Understanding Fragile X Syndrome: Genetics, Clinical Insights, and Interventions

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CONFLICT OF INTEREST DISCLOSURE

We have the following financial relationships with the manufacturer(s) of any commercial product(s) discussed in this educational activity:

Nicole Tartaglia, MD

Site Principal Investigator for industry-funded clinical trials of medications for Fragile X:
Shionogi, Inc / Tetra Pharmaceuticals
Harmony Biosciences / Zynerba Pharmaceuticals

Nicole Tartaglia and Susan Howell, MS, CGC

Consulting contracts for providing Fragile X education to:
Shionogi, Inc / Tetra Pharmaceuticals

Learning Objectives

1. **Explain the genetic basis** of Fragile X syndrome, including FMR1 gene mutations and inheritance patterns.

2. **Identify common clinical features** of Fragile X across developmental stages, including cognitive, behavioral, and physical characteristics.

3. **Describe the relationship** between Fragile X syndrome and autism spectrum disorder.

4. **Discuss current treatment options**, including behavioral, educational, and pharmacologic interventions.

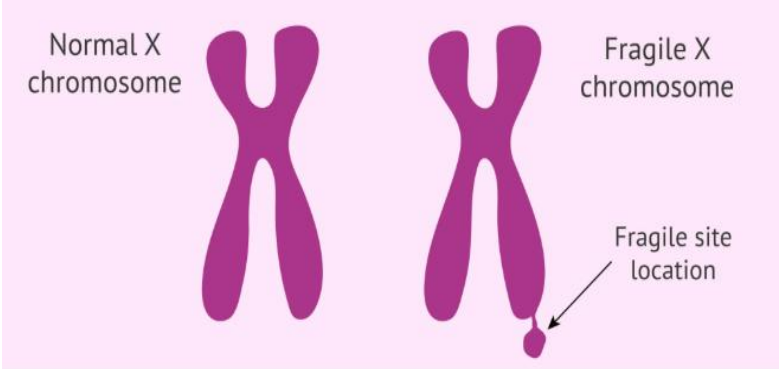
5. **Recognize the importance of family education and genetic counseling** in the management and support of individuals with Fragile X.

Journey to a Diagnosis

- At birth: Severely crossed eyes (strabismus)
- 3 months: Ear infections started & continued
- 4 months: Not tracking objects
- 6 months: Patching/eyeglasses started, diagnosed with hernia
- 8 months: Still not sitting up/crawling
- 9 months: PT evaluation: severe hypotonia; Started physical therapy
- 10 months: Delayed speech/motor skills
- 12 months: Ear tubes, Lots of crying
- 18 months: Multidisciplinary screening
- 20 months: Speech/Occupational therapy started, started walking (mostly on his toes), switched pediatricians - tested for FXS
- 22 months: Call from pediatrician: “Positive for Fragile X syndrome”

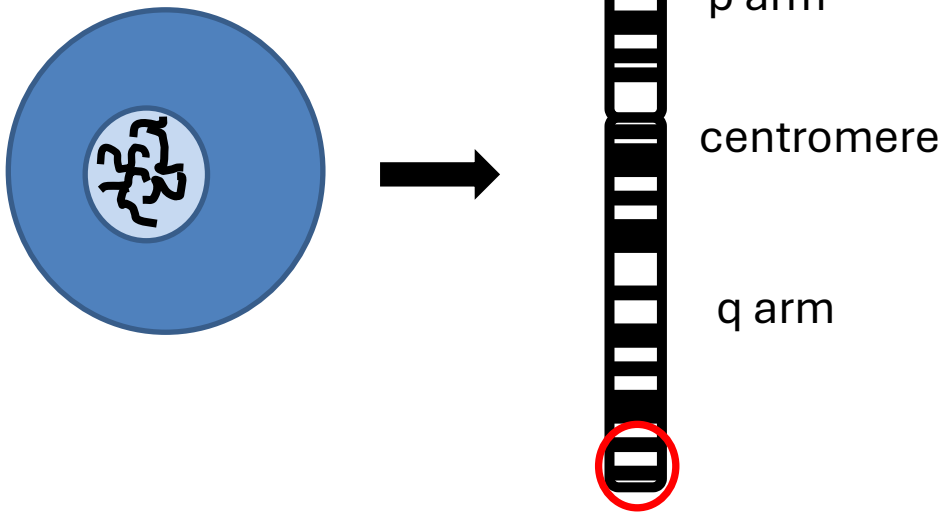
FRAGILE WHAT???

Prevalence

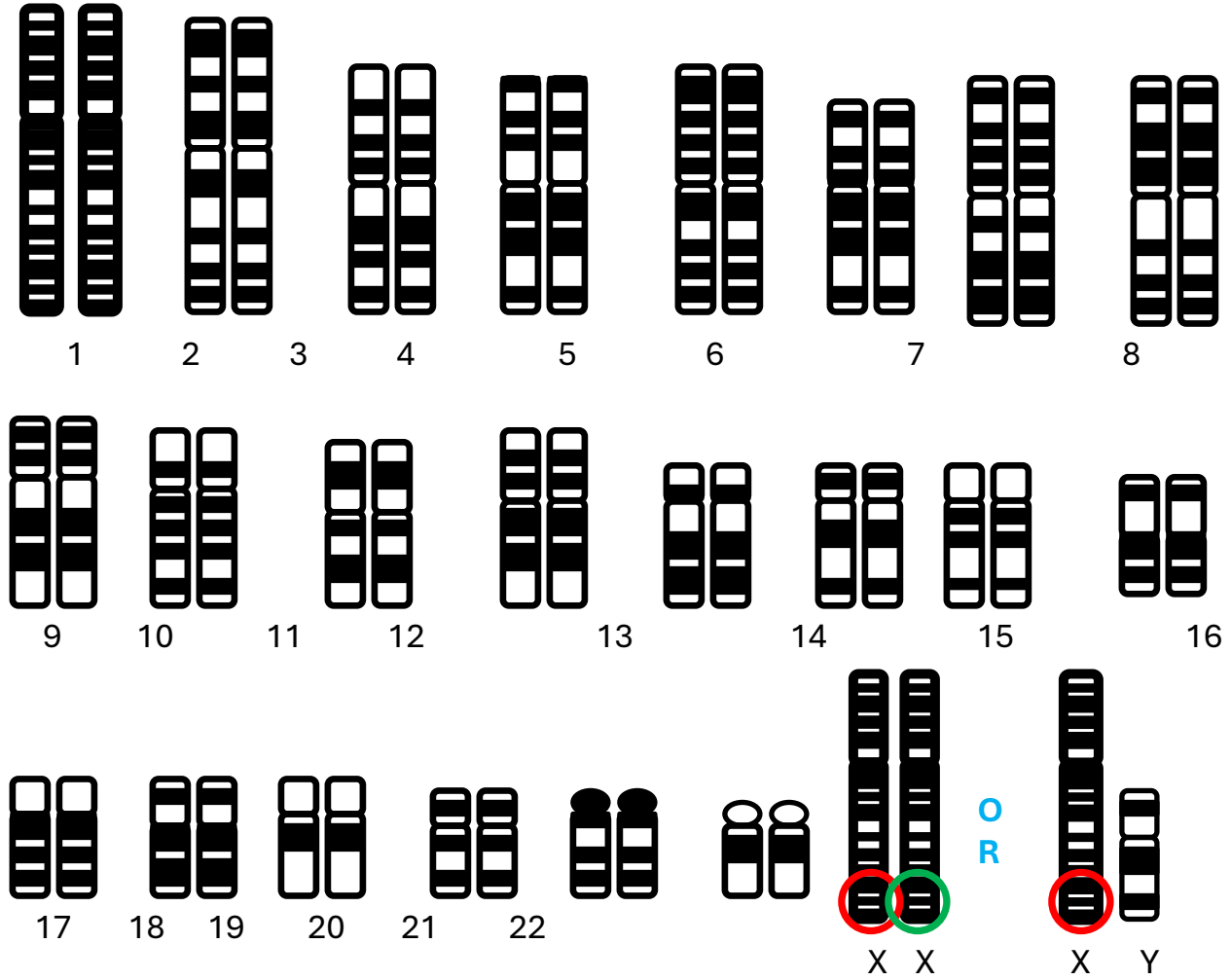


- Fragile X Syndrome is diagnosed in approximately
  - 1:4000 – 1:7000 males
  - 1:8000 – 1:11,000 females
    - Phenotype more variable due to 2nd X chromosome
    - Premutation is more common (~1:200 females, ~1:400 males)
- Most common inherited cause of intellectual disability
- Common genetic cause (single gene) of autism spectrum disorder
- Affects all races and ethnicities

