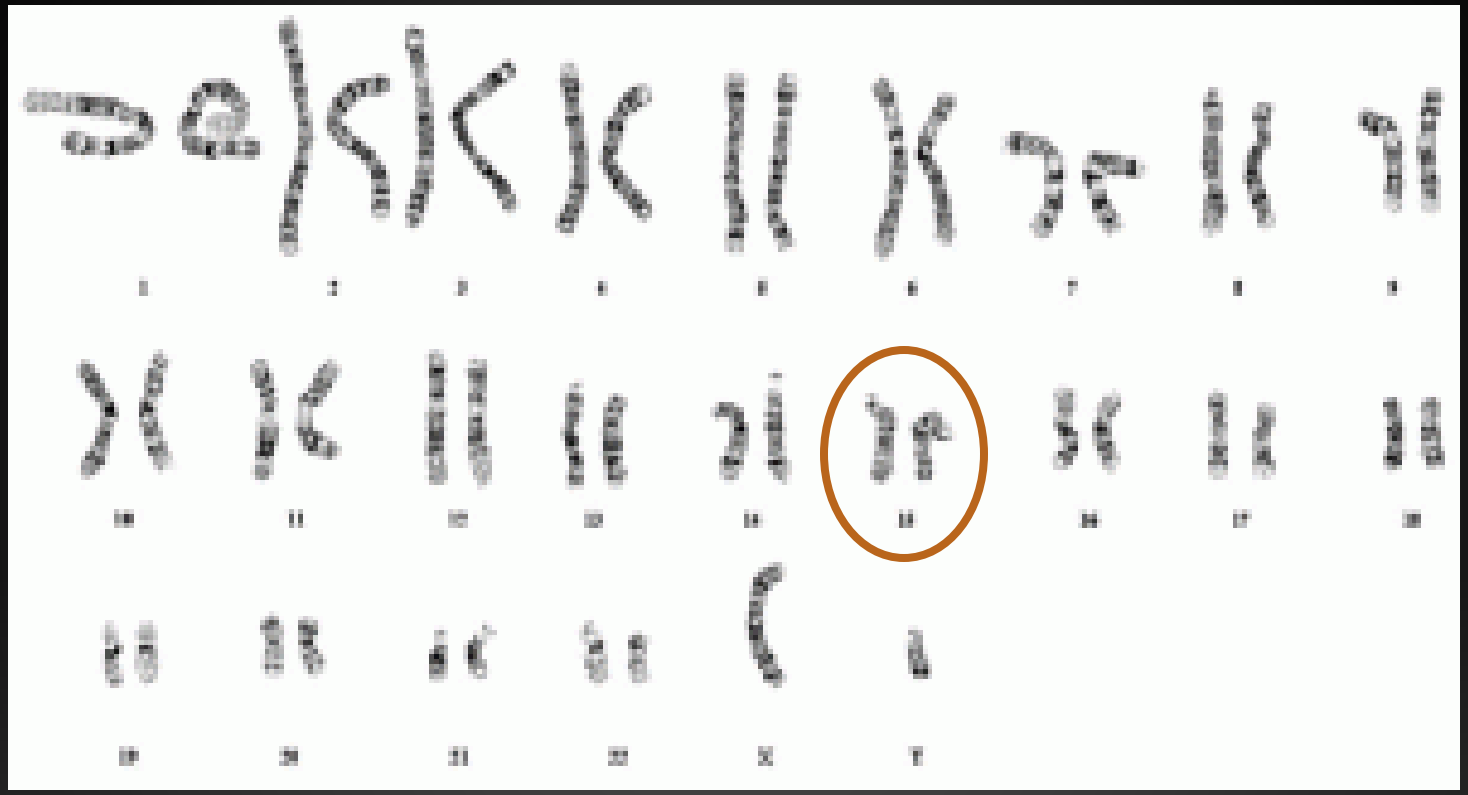
mom to Sophie 14yo del+

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

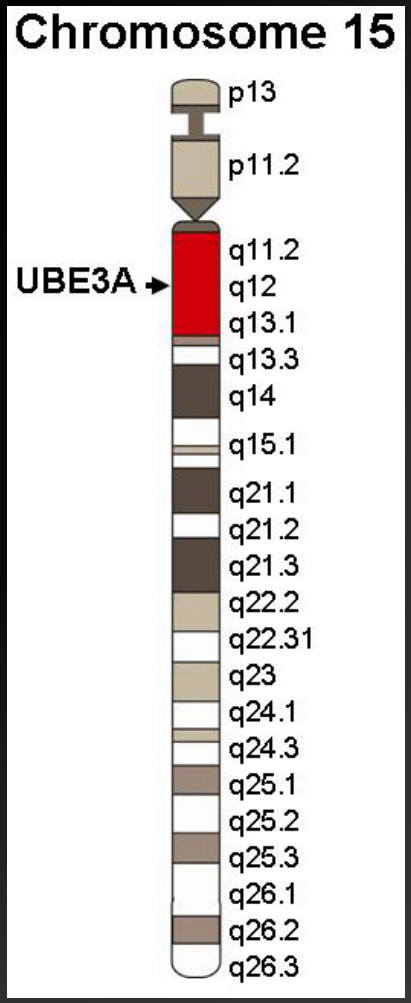
TODAY'S PRESENTATION

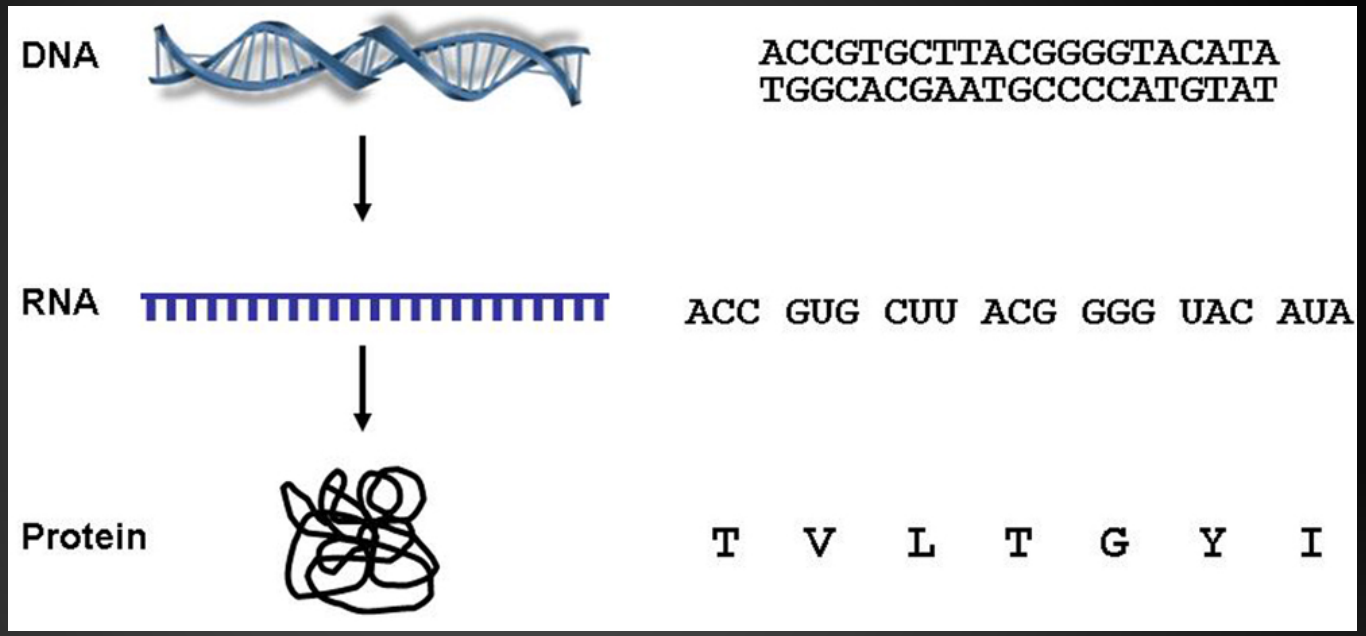
- Overview of genetics behind Angelman Syndrome
- Brief discussion of genotype/phenotypes in AS
- Where should I focus as a beginner?
- Why do we think better therapeutics are possible?
- What do I need to know about clinical trials in general?

