

OUR
FRAGILE 
WORLD

Fragile X Update - 2011

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My fragile X story



- 1986 Wife's uncle diagnosed FXS
- 1988 Daughter diagnosed FXS
- 1993 Began FX research
 - Longitudinal studies of early development
 - Longitudinal studies of family adaptation
 - National (U.S.) FX survey
 - FX newborn screening study
- 2006 – 2010 National Fragile X Foundation
 - Scientific and Clinical Advisory Committee
 - President, Board of Directors

Goals for Today

- Brief reminder of the biology and inheritance of fragile X syndrome and FX-Associated Disorders
- Provide updates on several topics:
 - How FX affects behavior and functioning
 - Recent findings on carrier effects
 - New medications & implications
 - Family and life circumstances

Genes are made up of DNA,
which carries instructions for
making proteins.

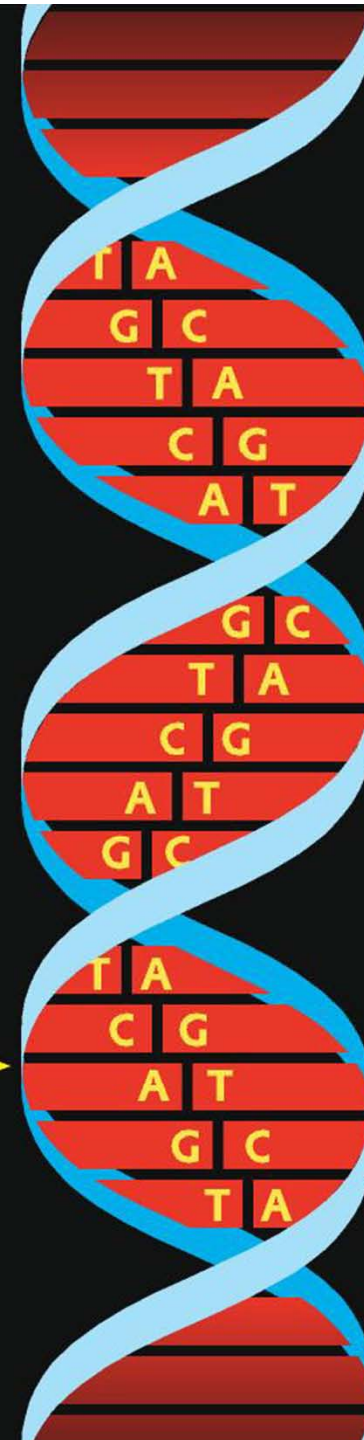
DNA consists of a linked
string of four types of
nucleotides:

- Adenine (A)
- Guanine (G)
- Thymine (T)
- Cytosine (C)

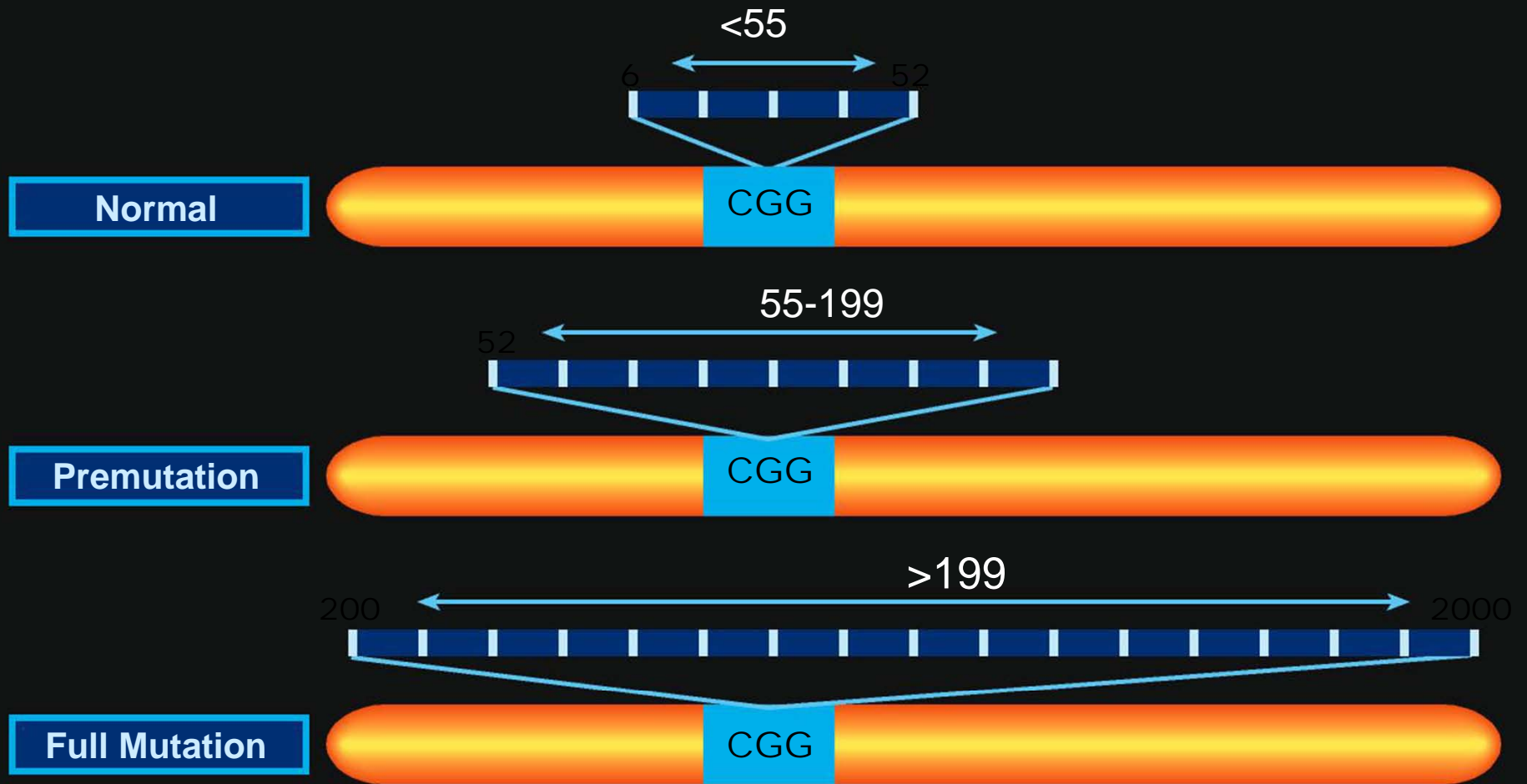
... arranged in a double helix



The order of these
nucleotides conveys
essential genetic information.



In Fragile X Syndrome there is an expansion of the CGG Trinucleotide repeats



The effect of this expanded trinucleotide repeat is a reduction or elimination of the FMR1 protein.