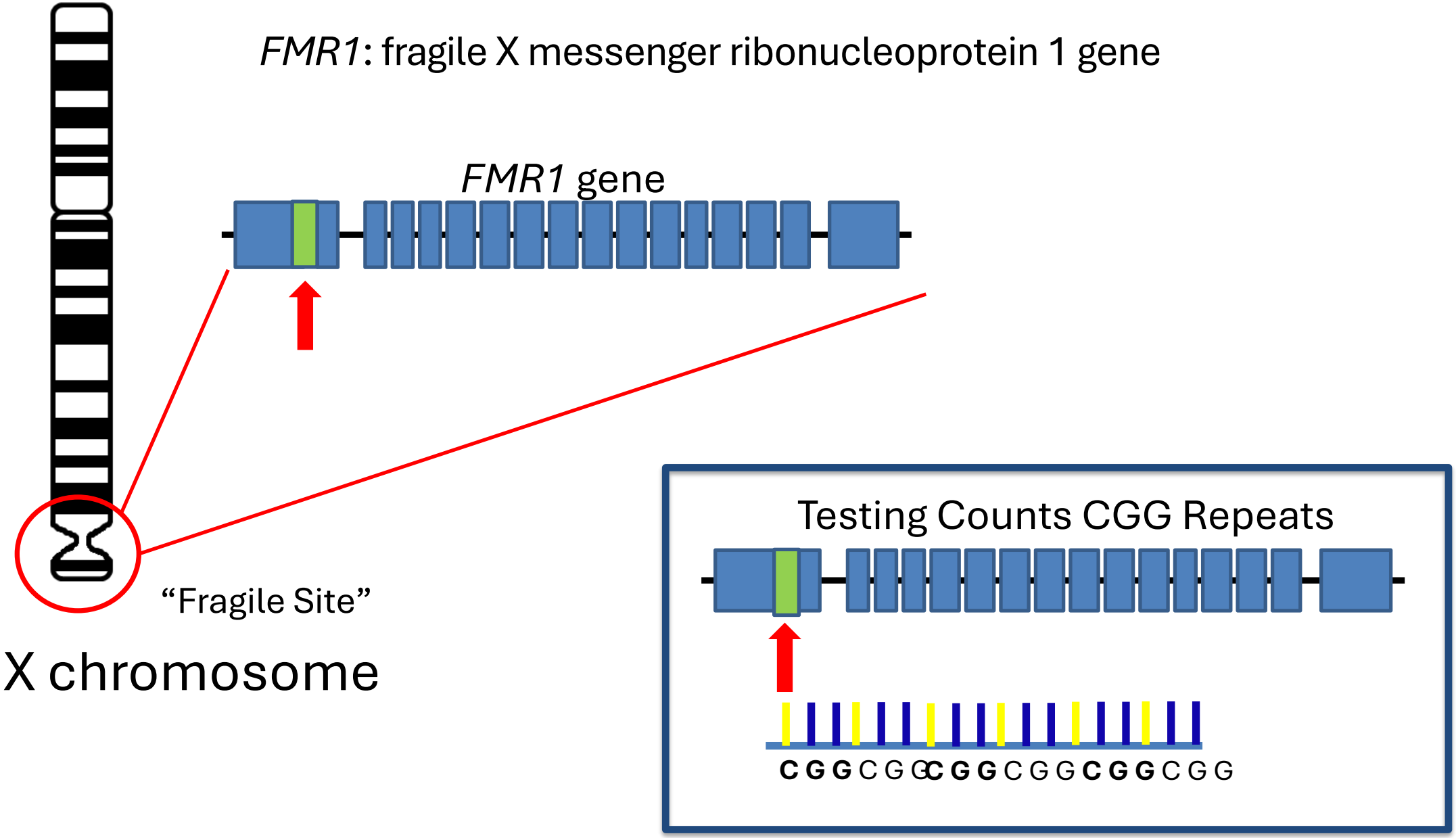
Diagnosis: Cells, Chromosomes, Genes



X Chromosome
(Xq27.3)



FMR1: fragile X messenger ribonucleoprotein 1 gene



Testing Counts CGG Repeats

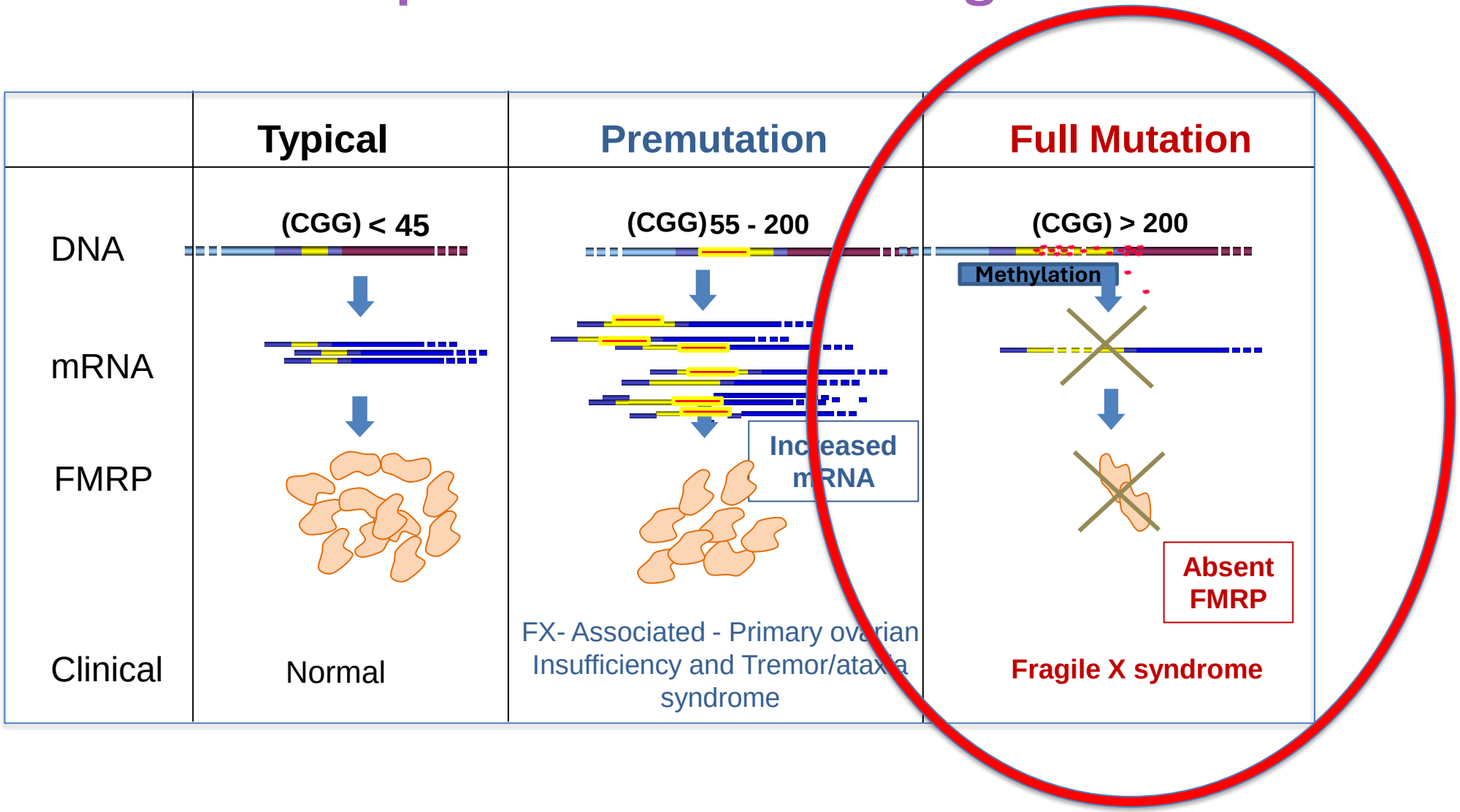
CGG = Trinucleotide Repeat

Common number of CGG repeats (6-44)

Premutation- Expanded number of CGG repeats (**55-200**)

Full Mutation- Expanded number of CGG repeats (**>200**)

Fragile X Related Disorders and the expression of the *FMR1* gene



VIDEO

https://www.youtube.com/watch?v=_byqoPW_XFk

Physical Features of Fragile X

Variable degrees of:

- Macrocephaly (large head circumference)
- Long face
- Prominent ears with cupping (smooth pinnae)
- High arched palate
- Soft, smooth skin
- Hyperflexible joints
  - Double jointed thumbs
  - Pes planus (flat feet)
- Hypotonia
- Macro orchidism (large testicles) in males (post pubertal)

Medical Features of Fragile X

	Approximate Prevalence in FXS
Recurrent Otitis Media (Ear infections)	52%
Strabismus (Lazy eye) Refractive errors (Needs glasses)	16% 17-30%
Seizures	10-12%
Pes Planus (flat feet)	50-80%
Scoliosis	10%
Gastrointestinal / Feeding Disorders - Feeding difficulties in infancy - Constipation - Loose Stools - Gastroesophageal Reflux - Others – overstuffing, rumination, picky eating	 10-25% 10-40% 5-20% 15-30% ?
Sleep disorders - Difficulty falling asleep, staying asleep - Sleep apnea	 25-50% 7-32%
Delayed toilet training	65%

Kidd et al, *Pediatrics*, Nov 2014
Davids et al, *J Bone Joint Surg Am,* Jul 1990

Features - Males

- Delayed Early Milestones in Males
  - Motor delays
    - Mean age first steps at 17.8 months
      - 45% Delayed (>18 months at first steps)
    - Later challenges with fine and gross motor coordination, motor planning
  - Speech-Language delays
    - Mean age first word: 26.2 months
      - 65% Delayed (>18 months at first words)
      - ~ 12% Nonverbal
    - Mean age 2-word phrases: 3.5 years
    - Later speech often includes rote phrases, stereotyped and repetitive speech, rapid rate of speech, atypical intonation

Raspa et al, *Pediatrics,* 2017
Hinton et al, *Developmental Neurorehabilitation,* 2013

Features - Females

- Delayed Early Milestones in Females
  - Much more variable
    - ~ 35% delayed milestones
  - Rates of delays lower than males
  - Delays diagnosed on average at 26 months of age for females