WE HAVE 23 PAIRS OF CHROMOSOMES IN OUR CELLS



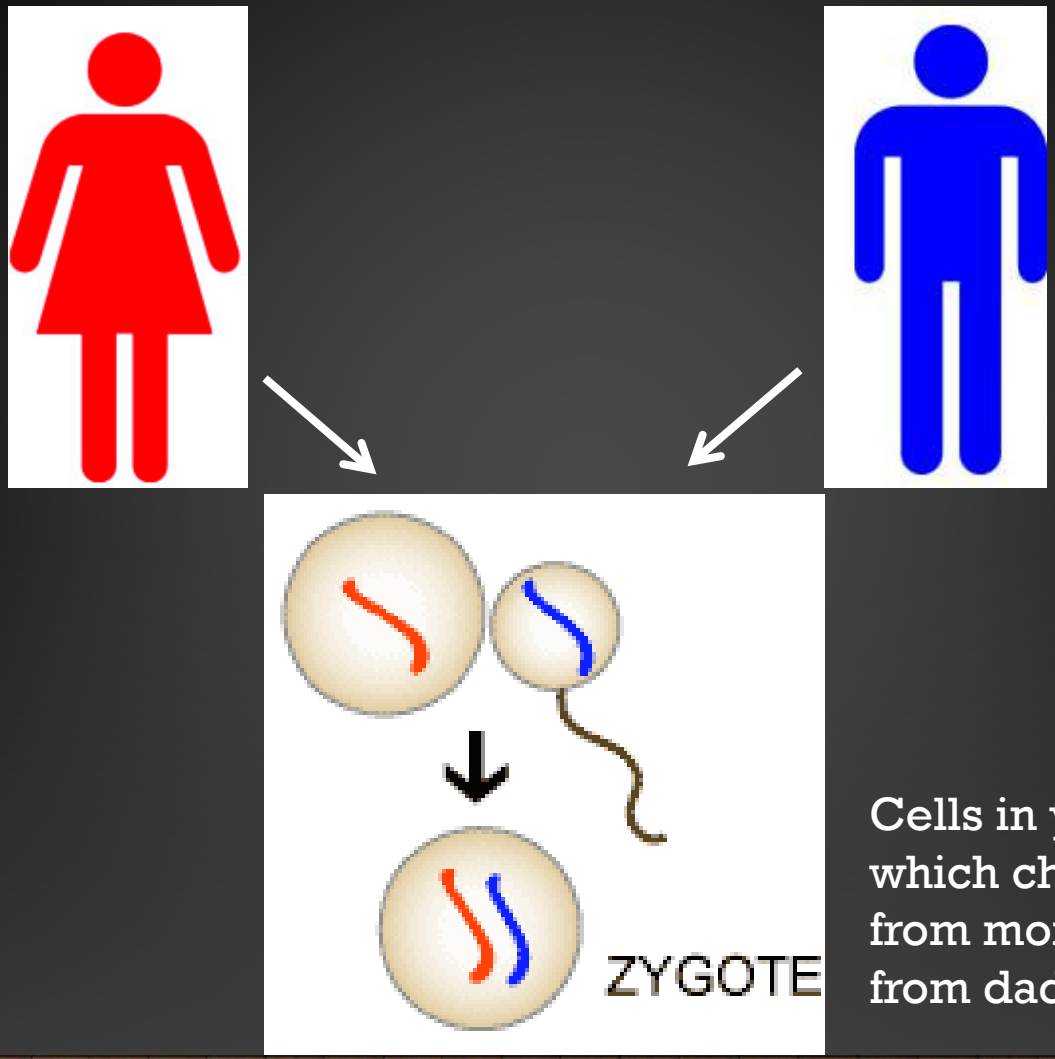
GENES ENCODE INSTRUCTIONS FOR MAKING PROTEINS





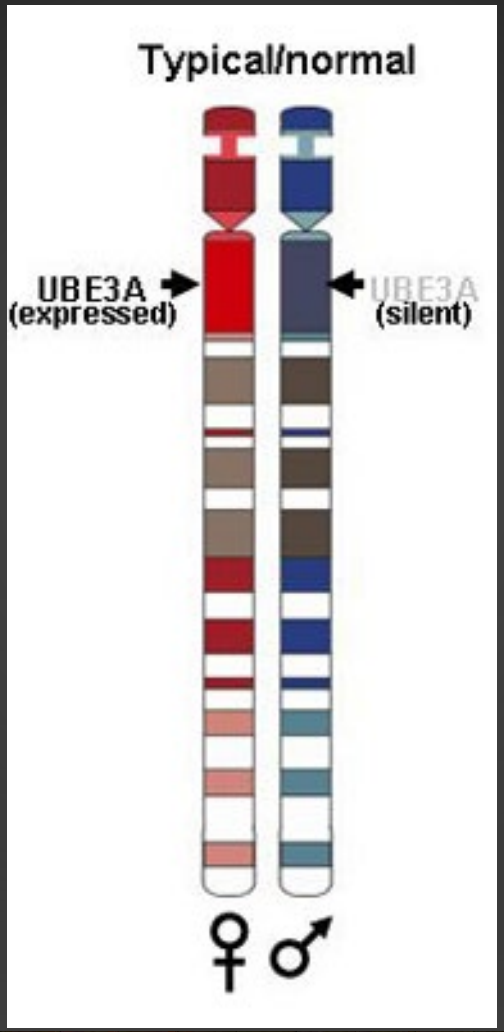
Proteins can be thought of as machines, signals, and structures

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

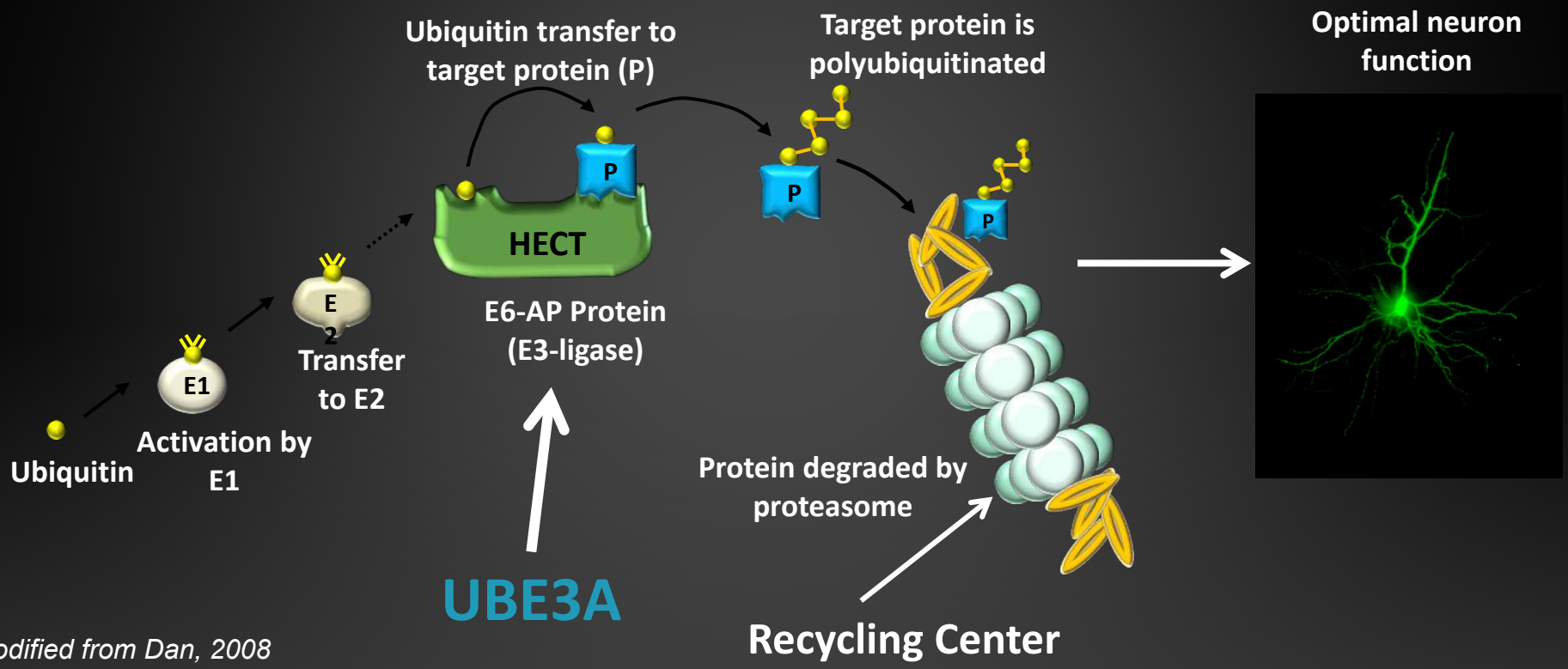


Cells in your body know which chromosome came from mom and which came from dad.