FX affects a wide range of function

Functional skills

Developmental trajectories

Memory

Executive function

Attention

Response inhibition

ADHD

Nonverbal IQ

Adaptive behavior

Self-injury

Problem behavior

Arousal

Autism

Mood and anxiety

Sensory-motor

Academic skills

Classroom behavior

Obesity

Seizures

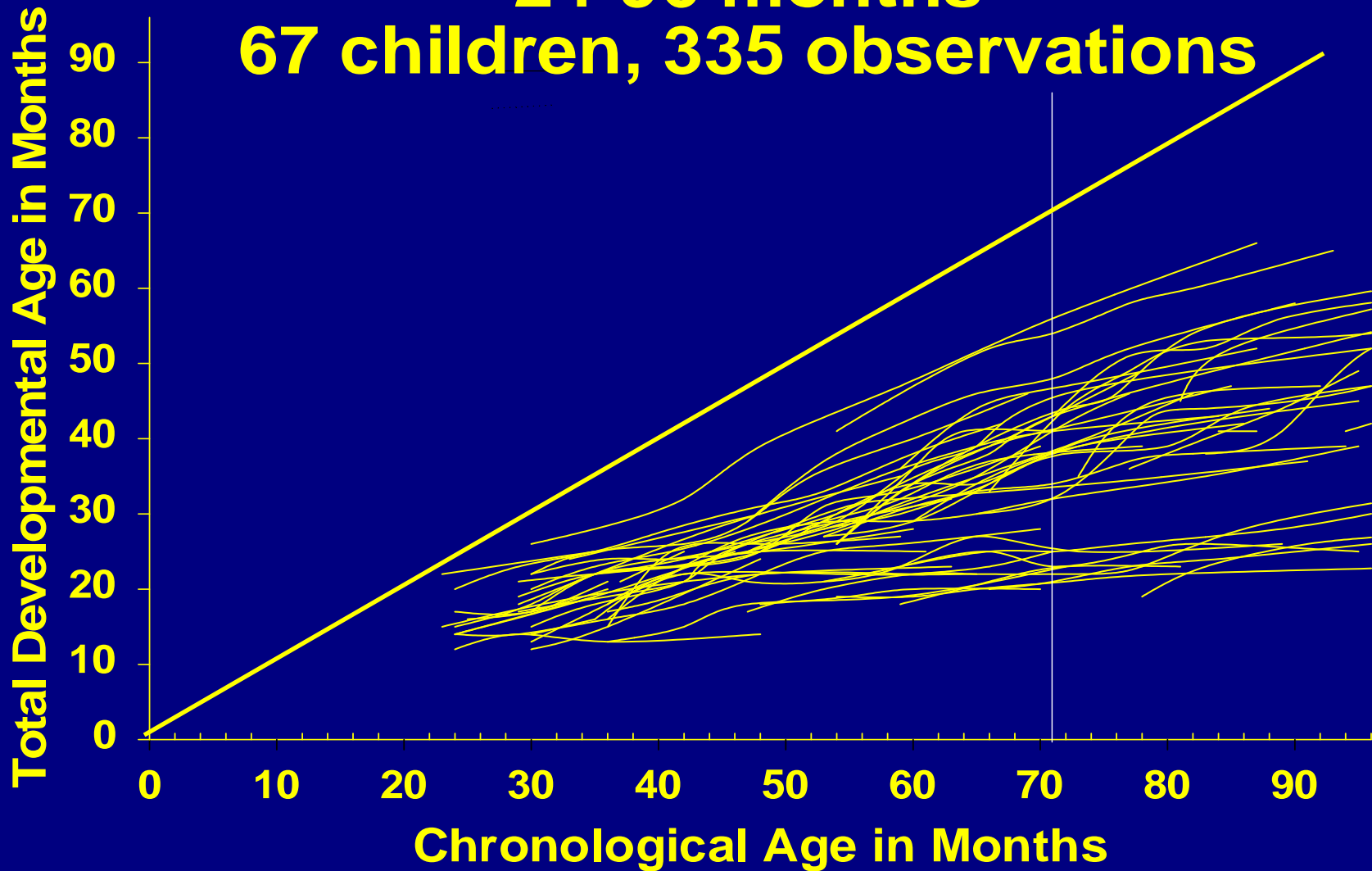
Sleep problems

Temperament

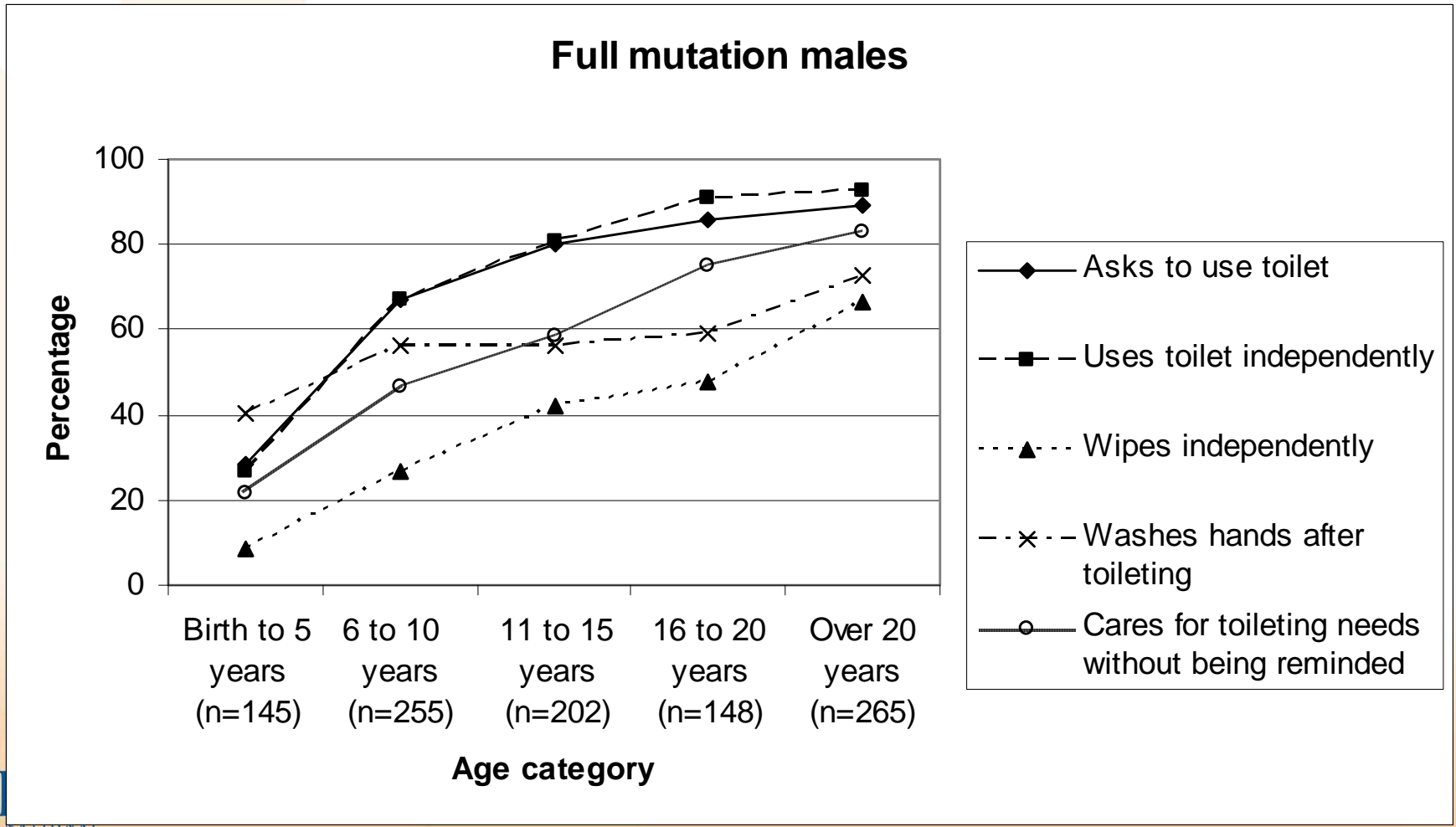
Behavioral style

Adult life

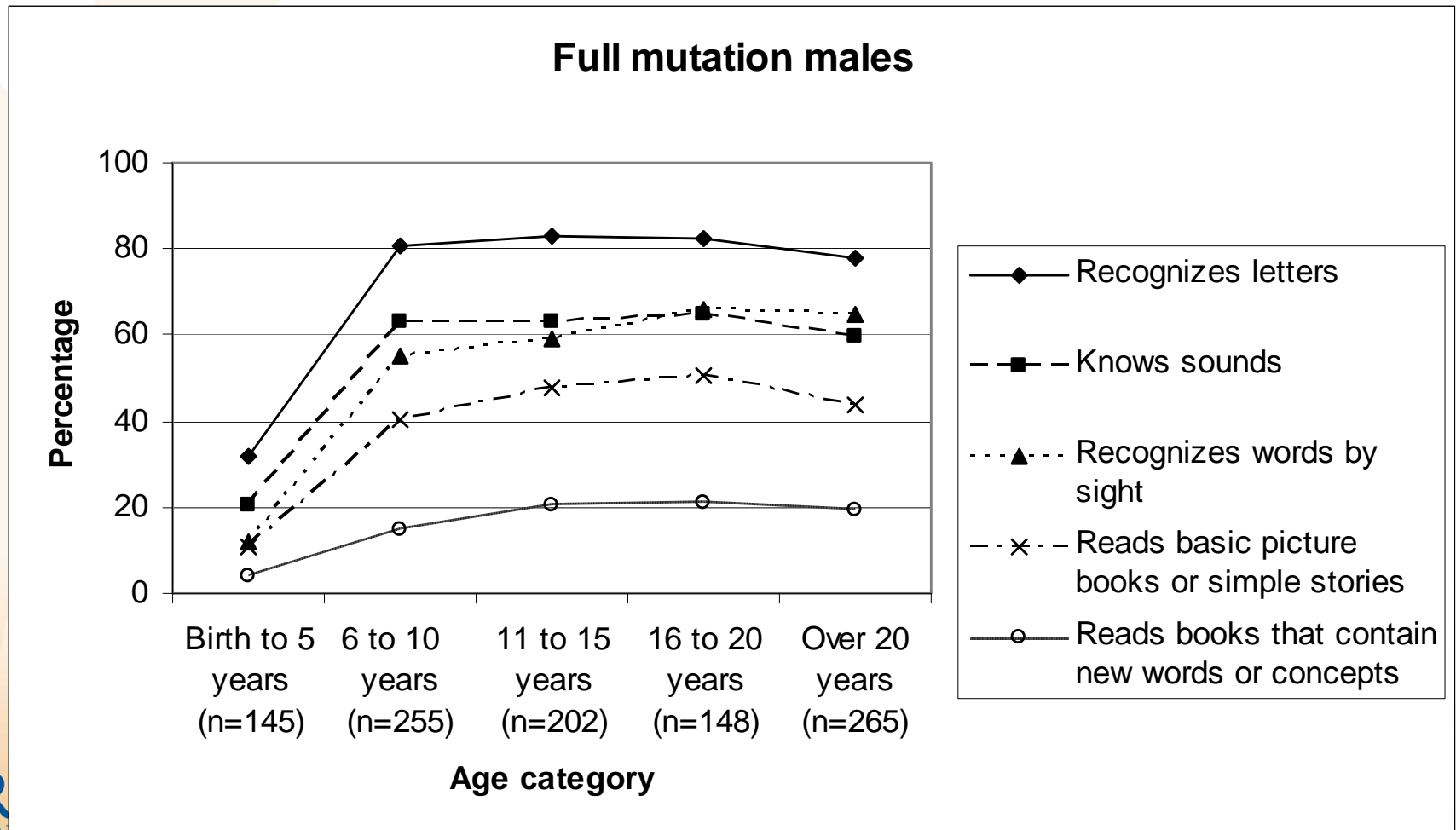
BDI Observed Scores 24-96 months 67 children, 335 observations