Raspa et al, *Pediatrics,* 2017

Cognitive Functioning

- Males – Intellectual Developmental Disorder (almost 100%)
  - Average Full-Scale IQ 40-55
  - Approx 10% nonverbal (expressive < receptive)
  - Adaptive Functioning / Life skills abilities broader overall compared to IQ
- Females
  - 1/3 with intellectual developmental disorder
  - 1/3 with learning disabilities (math learning disability most common)
  - Can have average IQ or above

Raspa et al, *Pediatrics,* 2017

Developmental and Behavioral Features

Sensory sensitivities

Anxiety

- Generalized anxiety
- Social anxiety
- Compulsive rituals / routines
- Selective mutism

Hand-biting, hand flapping

Repetitive motor behaviors (rocking, spinning)

Gaze / eye contact avoidance

Stereotyped and/or repetitive speech

Attention deficits, impulsivity, hyperactivity

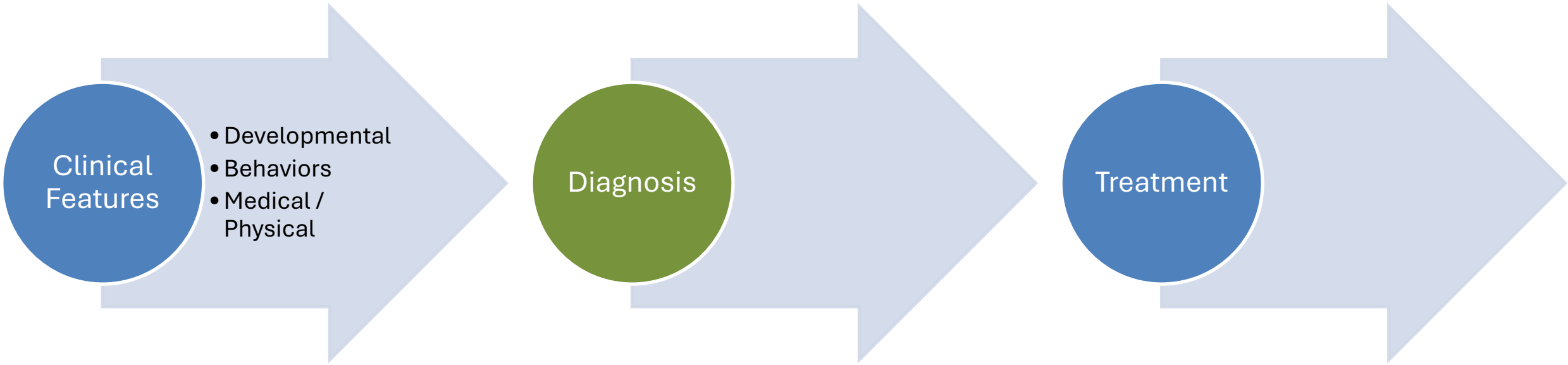
Mood instability / tantrums / aggression

Self-injurious behavior

Neurodevelopmental Disorders

Parent-reported symptoms and diagnoses	Males	Females
ADHD	84%	67%
Anxiety	70%	56%
Autism Spectrum Disorder	46%-50%	16%-20%
Self-Injury	41%	10%
Aggression	38%	14%

Bailey at al, *Am J Med Genet A,* Aug 2008
Kaufmann et al, *Pediatrics,* Jun 2017


Clinical Features
• Developmental
• Behaviors
• Medical / Physical
Diagnosis
Treatment

Diagnosis

- Average age of diagnosis (when no known Fragile X Syndrome (FXS) in family):
  - Males 36 months
  - Females 42 months (much broader range)
- Presenting symptoms:
  - Most commonly developmental delay, 2nd most common autism
  - Parental concerns at 12 months (males) and 16 months (females)
- In families who did not know about FXS in their family:
- 25% of families with male children had a second child with full mutation before 1st child was diagnosed
- 40% of families with female child had second child with full mutation

Bailey et al, *Pediatrics* (2009) 124(2):527–533

Indications for FXS Genetic Testing

1. All males, children and adults, with intellectual developmental disorder*
2. All males, children and adults, with autism*
3. All males with developmental delays*
4. Females with developmental delays, intellectual developmental disorder or autism, and family history of FXS-related disorders

Gene	Test Method	Allels Detected	Variant Detection Frequency by Test Method
FMR1	"Fragile X DNA" Targeted analysis for the CGC expansion • Blood • Cheek swab	**PCR.** CGG expansion in the non-coding sequence (allele sizes in the normal and lower premutation range) *prenatal, premutation screening. **Southern blot.** CGG expansion in the non-coding sequence (larger repeat ranges and methylation status)	>99% - diagnostic
FMR1	Carrier screening	**PCR.** **AGG genotyping.** Number of AGG trinucleotide repeats that may interrupt the CGG repeats of *FMR1* (0 - 2 AGG anchors)	May be helpful in calculating the risk of expansion of mothers with a premutation to a full mutation in children
FMR1	FISH	*FMR1* gene deletions	<1%
FMR1	Microarray	*FMR1* deletions/duplications	<1%
FMR1	Exome sequencing and Panel Testing	*FMR1* coding sequence variants	<1%

*AAP and ACGM recommendations

Fragile X Syndrome Management

New Diagnosis:

- Genetic counseling
- Facilitate cascade testing (siblings, etc.)
- Social work
- Community / disability services
- Family mental health / coping with diagnosis

Medical Evaluation / Screening for Fragile X associated conditions

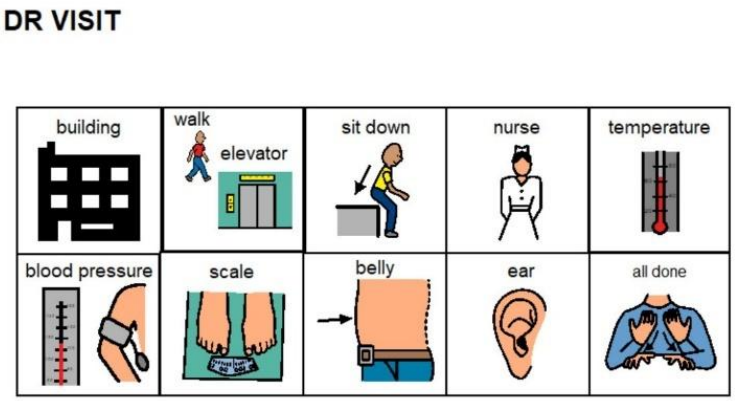
Medication treatments

Referrals:

- Early intervention
- Speech Therapy, Occupational Therapy, Physical Therapy
- Child Psychology – Cognitive & Adaptive functioning, Co-morbidities (evaluation and management of ADHD, Autism Spectrum Disorder)
- Behavioral Therapies

Facilitating Medical Care

- Medical appointments for patients with disabilities can be challenging
- Excessive anxiety / sensory sensitivities
- Waiting is very challenging (schedule as 1st appointment)
- Anxiety common in mothers (w/premutation or full mutation)
- Strategies:
  - Ask parents about best approach to examination
  - Be accommodating
  - Exam techniques for children with disabilities
    - Picture schedules, video modeling, “1-2-3 all done”
  - Practice visits / Desensitization
  - History by telehealth to shorten in-person visit



Management

	Management
Recurrent Otitis Media	Antibiotic Treatment , Low Threshold for referral to ENT, ~ 40% PE tubes at least once, Audiology Evaluations
Strabismus Refractive errors	Close Examination, Pediatric Ophthalmology
Seizures	Neurology for Evaluation & Treatment
Pes Planus	Referral to Orthopedics, Physical Therapy consideration of orthotics
Scoliosis	Examination, Referral as needed
Feeding Disorders Other GI (Reflux, Constipation)	Feeding therapy, Occupational Therapy Symptomatic management, GI referral
Sleep disorders	Careful sleep history Sleep hygiene strategies Sleep clinic, sleep study for suspicious of sleep apnea
Delayed toilet training	Toileting strategies, referral to disability toileting clinics & resources Prescriptions for diapers / supplies

Psychopharmacology in FXS

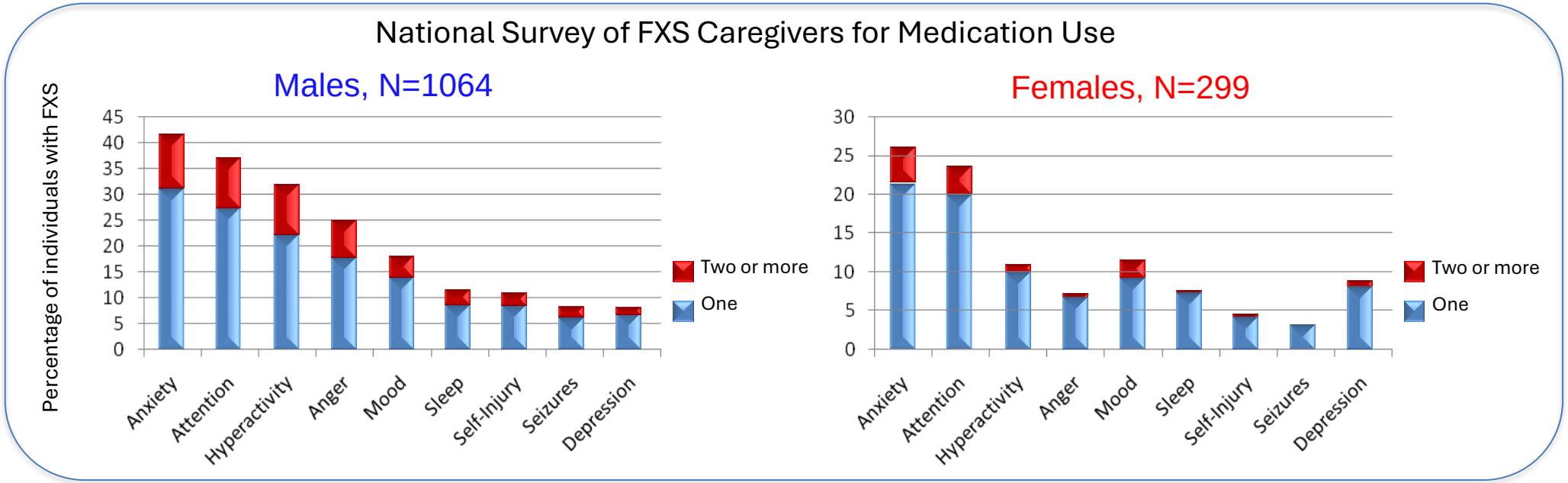
- Medications for behavioral problems (e.g. ADHD, stimulant)
- Medications for sleep difficulties (melatonin and alpha-agonists)
- Medications for seizures (antiepileptics)
- Medications under research (clinical trials)