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



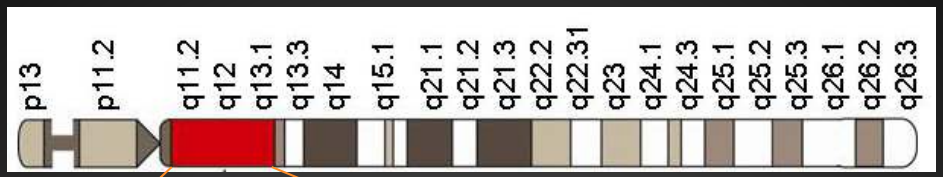
UBE3A MARKS PROTEINS FOR RECYCLING OR REMOVAL (DEGRADATION)

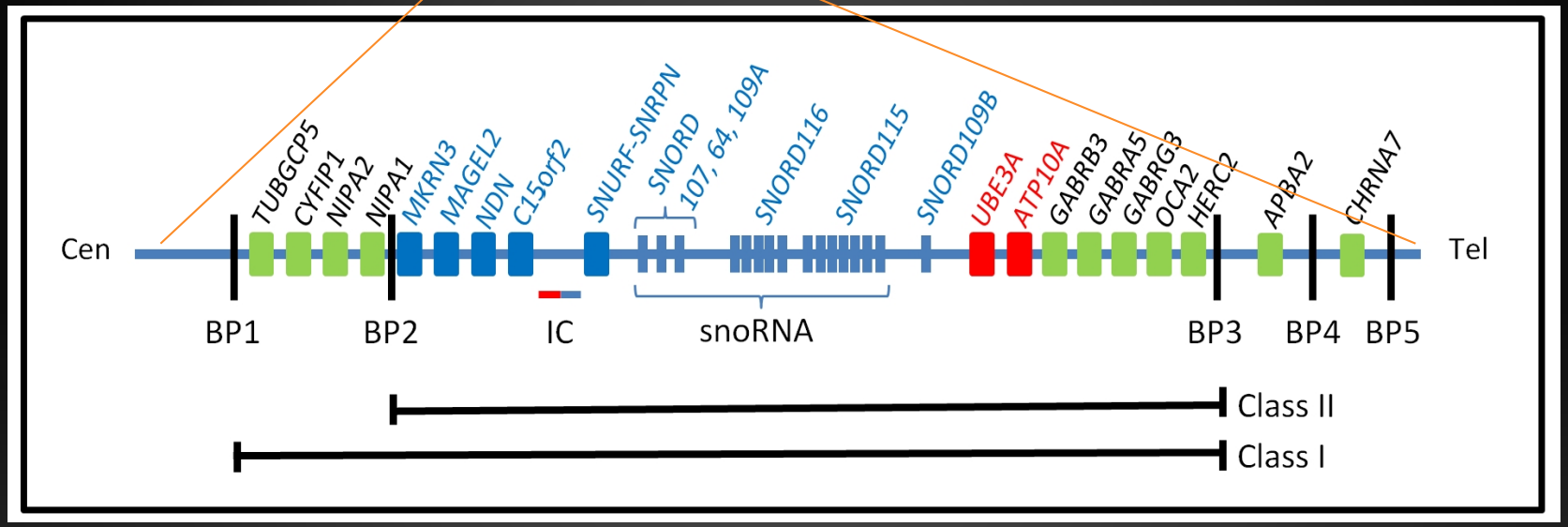


modified from Dan, 2008

KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME

MICRODELETIONS IN AS



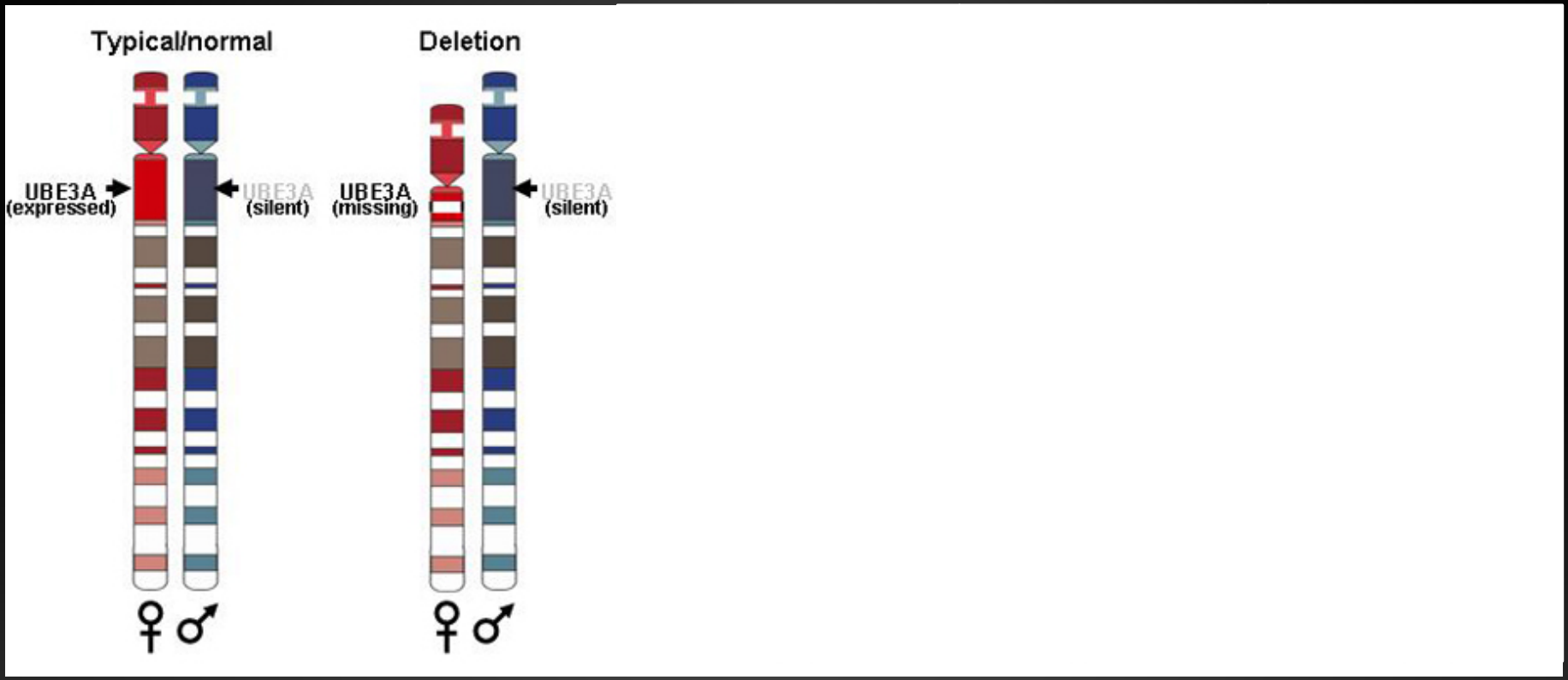


http://www.imprinting-disorders.eu/?page_id=276

Class I deletions are ~6MB

Human Genome is 3235 MB with around 20,000 genes

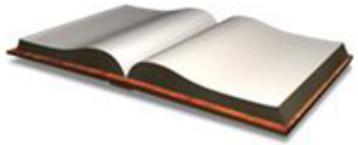
KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME