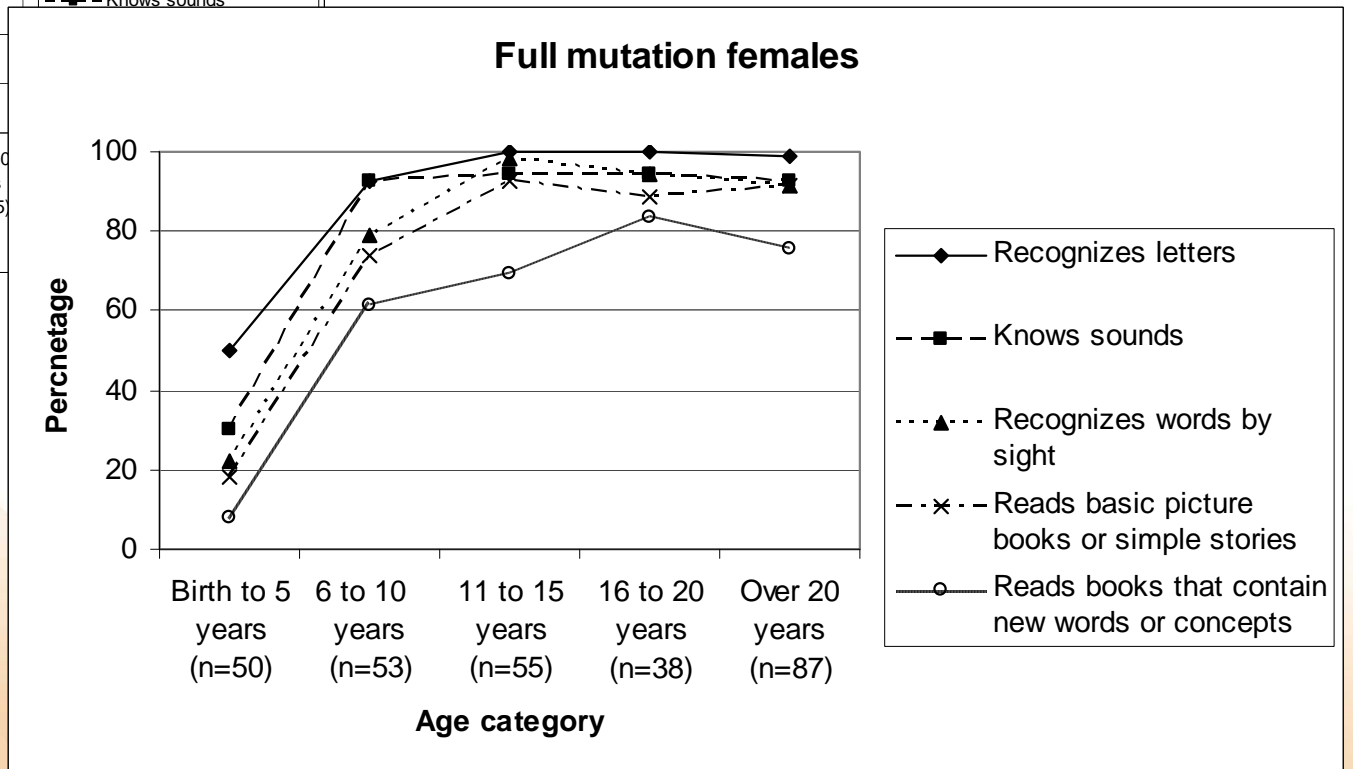
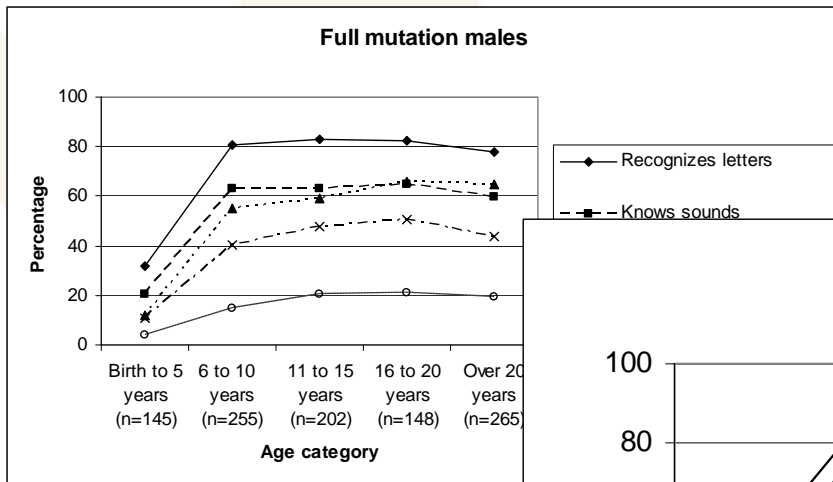
Toileting Skills



Functional Reading Skills



Functional Reading Skills (Females)



Recent Developments in Understanding FXS

- Research over the past 7 years has provided important insights into the core mechanisms that are affected by FXS
- This means that medications can be developed to target these core mechanisms rather than the symptoms of FXS
- Animal research has been VERY promising

FXS results in exaggerated mGluR receptor activation



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Rescue of behavioral phenotype and neuronal protrusion morphology in *Fmr1* KO mice

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CLINICAL IMPLICATIONS OF BASIC RESEARCH *Paul J. Lombroso, M.D., Marilee P. Ogren, Ph.D.*

Assistant Editors

Reversing the Effects of Fragile X Syndrome

MARILEE P. OGREN, PH.D., AND PAUL J. LOMBROSO, M.D.

Implications of New Medications for Families

- The animal research has led to high hopes for treatment efficacy in humans
- But, it is unlikely that these drugs will “reverse” or “rescue” FXS in humans
- The enormous range of effects in FXS will make it challenging to find one drug that fits all
- Almost certainly a combination of medications will be required
- Hopefully medication will treat major symptoms (anxiety, attention problems) and make learning easier
- “Who wants the ‘cure’?” has become an interesting topic of discussion!

But now we know that FX more complicated – leading to the term “FX-Associated Disorders”

- FX-Primary Ovarian Insufficiency (POI)
- FX Tremor Ataxia Syndrome (FXTAS)
- Other effects on carriers?



Ever Diagnosed or Treated for....

	Full Mutation Males (n = 1,167)	Full Mutation Females (n = 323)	•Premutation Males •(n = 65)	Premutation Females (n = 211)
Attention problems	78	62	43	14
Hyperactivity	60	29	28	4
Aggressiveness	35	13	17	5
Self-injurious behavior	38	11	8	4
Autism	43	16	17	1
Seizures	16	6	8	1
Anxiety	63	51	32	30
Depression	10	19	12	27
Developmental Delay	95	65	32	6

Many Aspects of FX Complicate Things for Families

- Getting a diagnosis remains a challenge
- Since FXS is inherited, identifying a child means that a parent is a carrier
- Other family members may have FXS or be carriers
- Different family members may be affected by FX in different ways
- FXS can affect family dynamics and communication, in positive or challenging ways