Medication Management

- Standard of care for behavioral problems **when behavior is causing impairment**
- Targets behavior to improve functioning
- Prevents dangerous behaviors
- Targets the most important or impactful behavior
- May need to treat multiple behavioral domains, but typically we don’t start with two meds at the same time
- The consensus recommendation is to start at a low dose, and raise the dose gradually and systematically

Medications For Behavioral Problems

In a national survey the majority of FXS patients received medication therapy

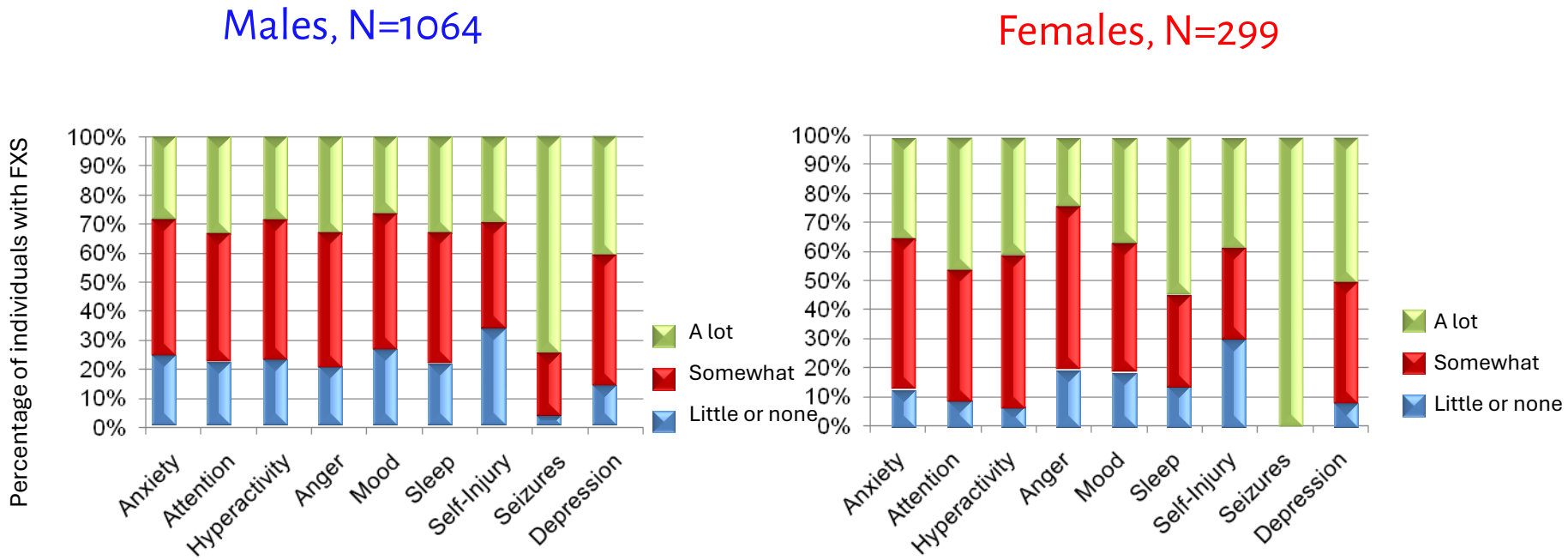


1. Bailey DB et al. *J Dev Behav Pediatr.* 2012;33(1):62-69.

Medications Perceived Efficacy

In a national survey the majority of caregivers considered medications to be at least “somewhat” effective for most symptoms

However, ~ 1/3 rated current medications as “a lot” effective



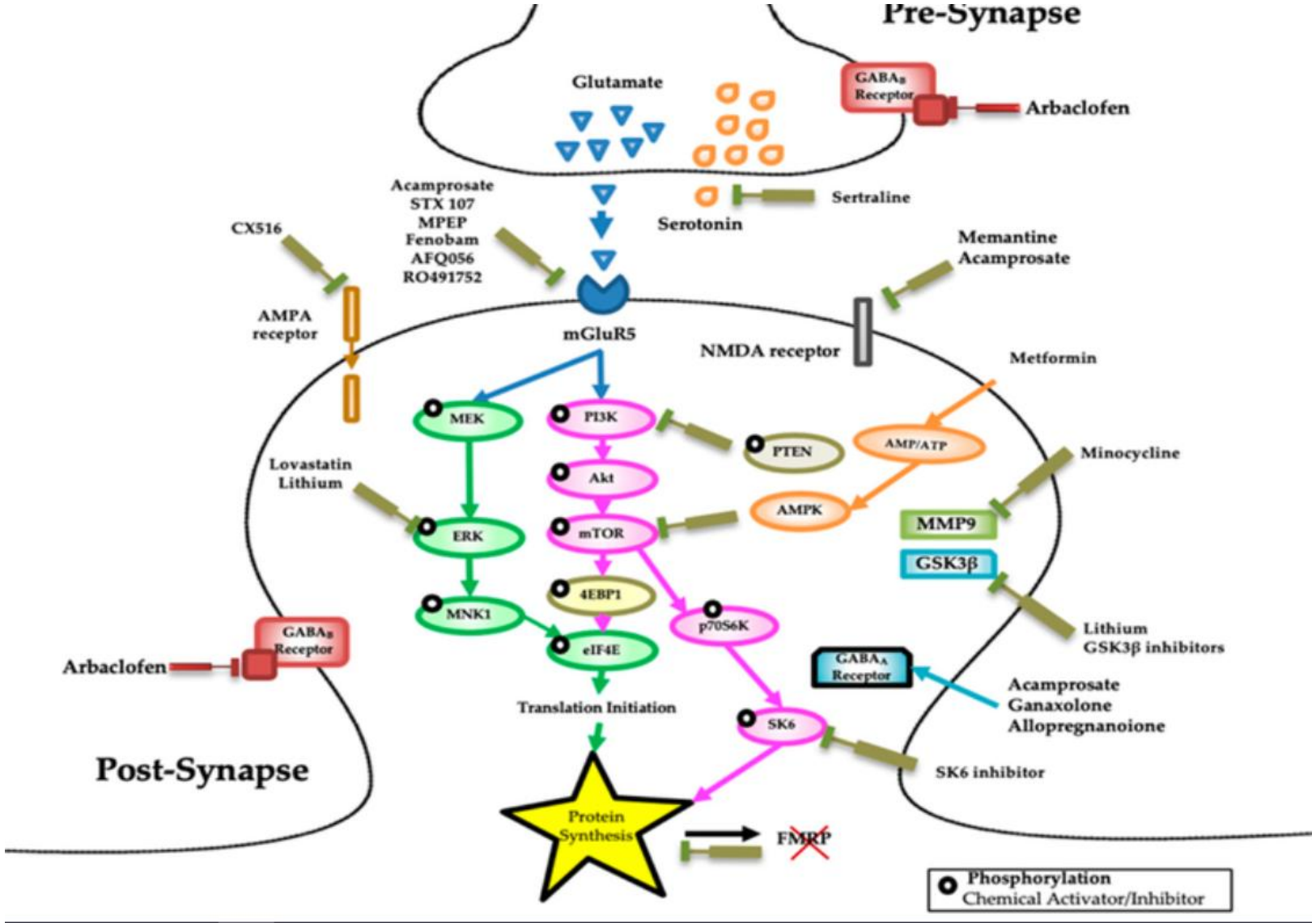
Bailey DB et al. *J Dev Behav Pediatr.* 2012;33(1):62-69.