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

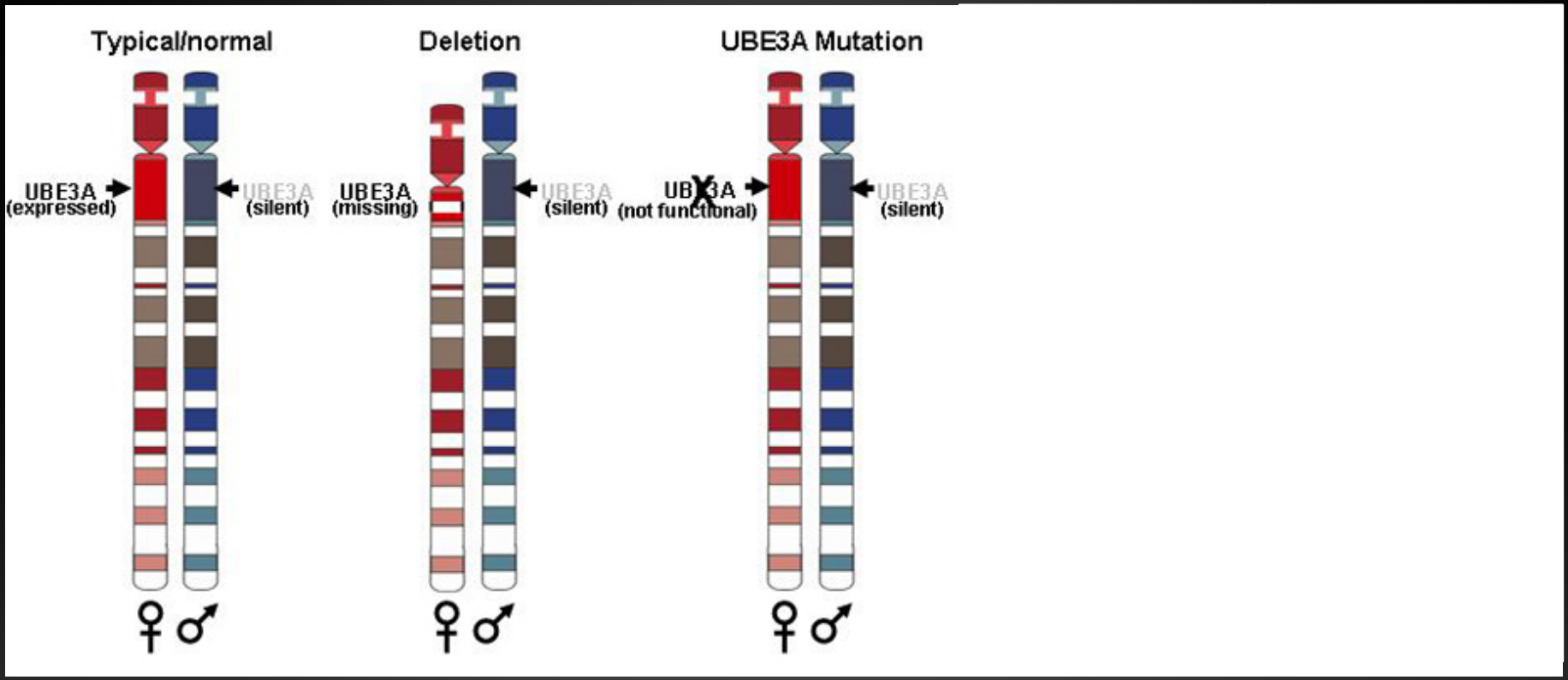
ACC GUG CUU ACG GGG UAC AUA

T V L T G Y I

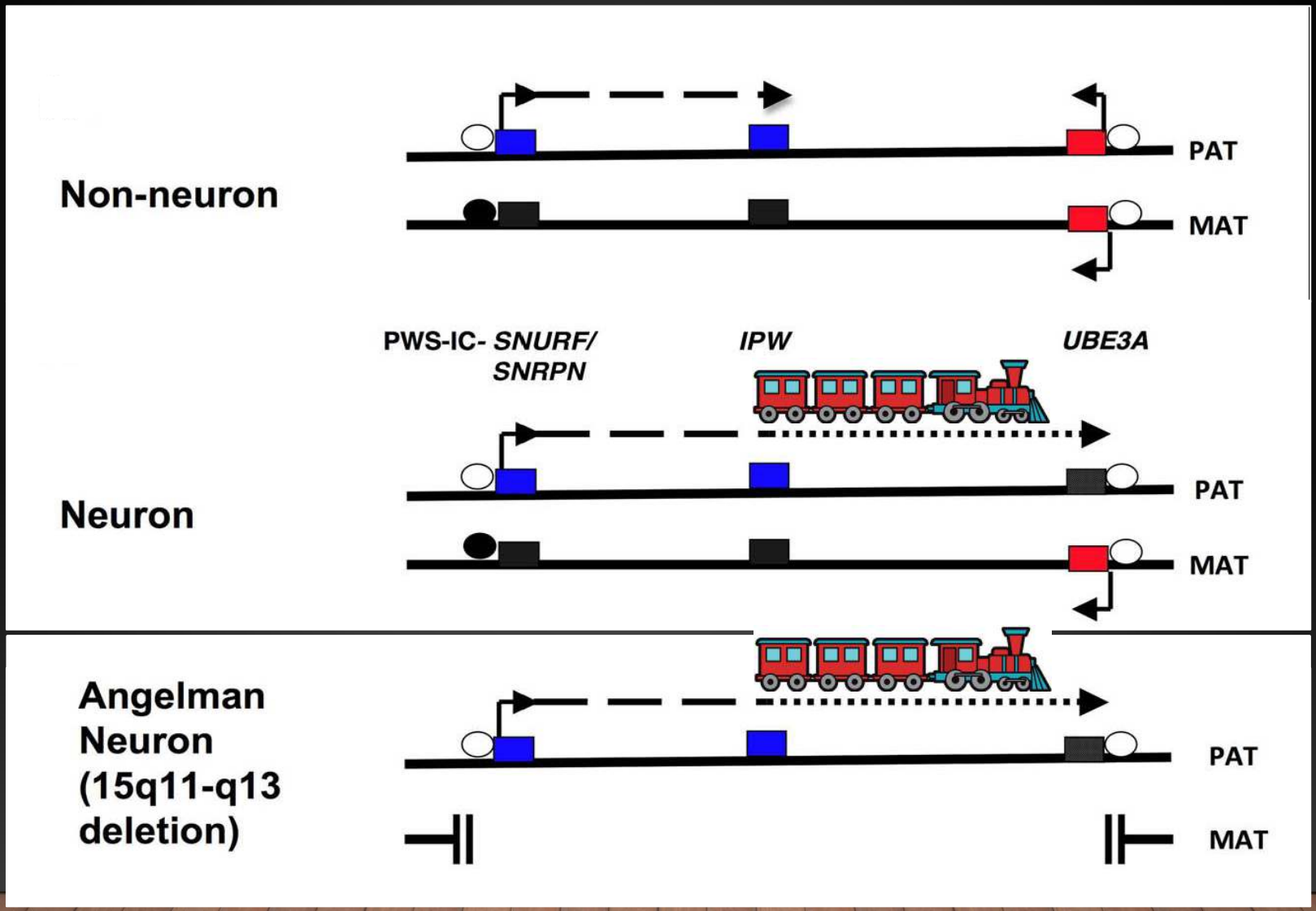


The UBE3A gene encodes a protein called a ubiquitin ligase.

KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME



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



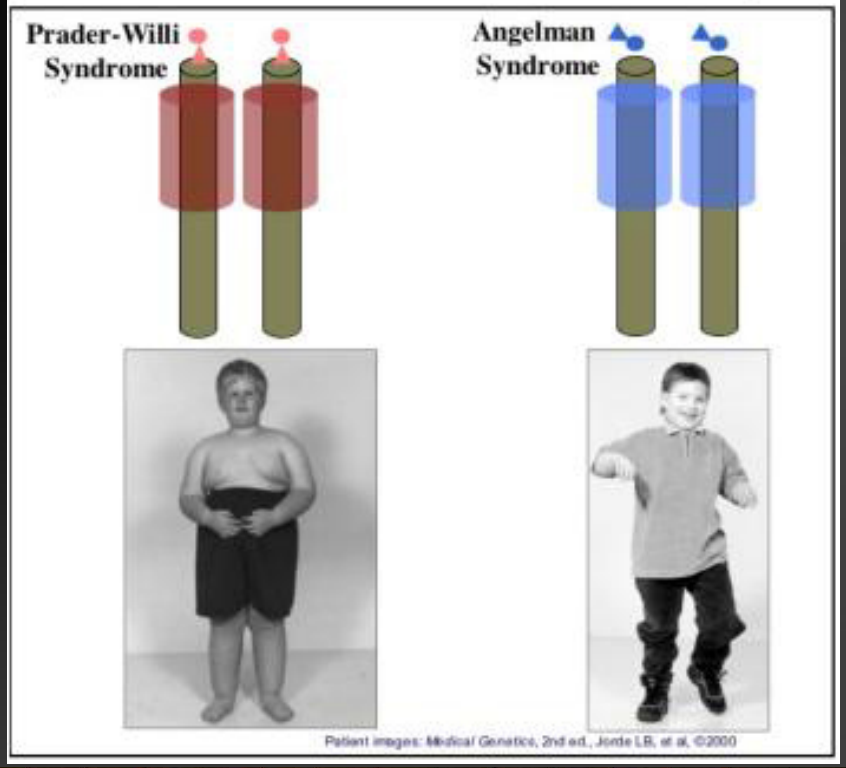
Chamberlain and Lalande J. Neurosci 2010