Challenges faced by families with FX

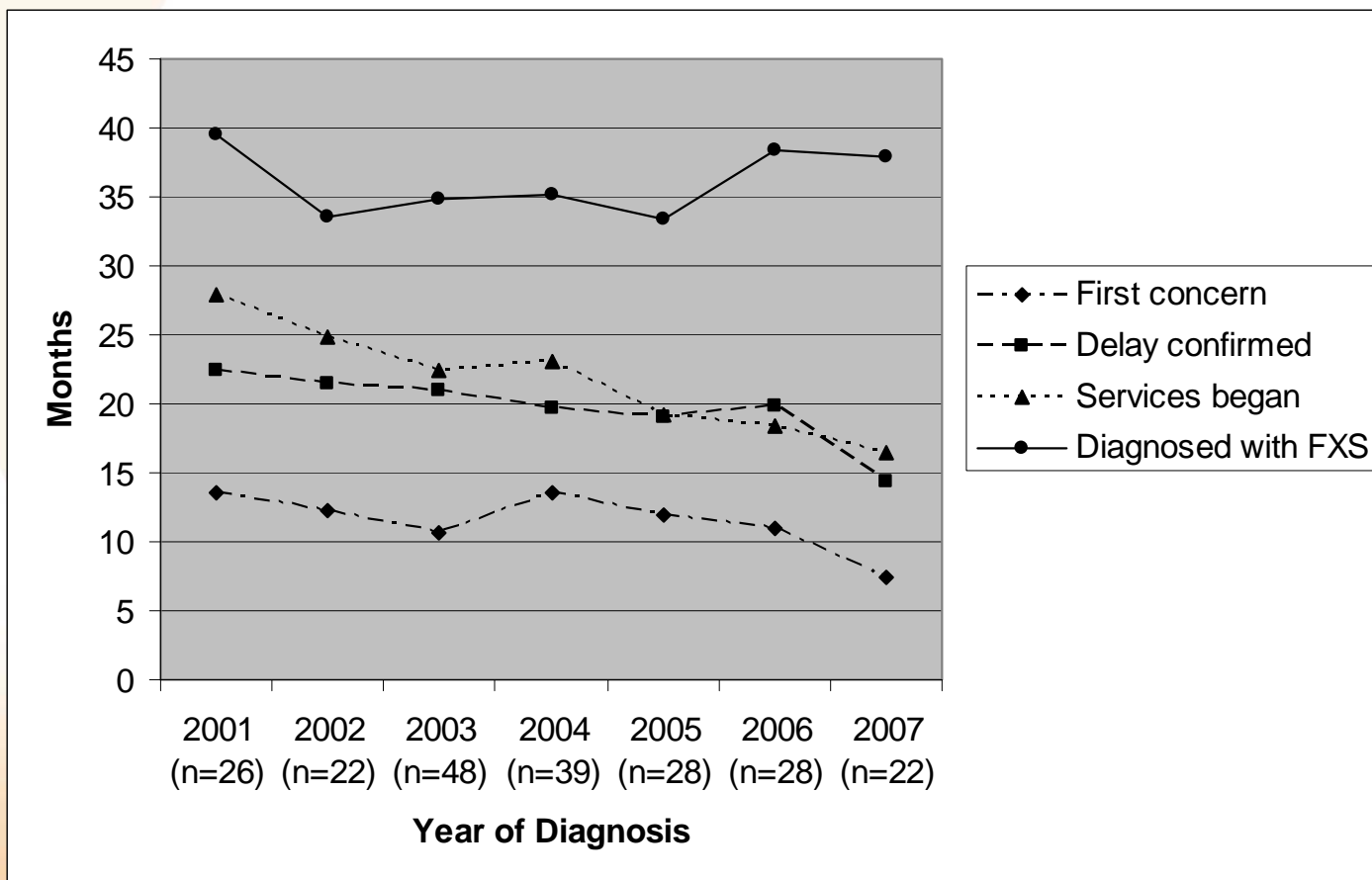
“Normal” Challenges

- Diagnostic odyssey
- Understanding child’s condition
- Dealing with learning and behavior problems
- Finding appropriate services
- Support from family and friends
- Ultimate skill attainment
- Life-long planning

“Unique” Challenges

- Informing extended family
- Future reproductive decisions
- Whether and when to test other children
- What and when to tell carrier children
- Dealing with carrier consequences
- Multiple affected children

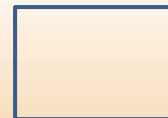
No Change in Age of Diagnosis



Options for earlier identification of FXS

- Systematic developmental screening of all infants in the context of pediatric practice
- FX genetic testing of all children with developmental delays
- Newborn screening
- Prenatal screening
- Preconception carrier screening

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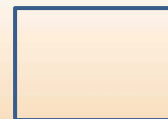
He seems
very fussy

My doctor keeps
saying he is OK

He should be
talking now

Maybe I'm doing
something
wrong...

Something is not
right



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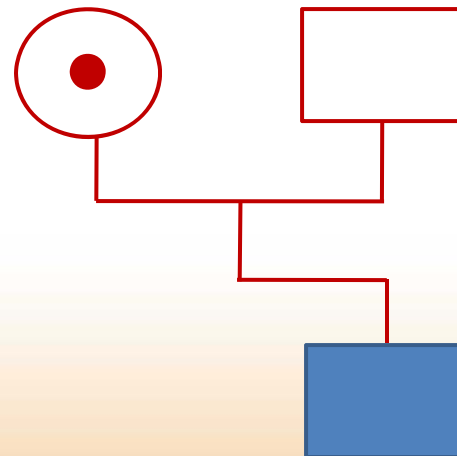
Is there a
cure?

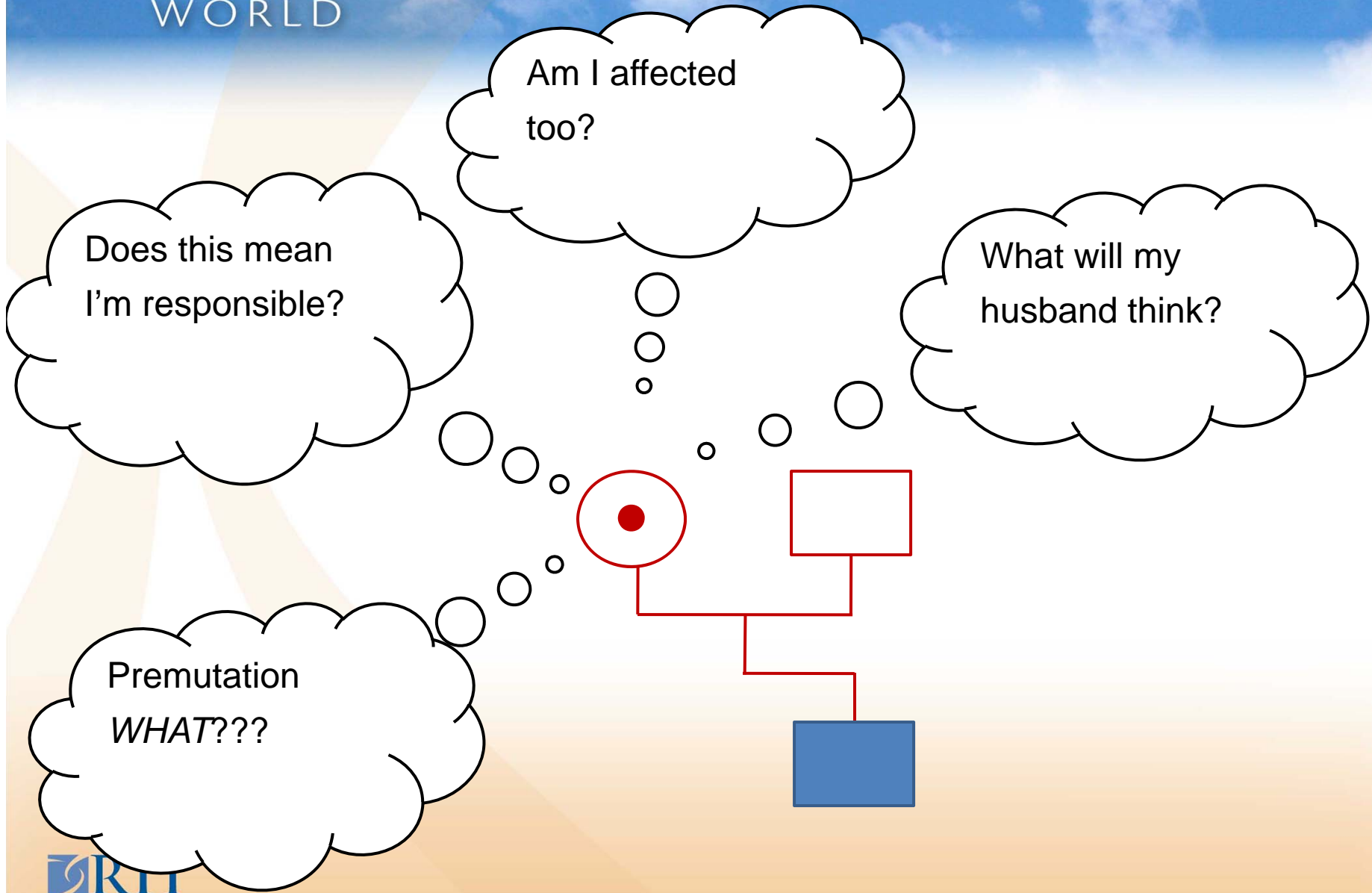
Will he always
be like this?

Why him?
Why me?
Why us?