Medications for Behaviors in Fragile X

Behavioral Symptom	Medication Class
Distractibility/ Hyperactivity	Stimulants Non-stimulants
Hyperarousal/ Hypersensitivity	Alpha-agonists
Anxiety/Obsessive compulsive behaviors/ Perseveration	Selective Serotonin Reuptake Inhibitors (SSRIs)
Mood Lability	Antidepressants, Antiepileptics
Aggression/ Self-injury	Atypical Antipsychotics
FRAGILE X	TARGETED TREATMENTS

Targeted treatments and Clinical Trials For FXS

https://www.clinicaltrials.gov/



Targeted Treatments

1. FDA approved for other indications but target Fragile X pathways
   - Metformin (AKT/mTOR): irritability/aggression
   - Sertraline (BDNF): speech / motor development in FX+ASD
   - Cannabidiol (CBD): endocannabinoids
   - Also: minocycline (MMP9), lithium (mGluR),
2. Industry sponsored Clinical Trials
   - Tetra Pharmaceuticals / Shionogi (EXPERIENCE Trial): zatolmilast phosphodiesterase inhibitor – primary outcome COGNITIVE SKILLS (NIH Toolbox)
   - Zynerba Pharmaceuticals / Harmony Biosicences (RECONNECT-FX Trial): Zygel (transdermal cannabidiol) – primary outcome SOCIAL AVOIDANCE

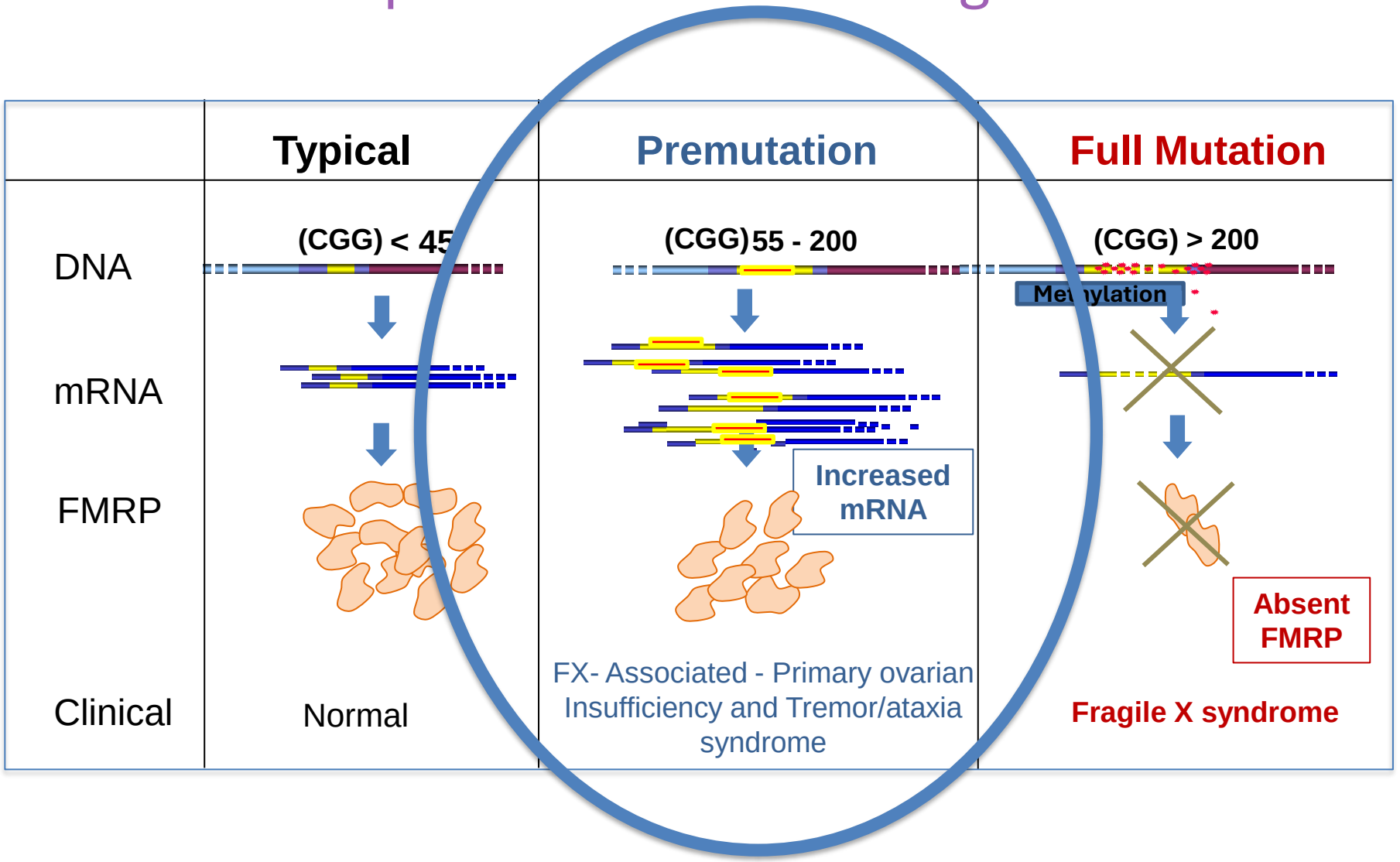
Genetic Counseling

☑ Understanding the child's diagnosis.....and more

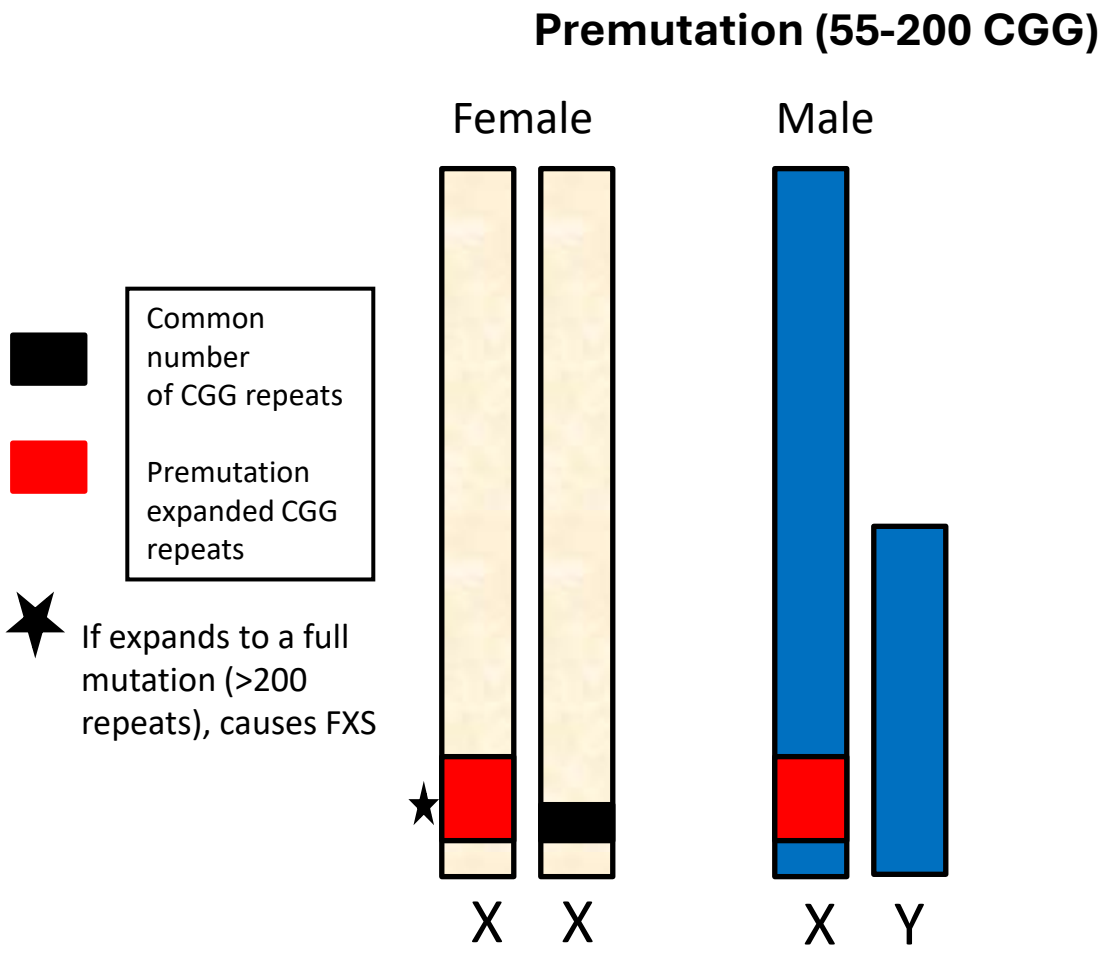
The counseling session also includes discussions about:

- Inheritance patterns and risk
- Family planning options
- Cascade testing – all family members at risk
- *FMR1* Premutation Associated Conditions
- Psychosocial issues