FIRST IMPLICATIONS OF GENOMIC IMPRINTING IN DISEASE

NATURE · VOL 342 · 16 NOVEMBER 1989

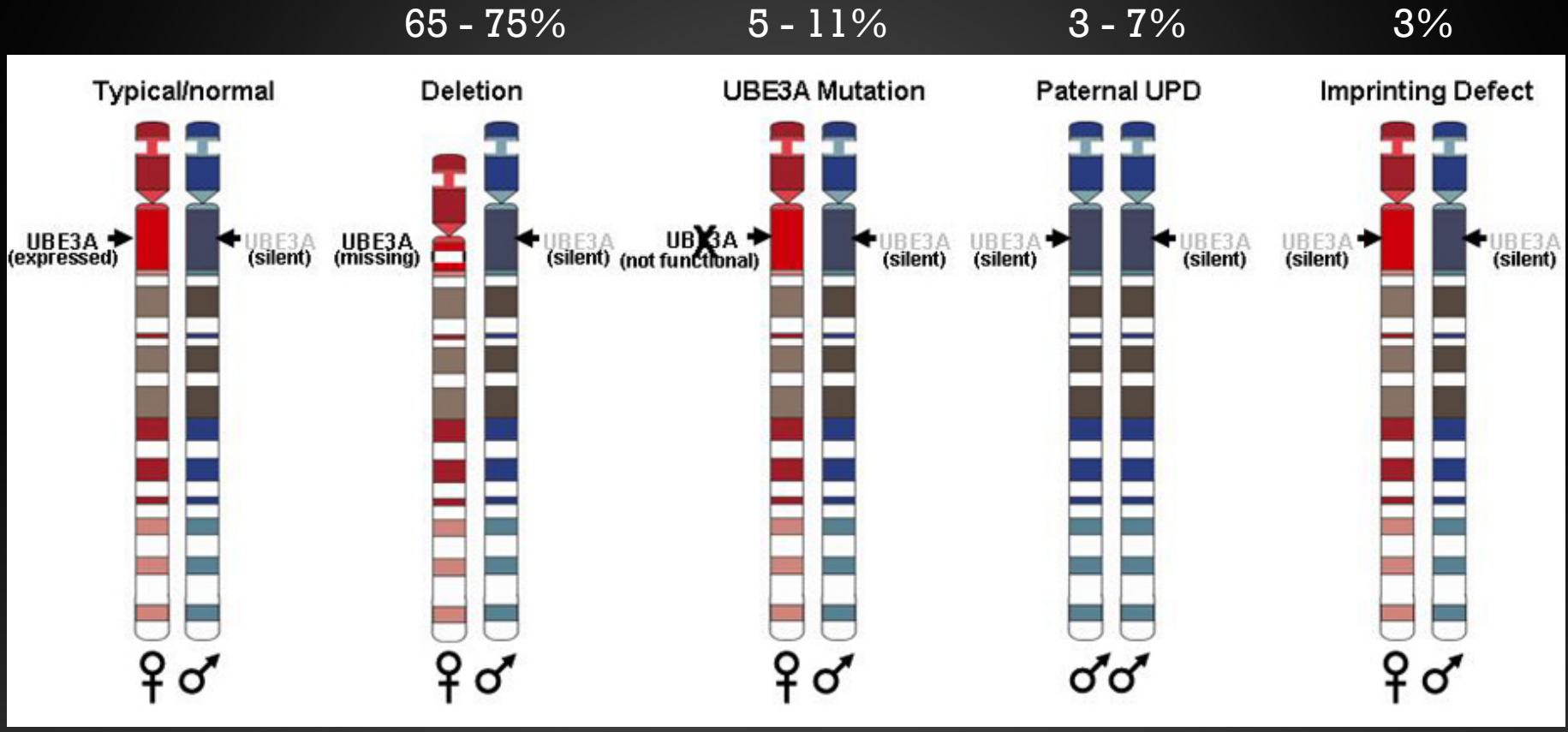
Genetic imprinting suggested by maternal heterodisomy in non-deletion Prader-Willi syndrome

Robert D. Nicholls*†‡, Joan H. M. Knoll†, Merlin G. Butler§, Susan Karam‖ & Marc Lalande*†¶



UPD = uniparental disomy

KNOWN MECHANISMS THAT RESULT IN ANGELMAN SYNDROME



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

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

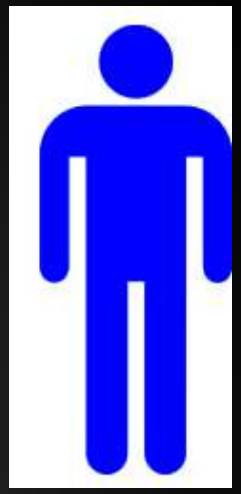
3. Community

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

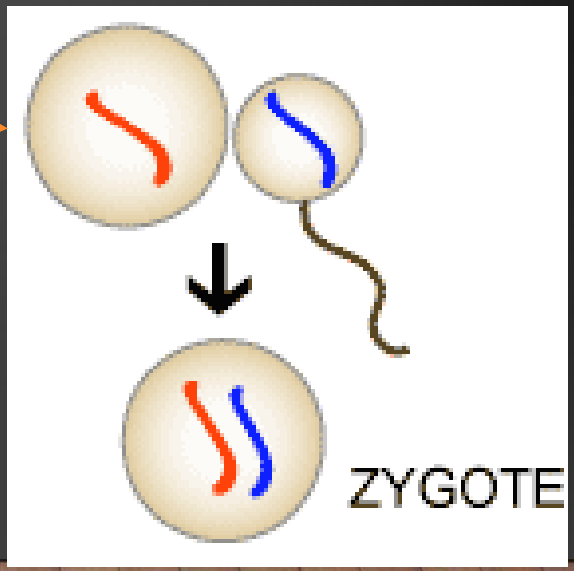
Grandmom

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	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!

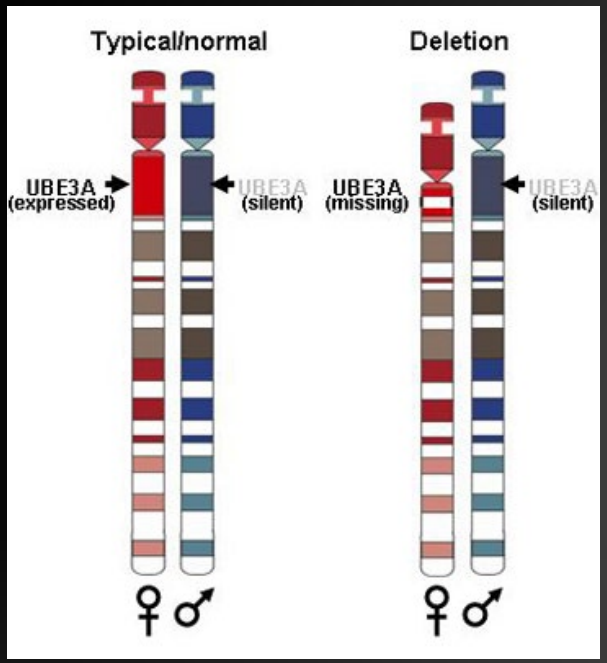
WHAT QUESTIONS DO YOU HAVE SO FAR?


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



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)