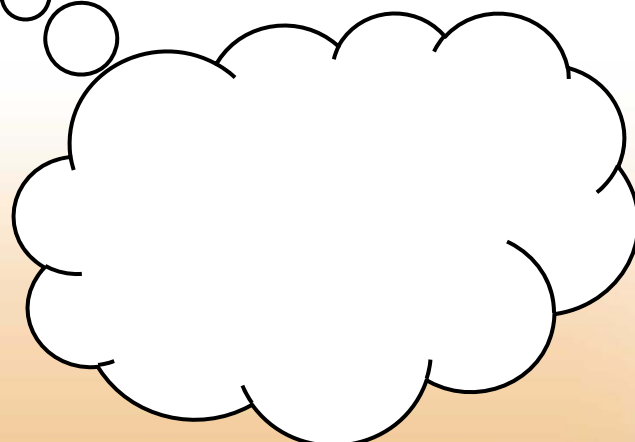
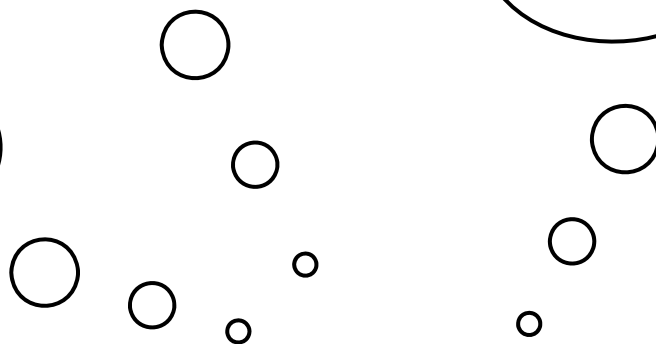
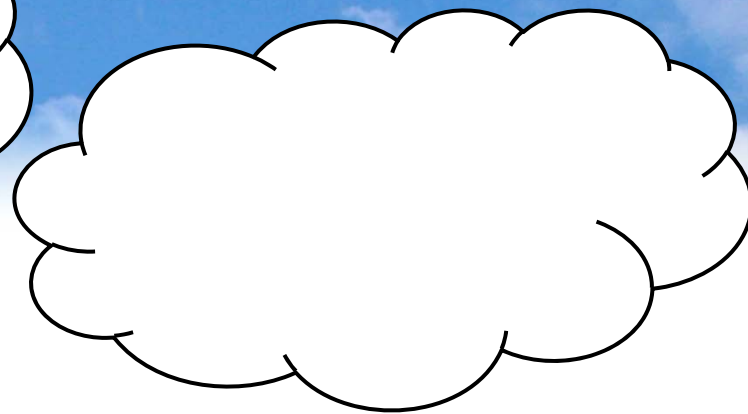
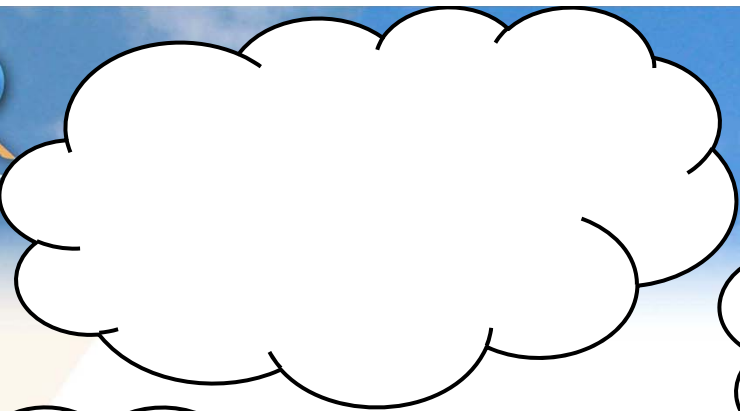
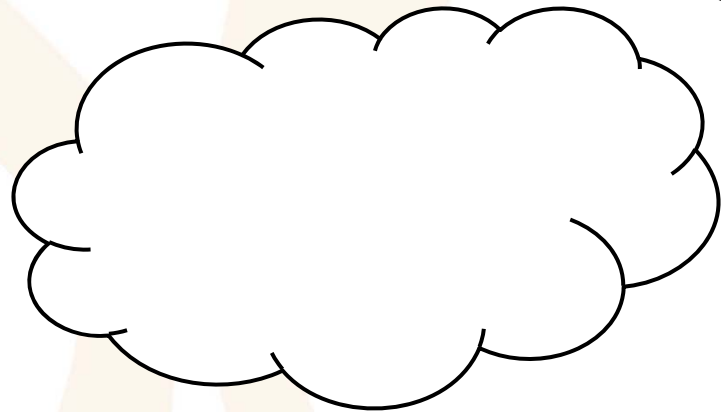
Fragile
WHAT???

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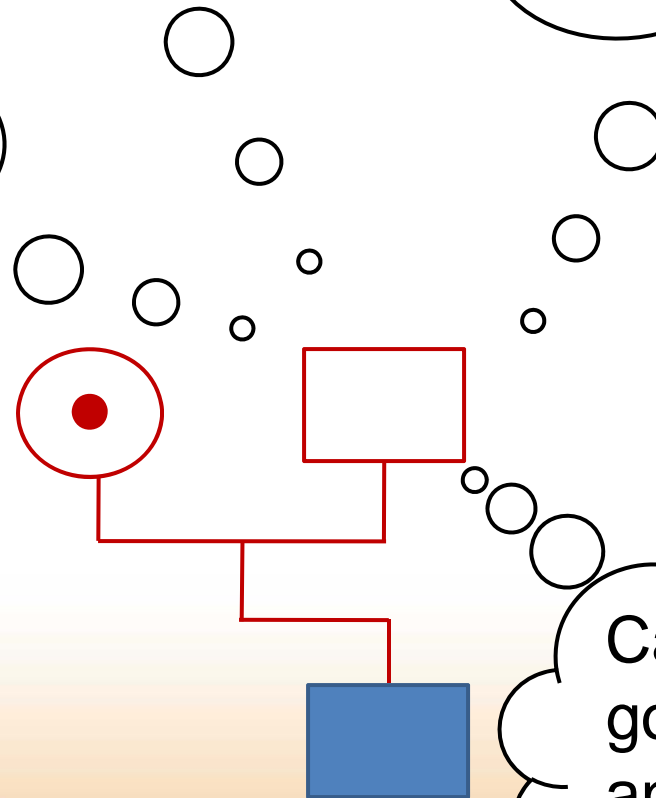




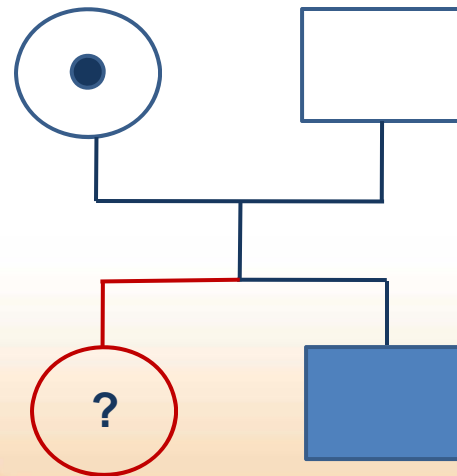
Will he ever
play baseball?

What will the
other guys or my
boss think?

I think our
lives are going
to change



Can I be a
good father
and
husband?

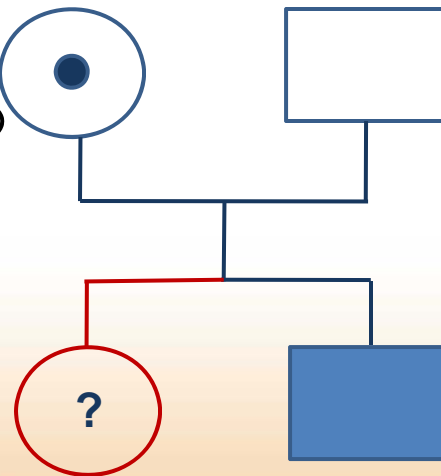




Should we have her tested?

You mean our daughter could have it? She looks so normal!

When? Why?
What good would it do?



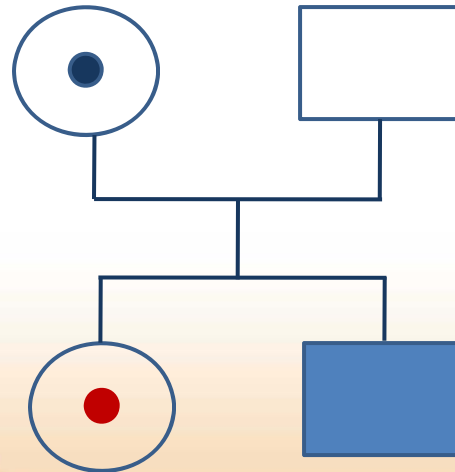


Do we want other people to know?

When and how should we tell her?

Will she have POI?

What does this mean for her?