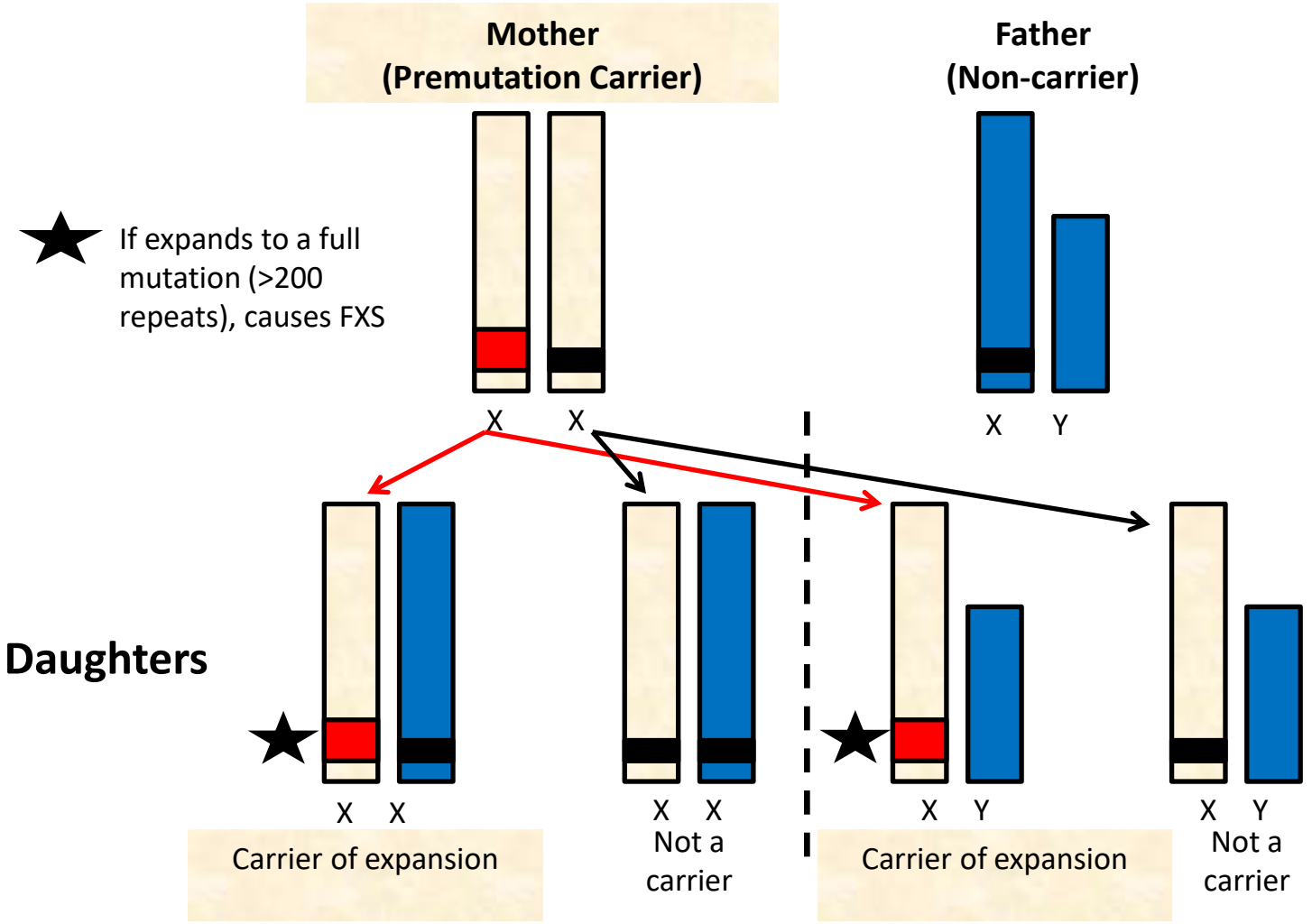
Fragile X Related Disorders
Expression of the *FMR1* gene



Fragile X has an X-Linked Inheritance Pattern

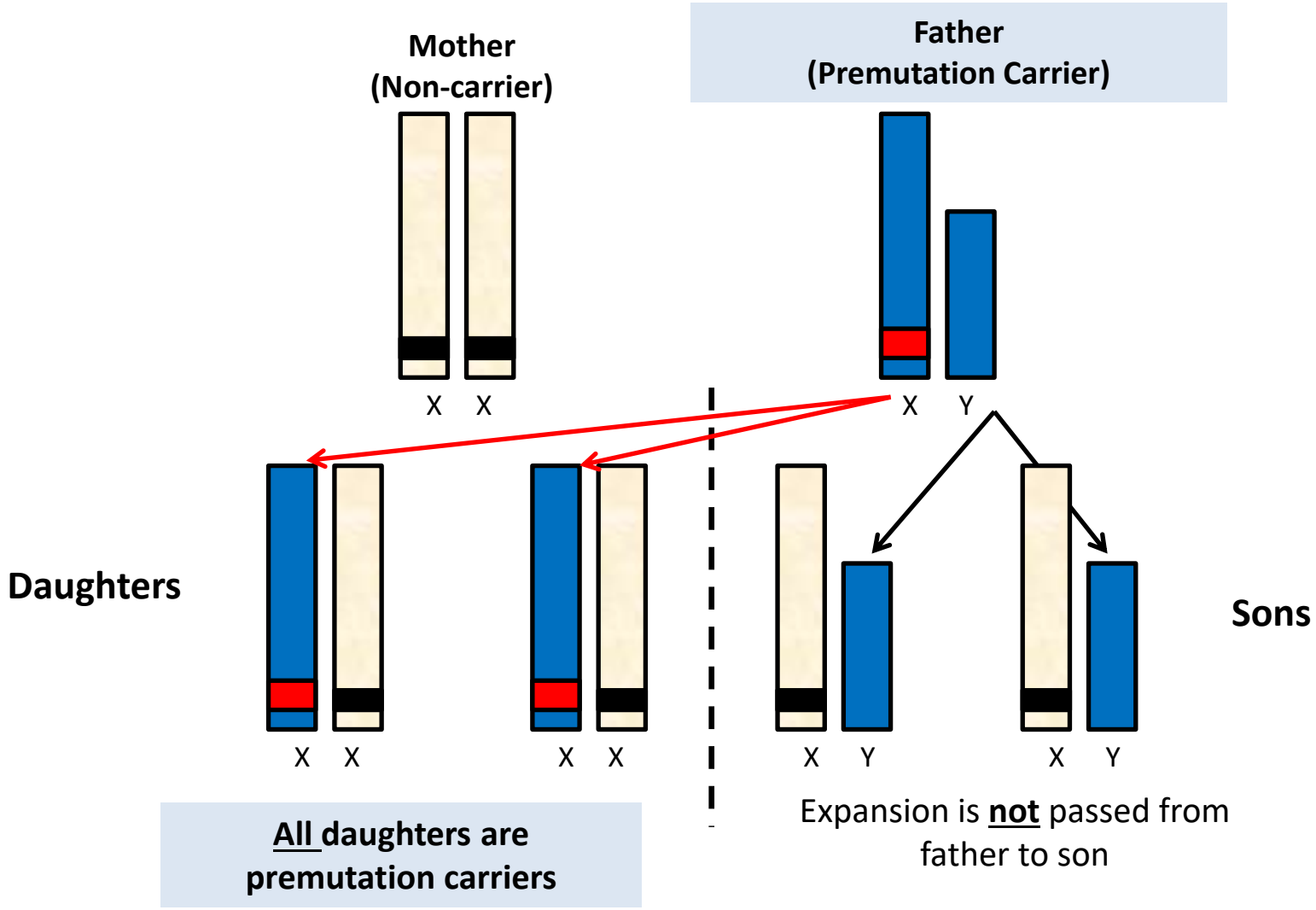


Inheritance



More likely to expand when passed down from the <u>mother to child</u>

Inheritance - Father



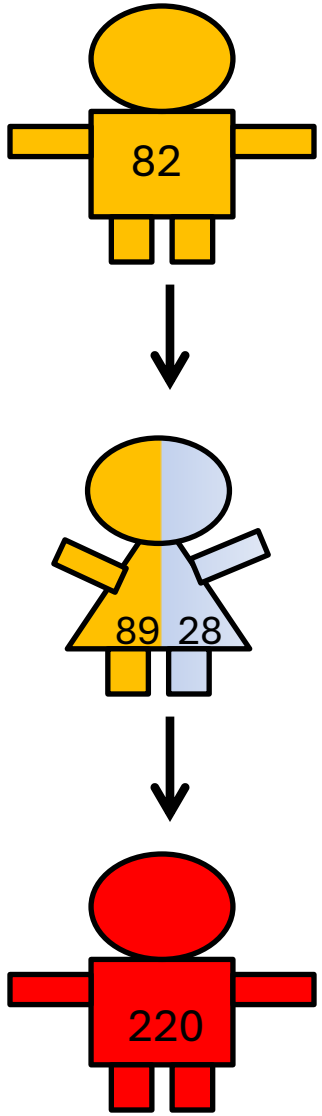
The premutation does not typically expand when passed from the father

Genetic Anticipation

More likely to expand when passed down from the mother to child

Dependent on:

1) CGG repeats
2) AGG interruptions

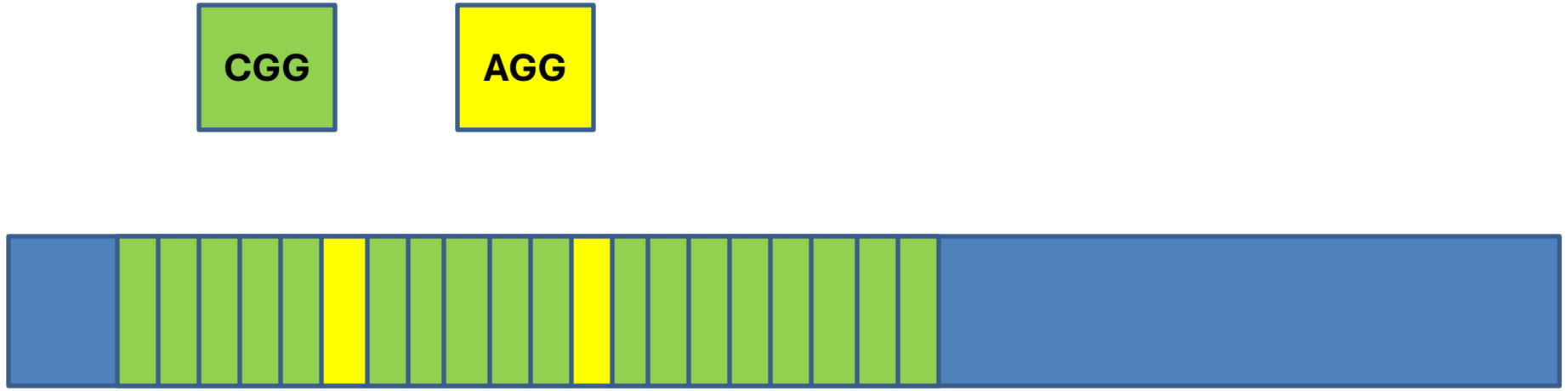


Generalized CGG Repeat Expansion Risk

Maternal Repeat Size	Risk for Expansion to Full Mutation
59	0.5%
60-69	4%
70-74	21%
75-79	47%
80-84	62%
85-90	81%
90-200	>85%