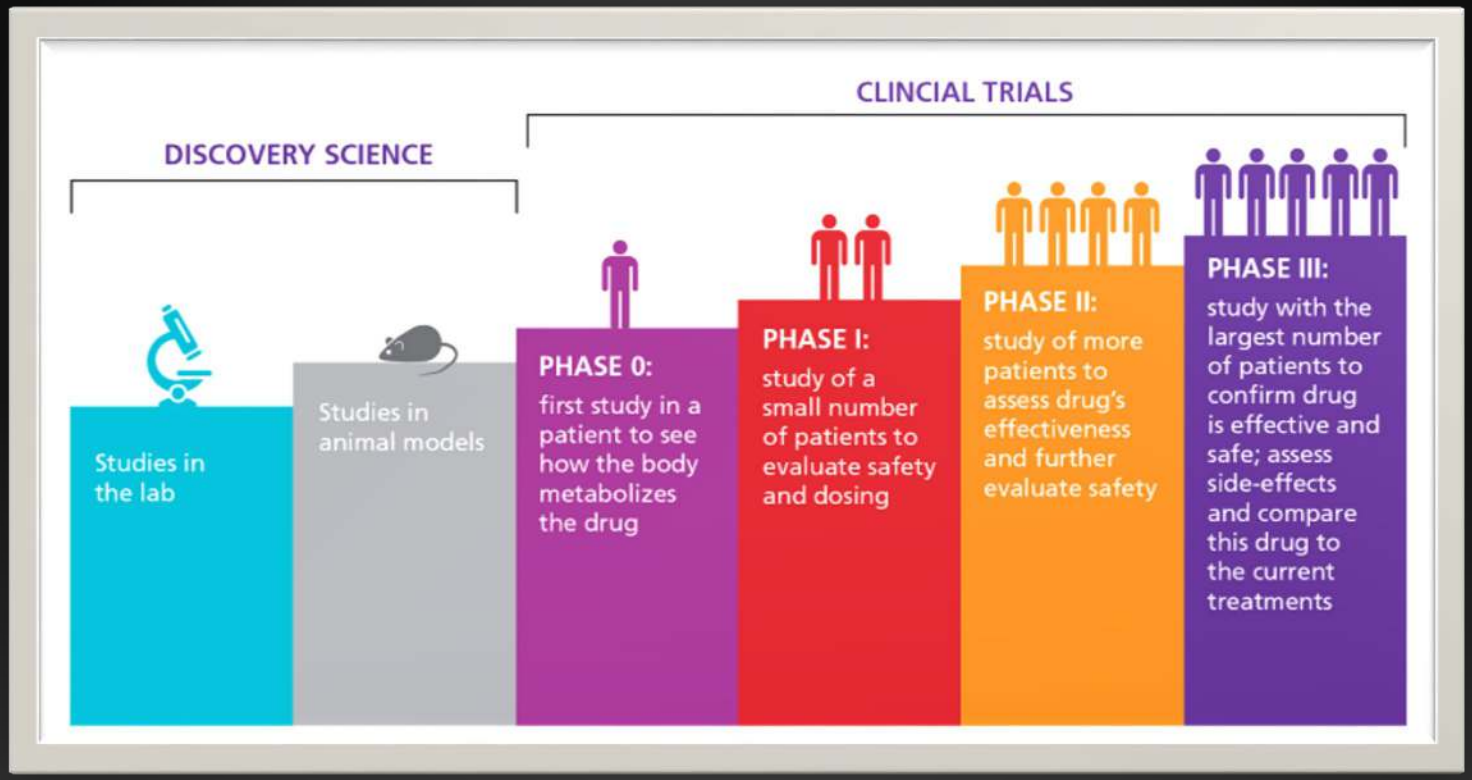
BOTTOM LINE

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

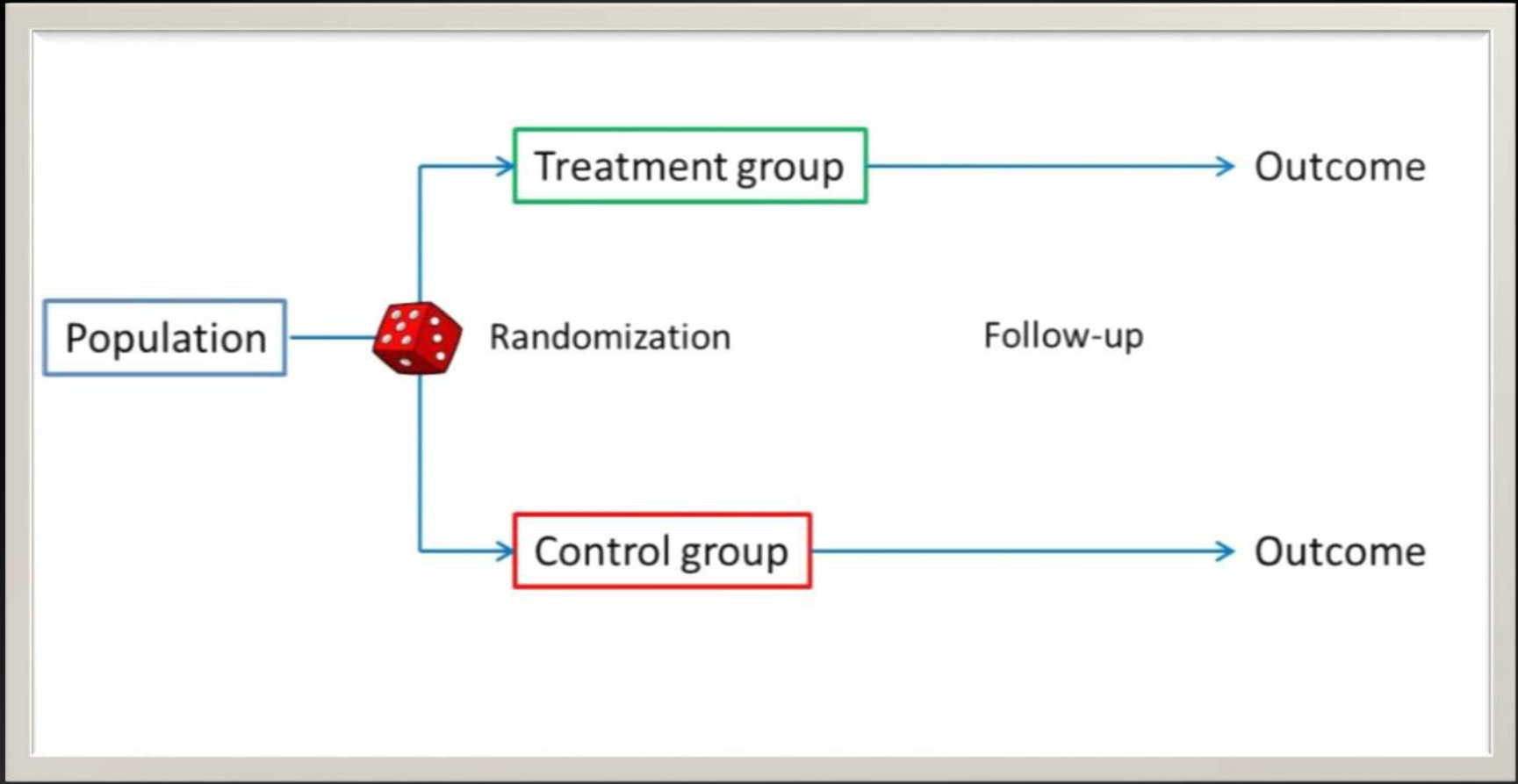
PHASES OF TESTING INTERVENTIONS/THERAPEUTICS



WHAT ARE OUTCOME MEASURES?

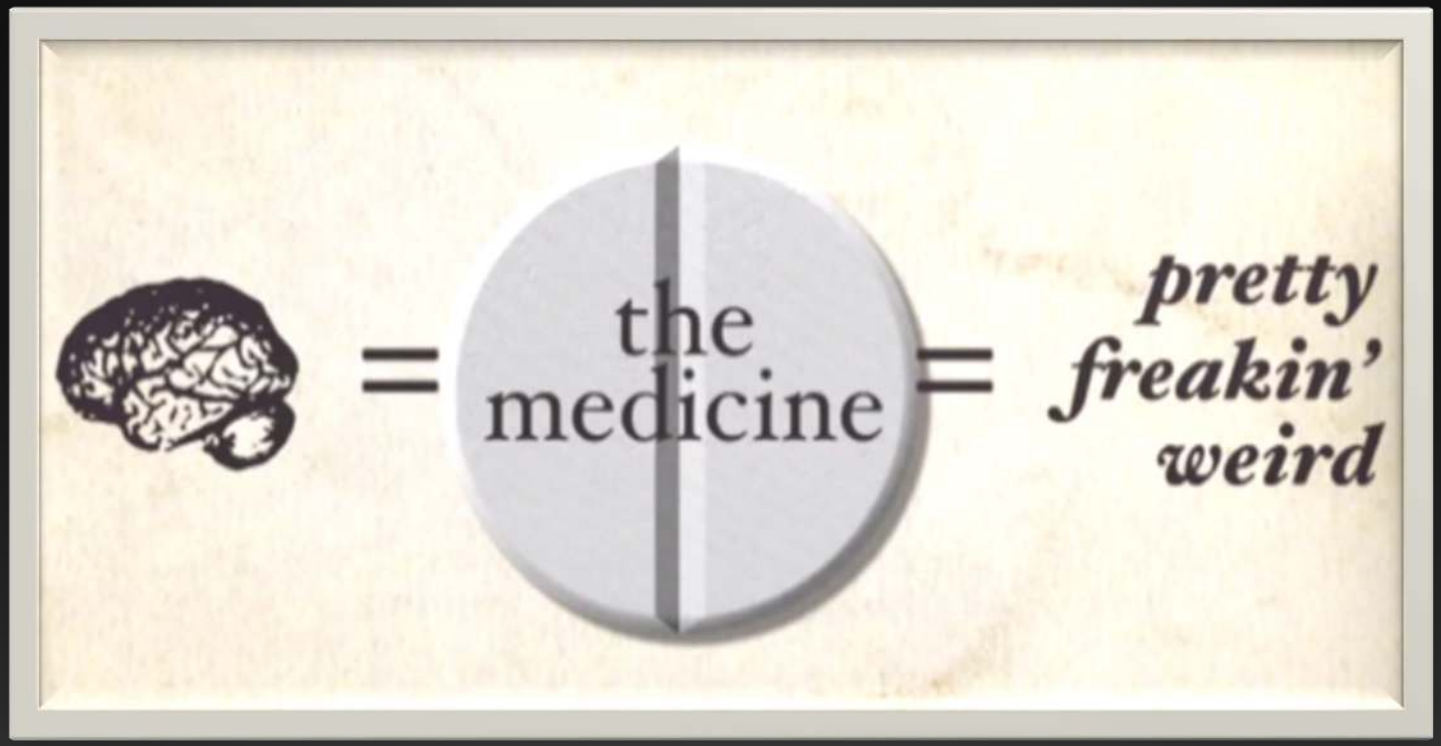
- Tests that accurately assess function at baseline before treatment.
- Can be used during and after treatment to assess change/efficacy.

VERY BASIC TRIAL DESIGN



WHY DO WE NEED PLACEBO CONTROLLED TRIALS?