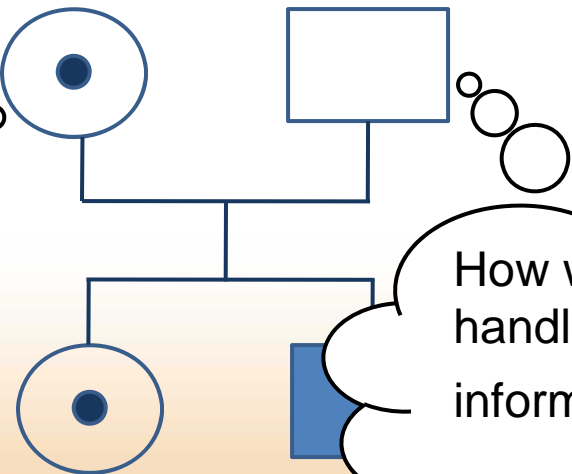




Could grandpa have FXTAS?

What good would it do?

Should my parents be tested?

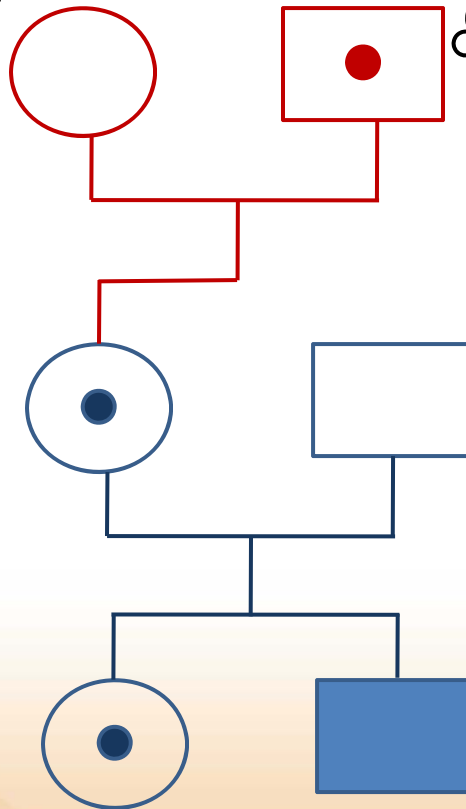


How would they handle the information?

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What are genes?
What is DNA?

You mean its my fault
that my grandson has
this?



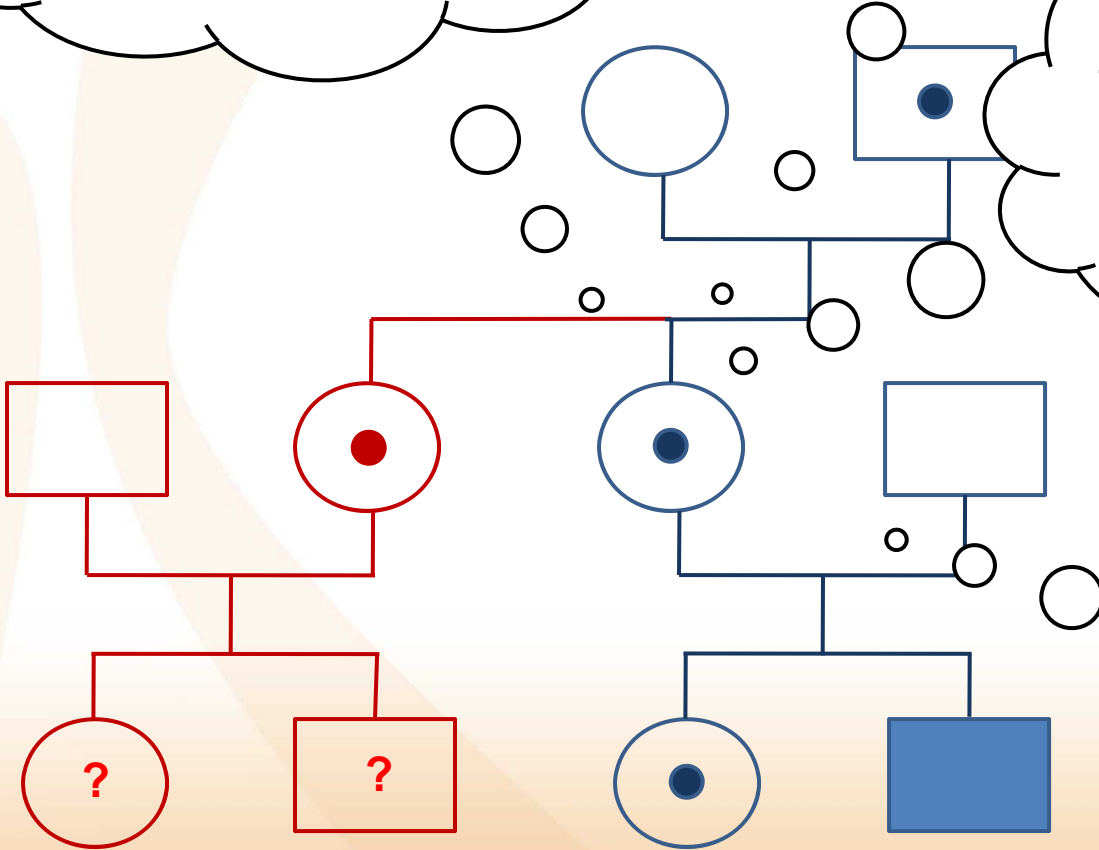
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Dad is a carrier, so my sister HAS to be a carrier

Who will tell her?

She's a new mom - how will she handle it?

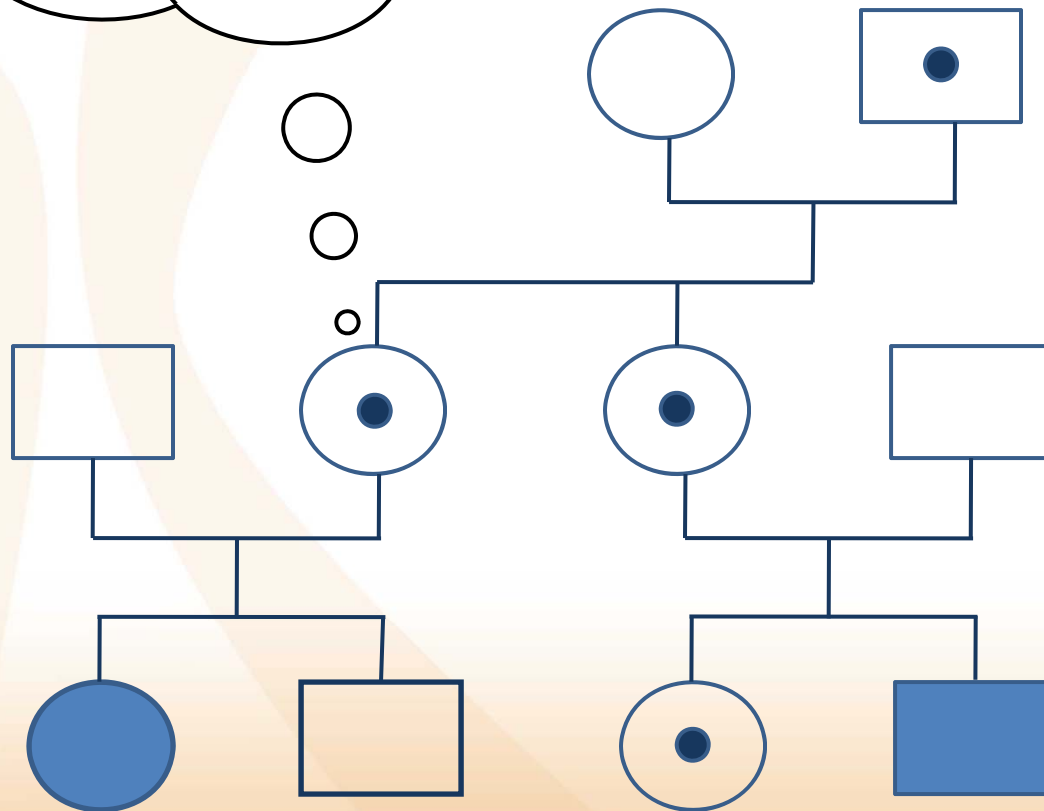


What about her children?