(Nolin et al. 2015)

AGG Interruptions (Anchors)



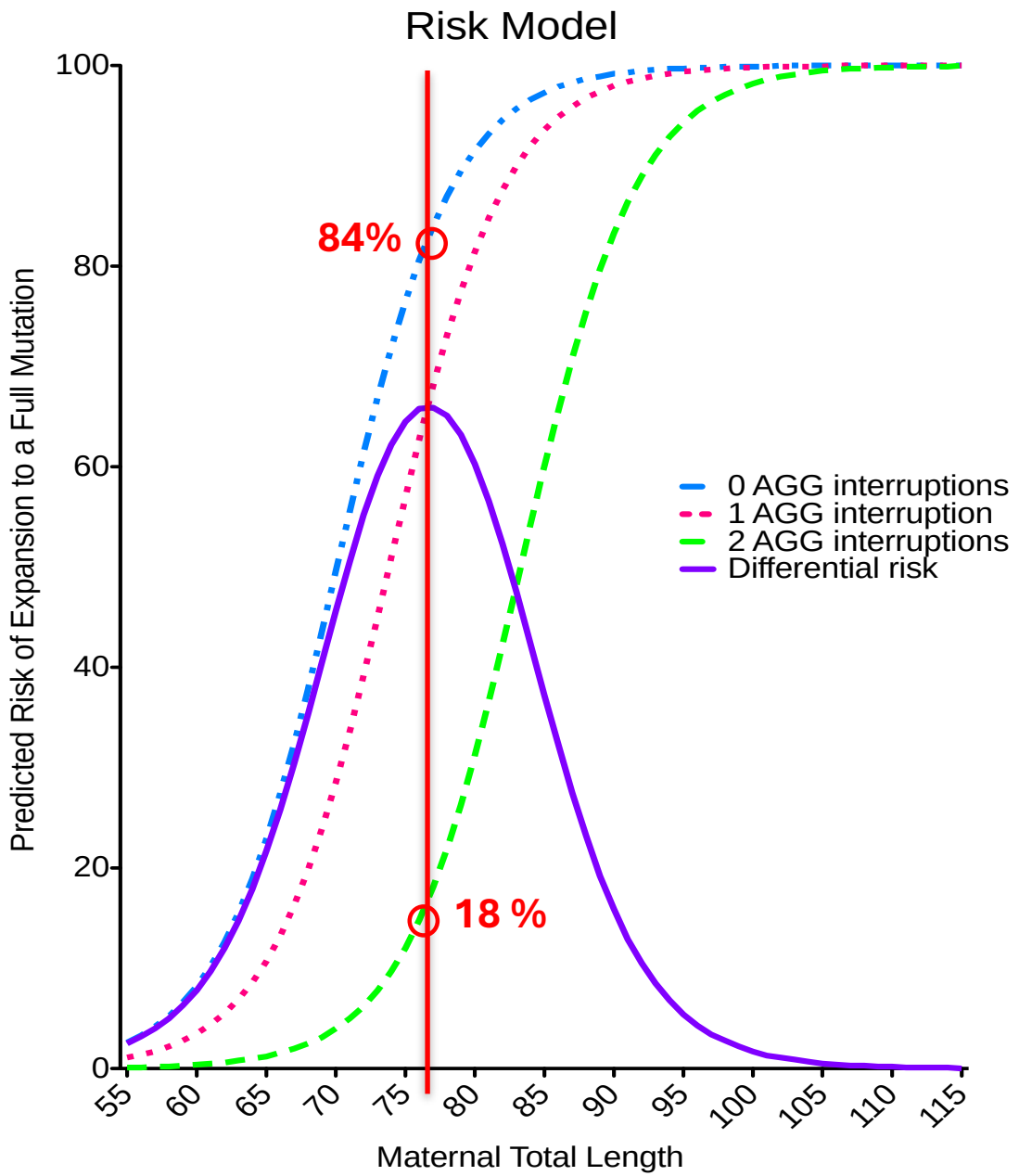
- AGG interruptions are present in normal CGG repeats
- 0, 1, 2, or 3 interruptions are common
- Typically occur around every 9-10 CGG repeats
- When present, AGG interruptions have a stablizing impact on CGG transmission
- The more AGGs, the more stable in transmission

AGG Impact

Test for Personalized Risk

AGG Impact:

- Women who carry 60-90 CGG
- The more AGGs the more stable
  - AGGs lower risk to expand to full mutation in next generation



Yrigollen et al., 2012

Not Just Reproductive Risks
FMR1 Premutation Associated Conditions

Fragile X Tremor Ataxia Syndrome (FXTAS)

- Progressive neurodegenerative disorder
- Onset >50yo
- Motor (tremors, ataxia, Parkinson-like, balance probs)
- Cognitive (memory, EF deficits, dementia)
- Mood disorders (irritable, anxiety, depression)
- MRI findings

Fragile X Primary Ovarian Insufficiency (FXPOI)

- Menopause <40 yo
- Curve-linear relationship with CGG premutation repeats
  - Highest risk ~85 CGG
- Residual risk for pregnancy
  - ~15% pregnancies in women with FXPOI

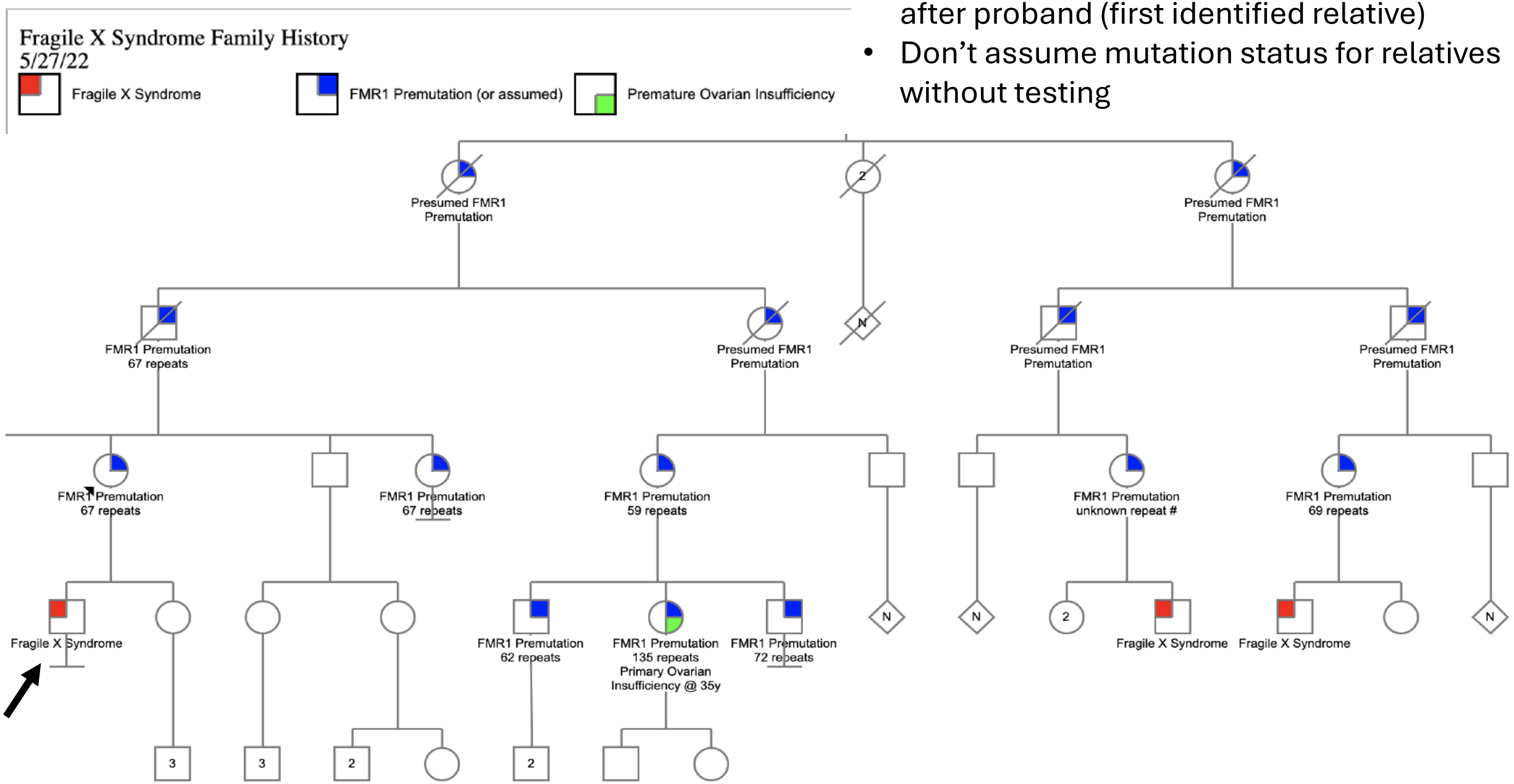
Fragile X–Associated Neuropsychiatric Disorders (FXAND)