AKA: I know myself and I know my child



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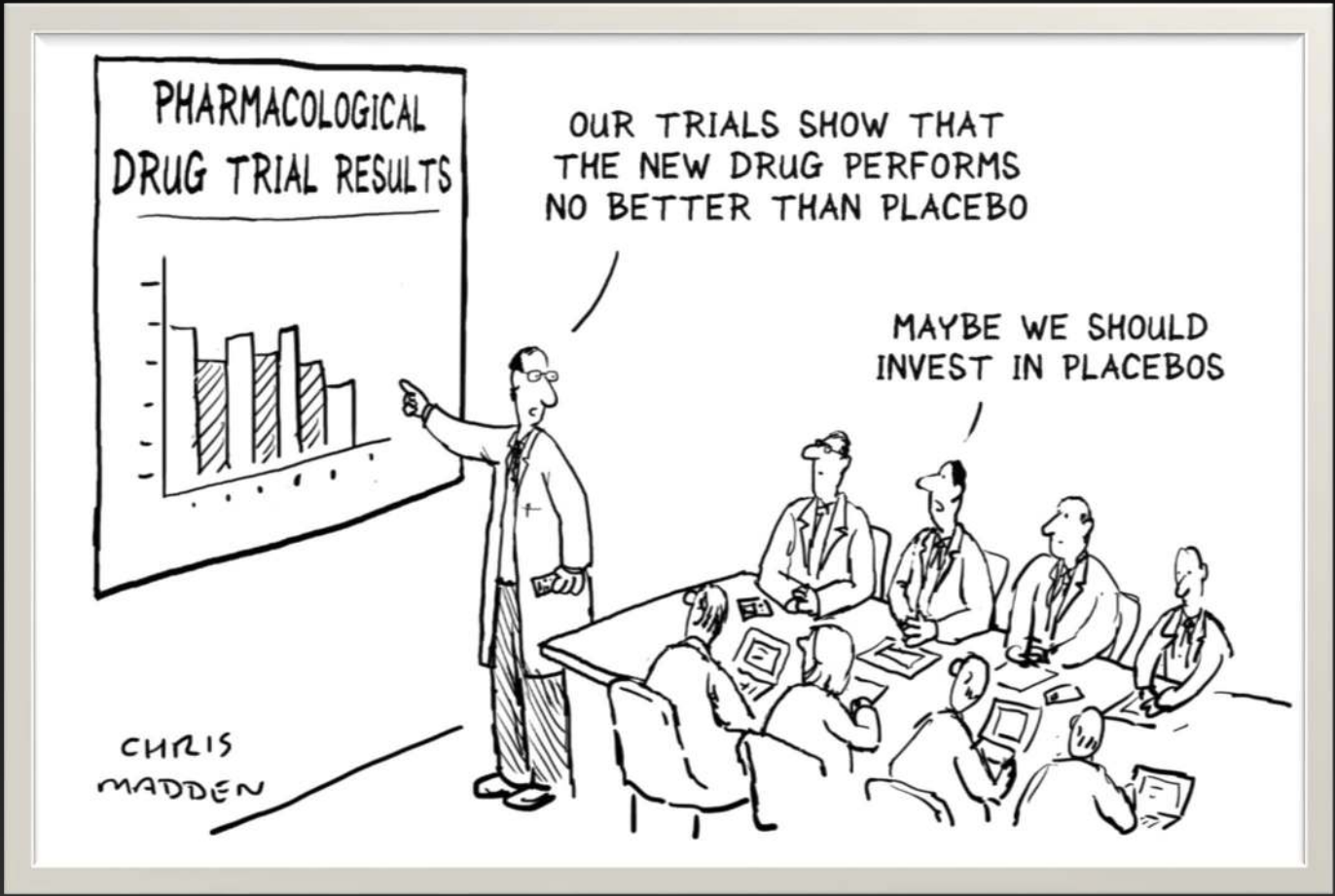


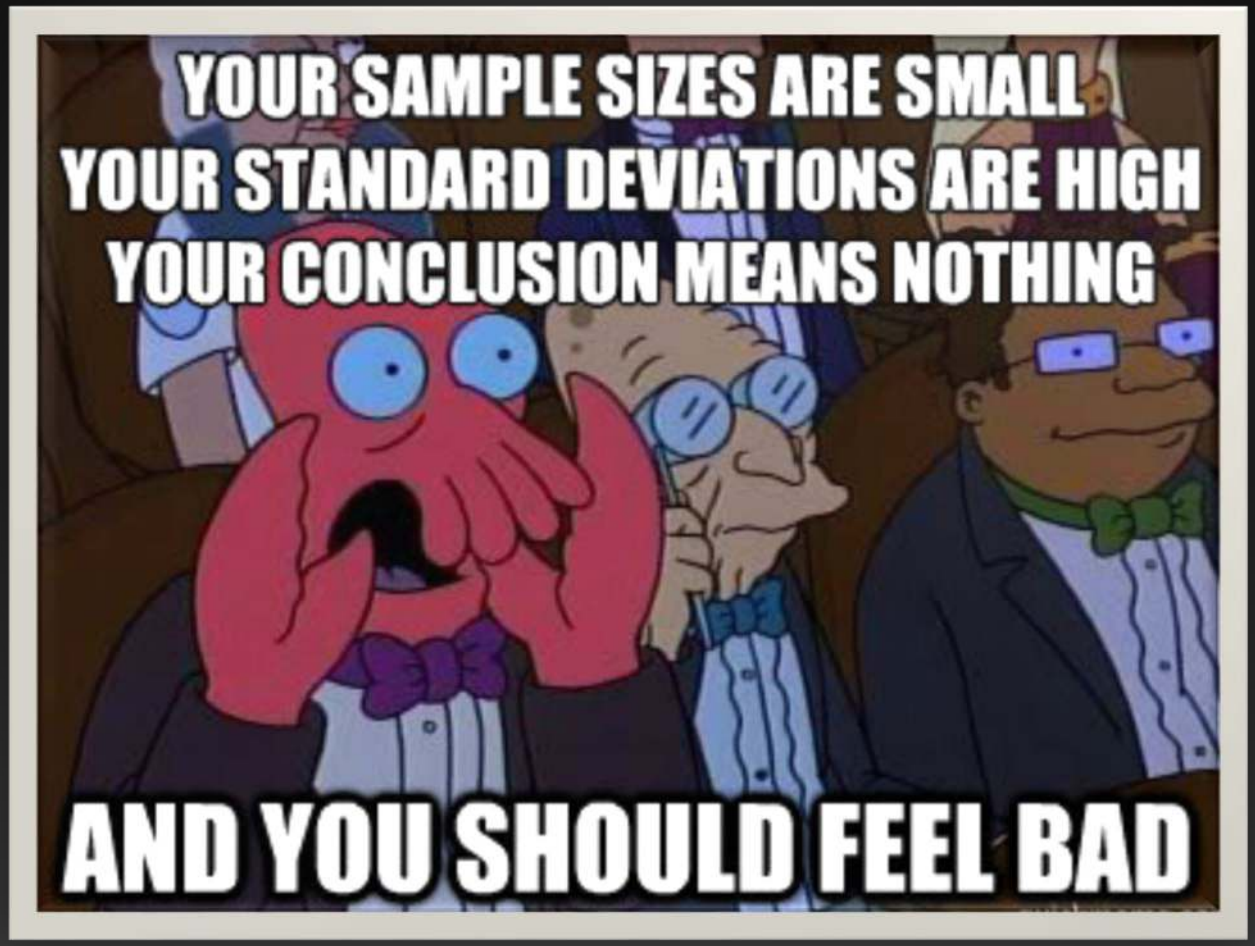
THE FLIP SIDE OF THE PLACEBO

Nocebo:

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

SO WHAT DO WE DO?