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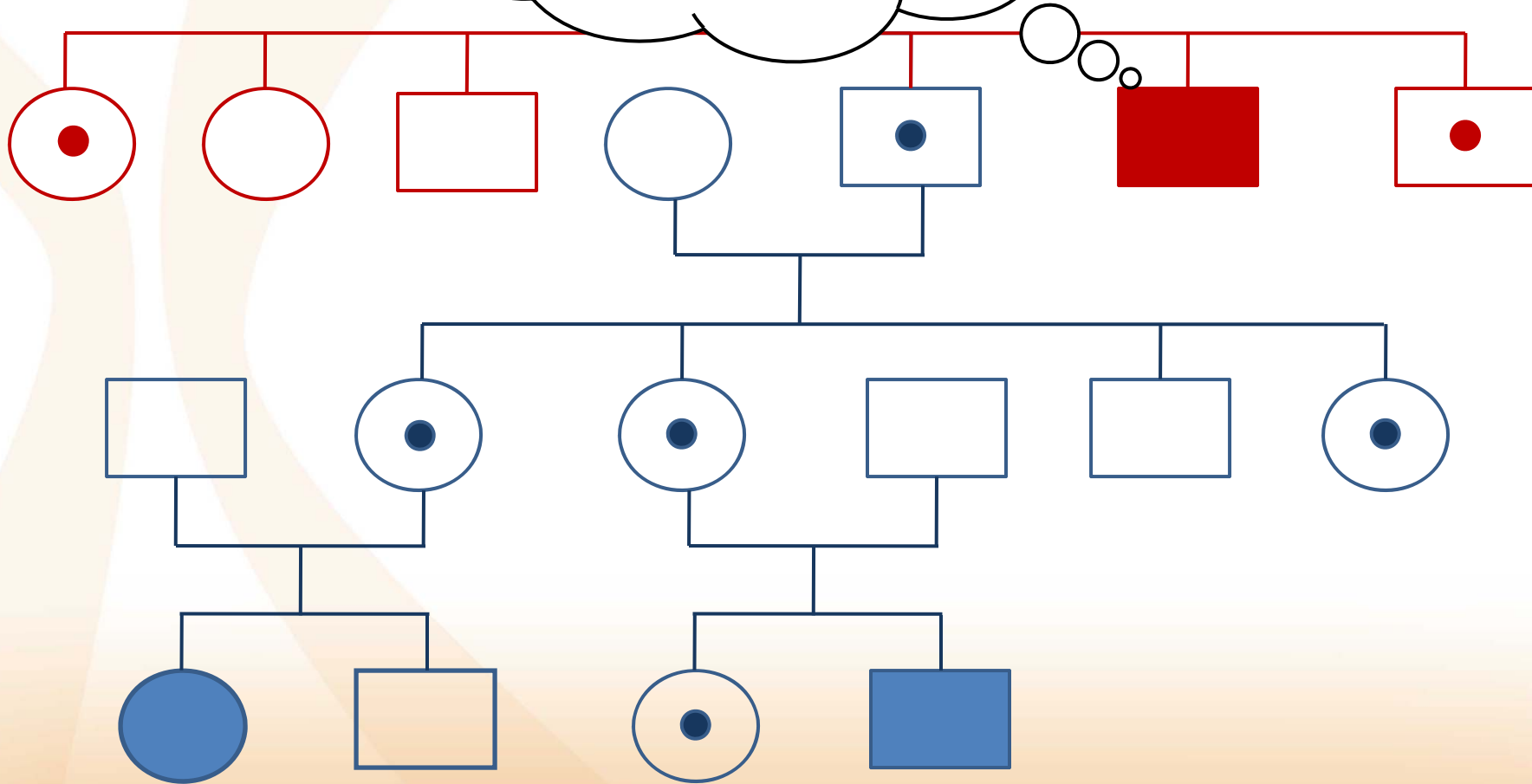


My newborn has
fragile X.... I had no
idea....



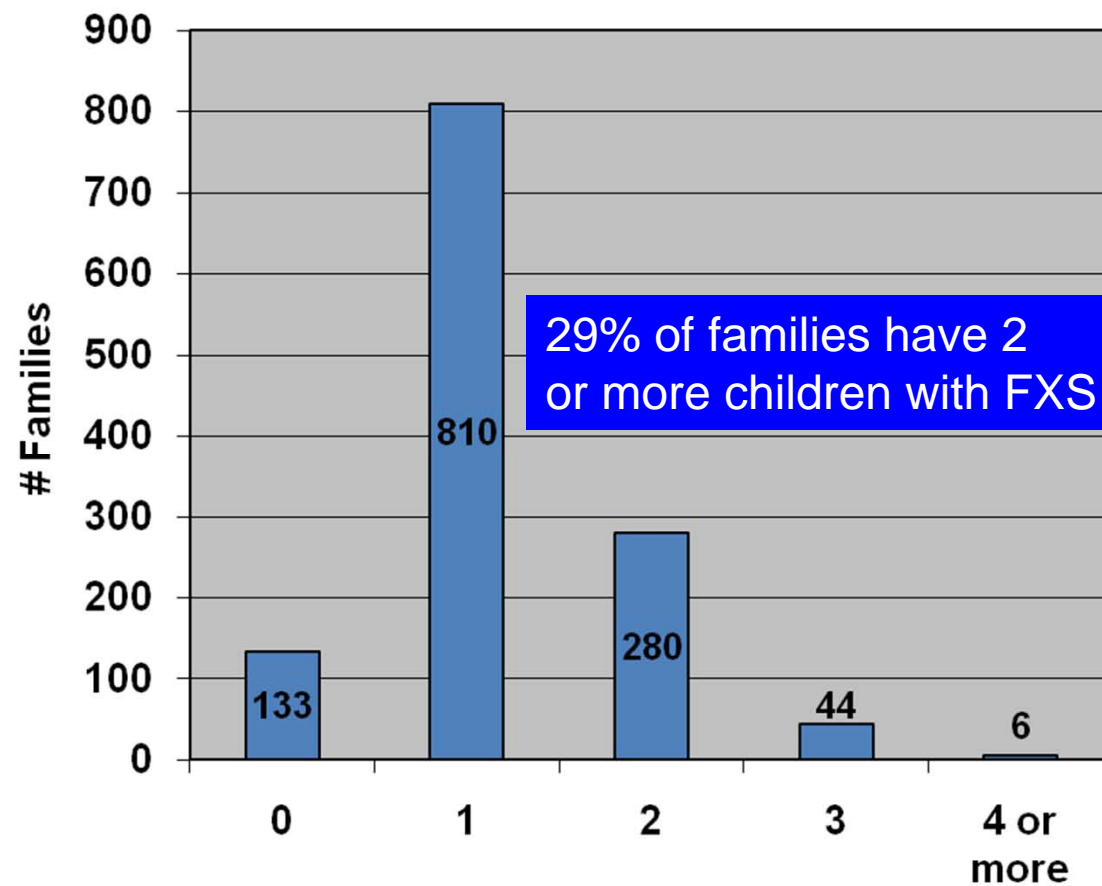


This explains Uncle Joe...





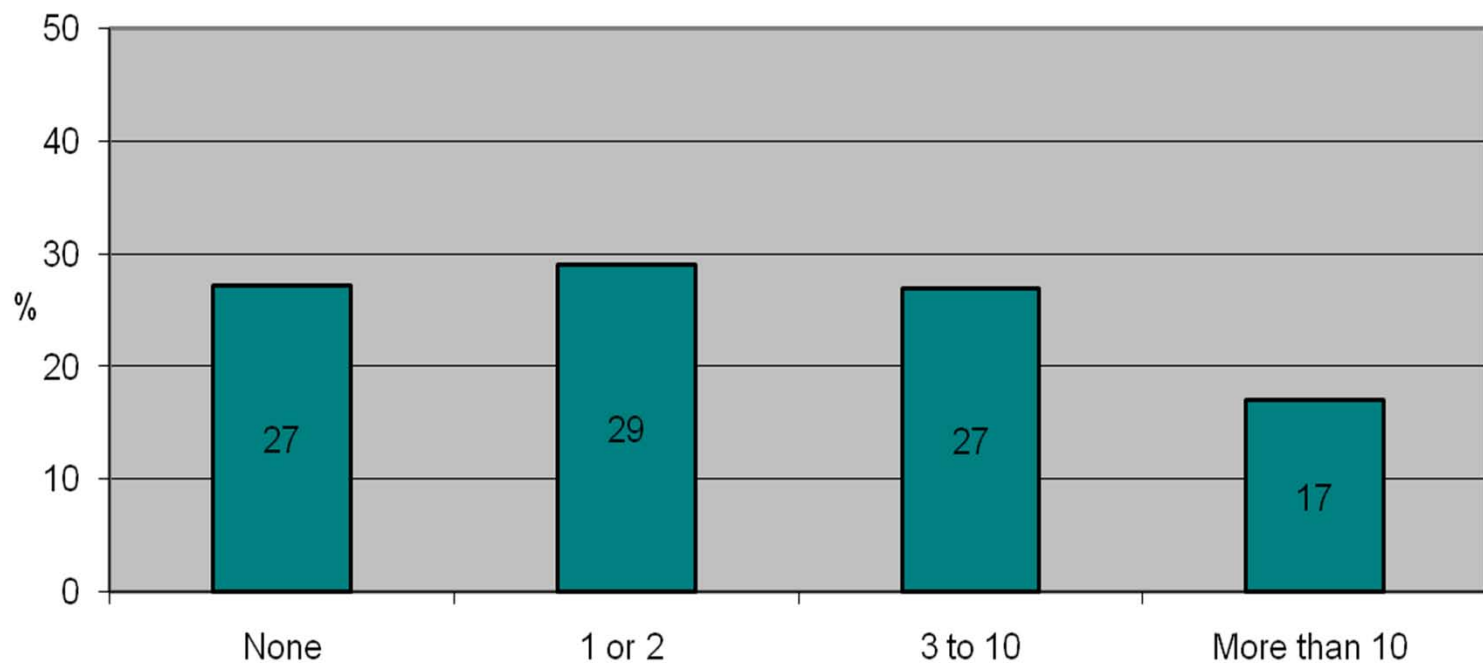
Many families have more than one child with FXS