- Psychiatric and neurodevelopmental symptoms
  - Anxiety (esp social) / Depression
  - OCD
  - Mood instability
  - ADHD
  - ASD- like traits
  - Sensory problems
  - EF Deficits

Other Symptoms

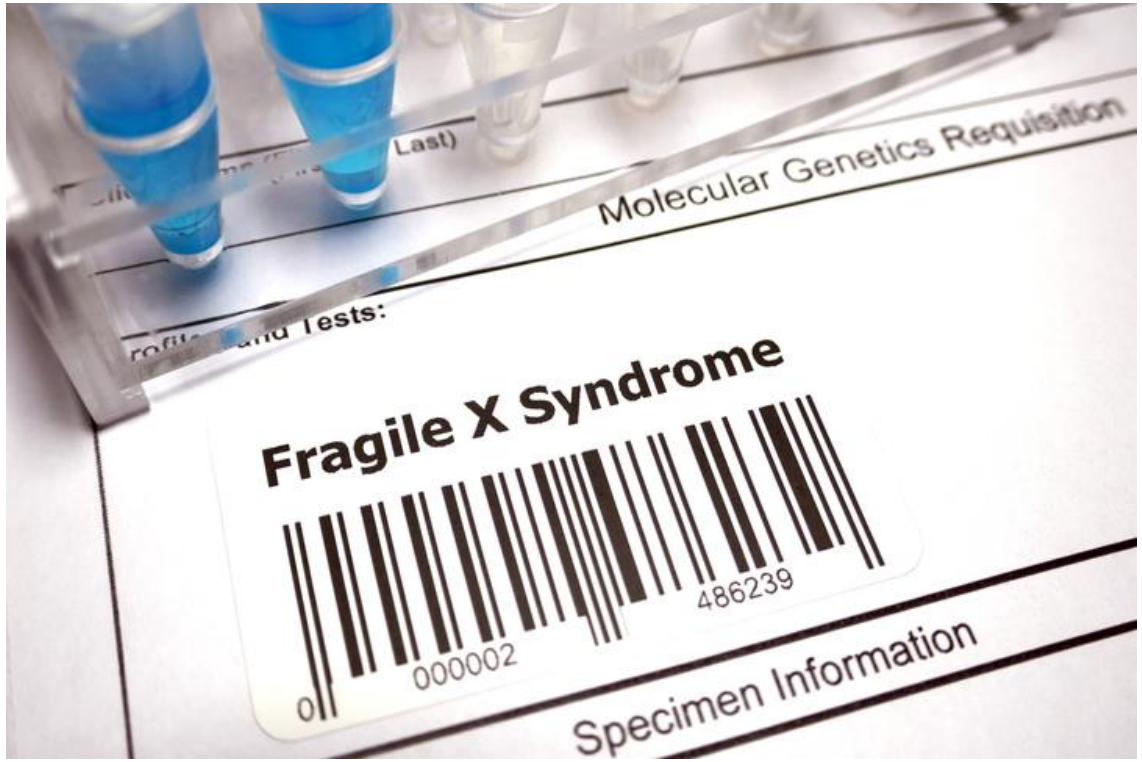
- Autoimmune (thyroid)
- Fibromyalgia
- Neuropathy
- Migraines
- Speech delays
- Learning probs (esp math)
- HTN

- ~5-10 additional family members identified after proband (first identified relative)
- Don’t assume mutation status for relatives without testing



Telling Others – Family Diagnoses

- First – My child & myself. No one else in our family has this.
- My baby? Does he/she have it?
- My parents and siblings and their children?
- My grandparents, cousins, aunts, uncles?
- Until you start (and people agree to) testing, you don't know what side of the family to inform.
- It's met with mixed reactions – from "Let's test everyone" to "I don't care."
- That is why it is good to meet with a genetic counselor



Psychsocial Impacts

- New Diagnosis is blindsiding
  - Future / Prognosis
  - Inherited risk to other children
  - FXPOI & FXTAS risk
  - Financial impacts
- Diagnosis is an emotional journey
  - Family and individual supports
  - Guilt with inheritance
  - Do other family members know and how to disclose

Resources

AAP Health Supervision for Children With Fragile X Syndrome
https://publications.aap.org/pediatrics/article/127/5/994/64903/Health-Supervision-for-Children-With-Fragile-X

AAP Patient Care Information: Fragile X Syndrome
https://www.aap.org/en/patient-care/fragile-x/

AAP HealthyChildren.org: What is Fragile X Syndrome: A Guide for Parents
https://healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Fragile-X-Syndrome-Information-for-Parents.aspx

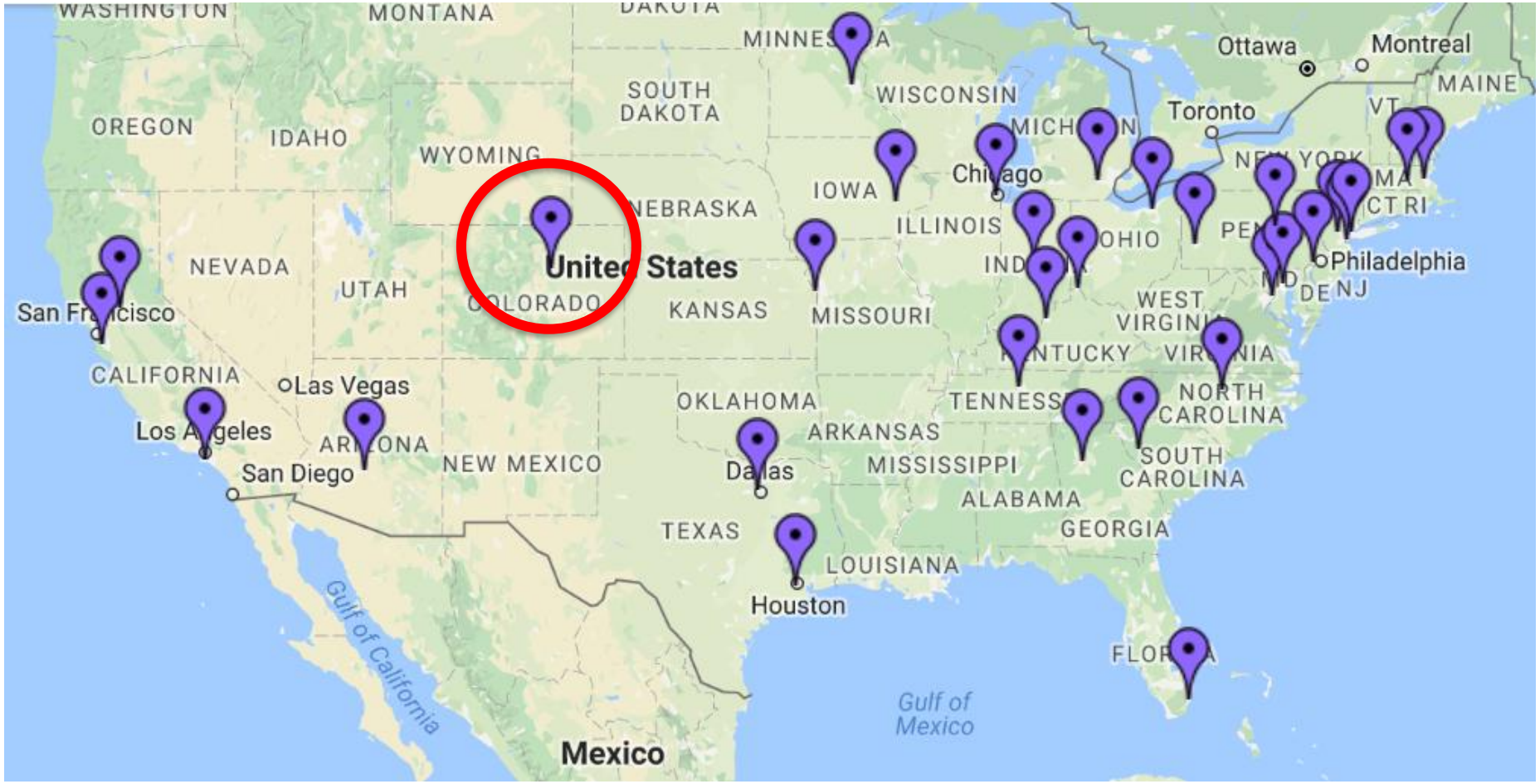
National Fragile X Foundation
https://fragilex.org/

Fragile X Syndrome Treatment and Intervention Recommendations
https://fragilex.org/our-research/treatment-recommendations/

Fragile X Clinics
https://fragilex.org/our-research/fragile-x-clinics/

Centers for Disease Control and Prevention: Fragile X Syndrome Resources
https://www.cdc.gov/ncbddd/fxs/index.html

Fragile X Clinics



FRAGILE X CLINICAL & RESEARCH CONSORTIUM

CDC-Funded
Natural History Study

FORWARD MARCH
MULTIPLE ASSESSMENTS FOR RESEARCH CHARACTERIZATION

Thank you!