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-fla
- Speech impairme

B. Frequent (more tha
- Delayed, disprop
  Microcephaly is
- Seizures, onset u
- Abnormal EEG, v
  precede clinical f

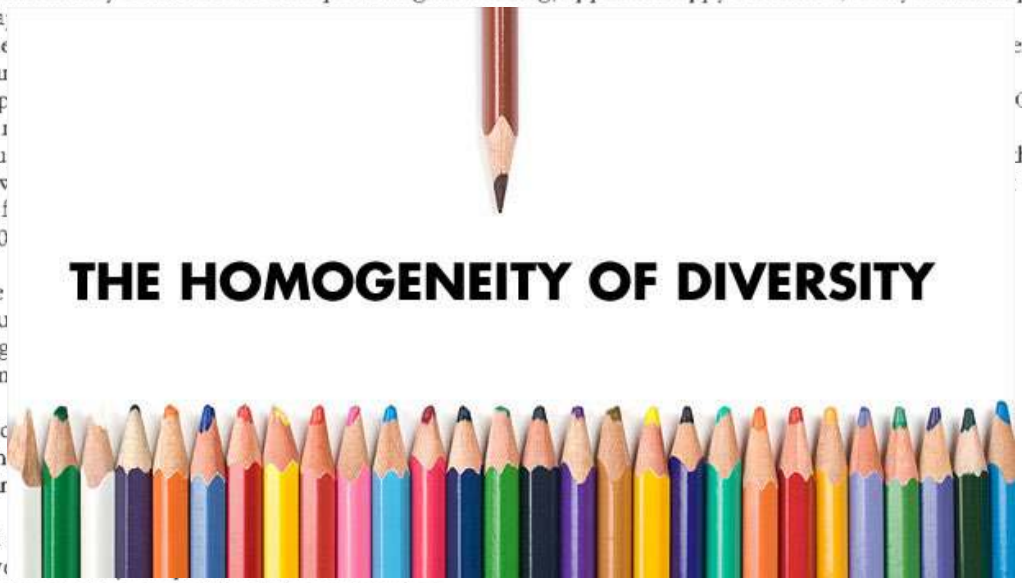
C. Associated (20%–80
- Flat occiput
- Occipital groove
- Protruding tongu
- Tongue thrusting
- Feeding problem
- Prognathia
- Wide mouth, wi
- Frequent droolin
- Excessive chewi
- Strabismus
- Hypopigmented
- Hyperactive low
- Uplifted, flexed arm position especially during ambulation
- Wide-based gait 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

erbal ones

C) by age 2 years.

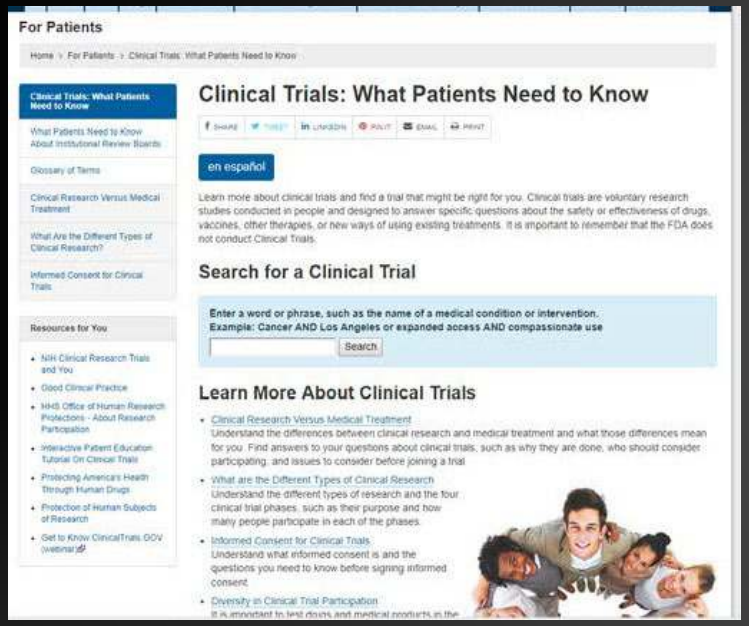
hroughout adulthood

2 years of life and can



WHAT CAN THE AS COMMUNITY DO?

Get Informed about trials in general



www.fda.gov/forpatients/clinicaltrials

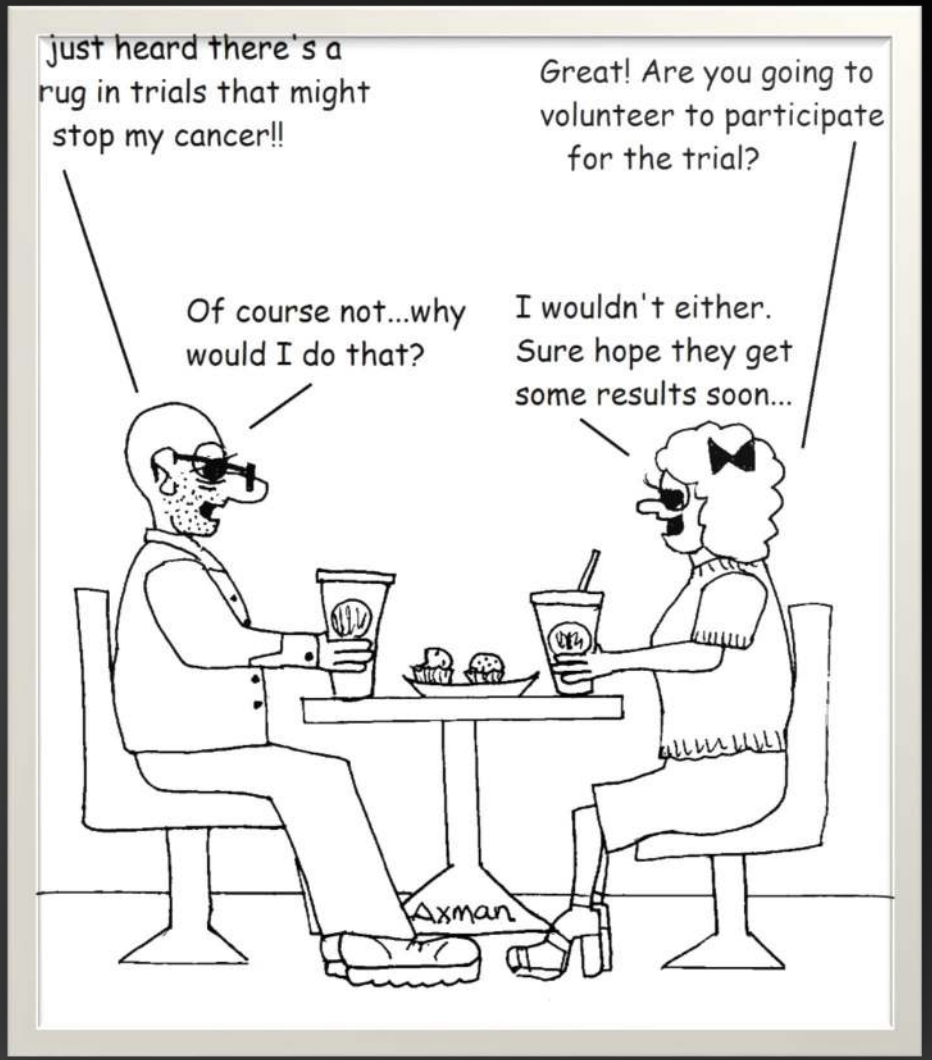
www.angelmanclinicaltrials.com

WHAT CAN THE AS COMMUNITY DO?

PARTICIPATE!

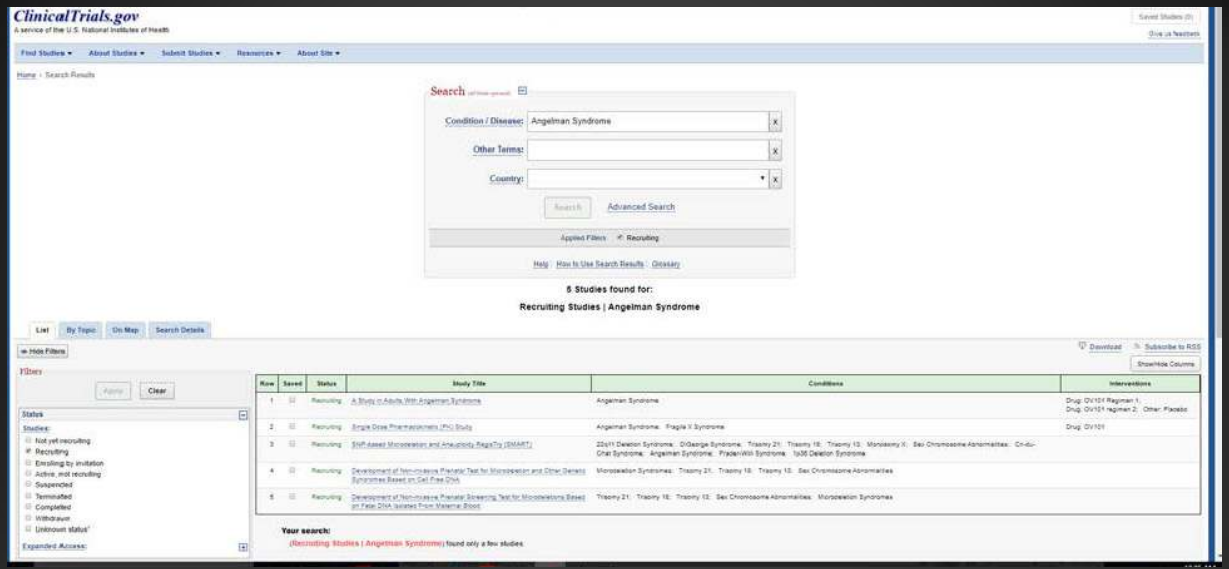
- Save medical records
- Visit AS Clinics
- Participate in Natural History Studies
- Participate in surveys
- Contribute to ongoing studies and trials

- 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!