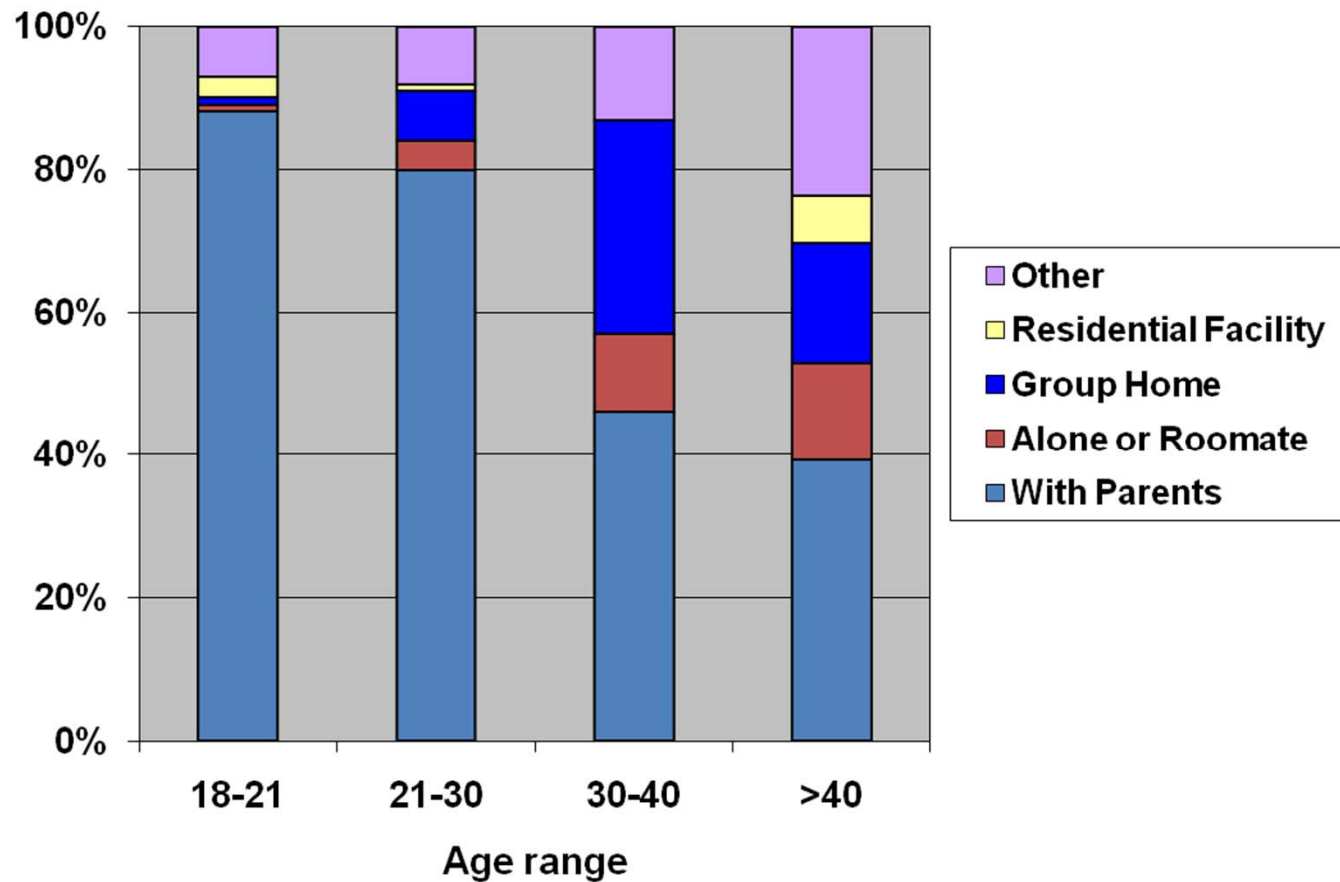
Family Support

How many families do you know that have a child with FX, not including relatives (n=1074)?



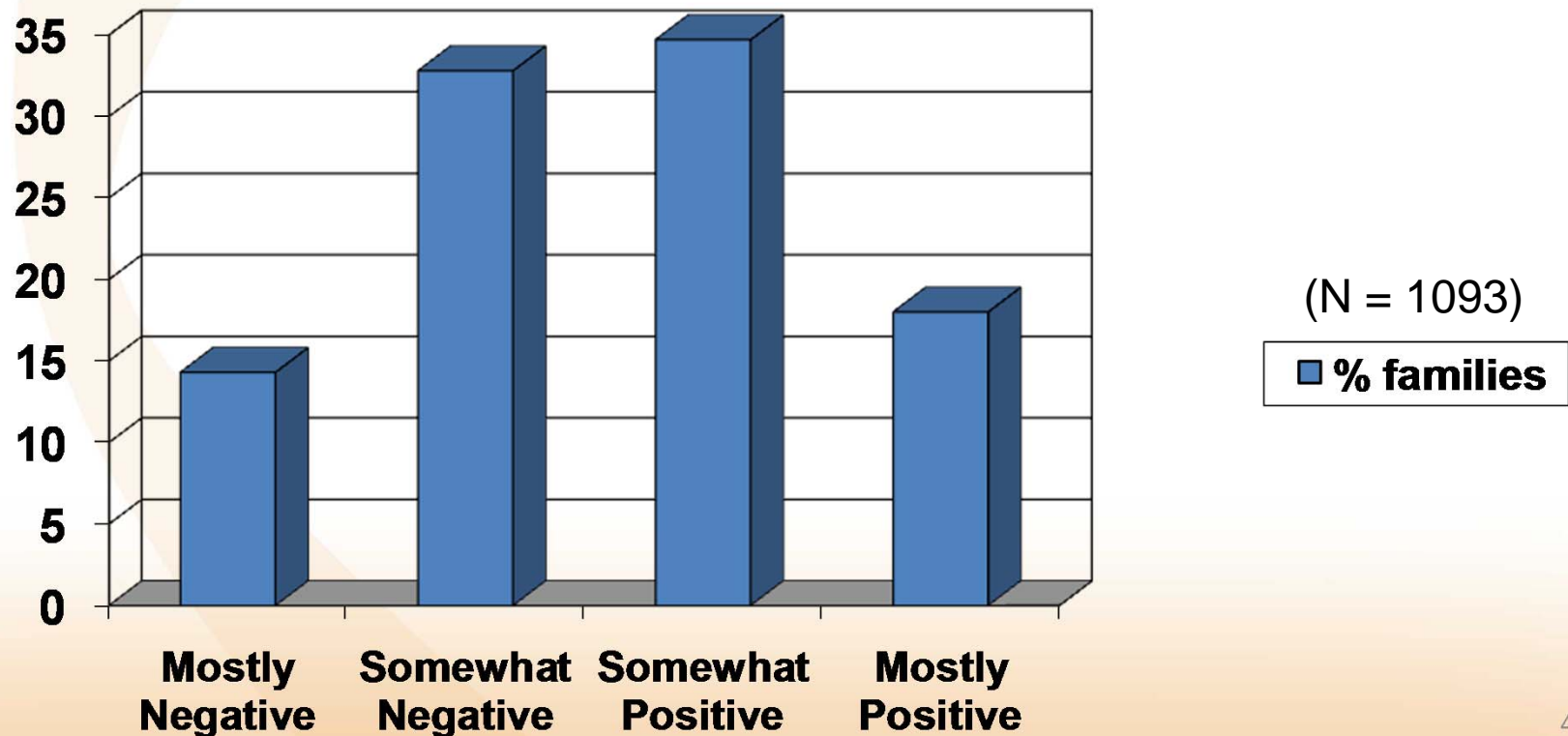


For many parents of children with FXS, parenting is a lifelong journey – e.g., where do adults with FX live?





Overall, thinking about the impact of FX on your family, has it been....



Concluding Thoughts

- Fragile X is a complicated condition, both at the biological level and at the level of lives lived
- The range of effects is enormous, both for individuals and families
- Prospects for early identification and better treatments make this an exciting time
- In the meantime, families still need to get up in the morning and live “the fragile X life”