CLINICAL PROFILES OF CHILDREN WITH FXS+ASD

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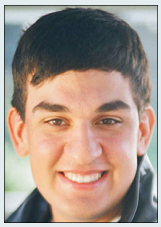
AGENDA FOR TODAY

- Describe FXS and genetic implications
- Gender Differences
- FXS group characteristics
- FXS+ASD
  - Diagnostic considerations
  - Language characteristics for FXS-Only and FXS +ASD

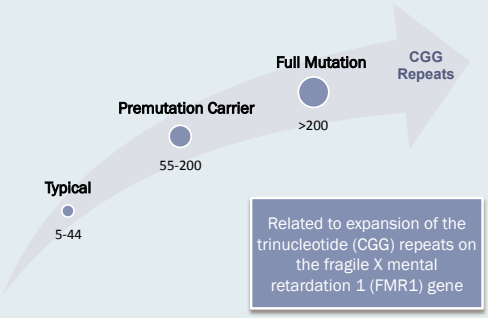
WHAT IS FRAGILE X SYNDROME (FXS)?

FXS

- Leading inherited cause of intellectual disability
- Males 1 in 2,500; females 1 in 6,000
- Mutation of FMR1 gene on X chromosome

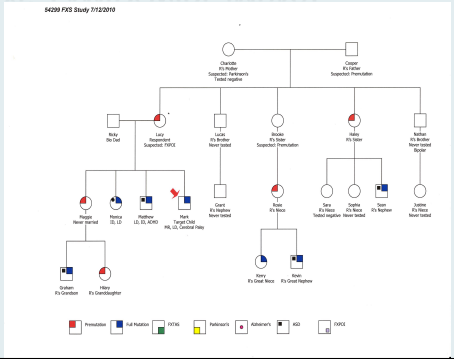


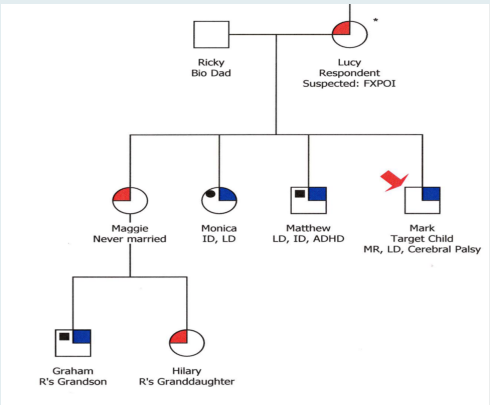
GENETIC IMPACT



Related to expansion of the trinucleotide (CGG) repeats on the fragile X mental retardation 1 (FMR1) gene

FXS: FAMILY-WIDE IMPACT





GENETIC IMPLICATIONS (McConkie-Rosell et al., 2005)

FEMALE CARRIERS	MALE CARRIERS
× Premutation: + 50% risk of passing to affected X to son or daughter + Gene could pass in premutation form or expand to full mutation × Full Mutation: + 50% risk with each pregnancy to pass the full mutation to son or daughter + Rare cases of passing decreased numbers of the repeat	× Premutation: + All daughters will be premutation carriers + No sons will inherit the mutation × Full Mutation: + Some rare reports of fathers with full mutation passing full mutation to daughters + No sons will inherit the mutation

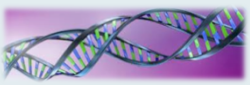
FXS TESTING GUIDELINES

American College of Medical Genetics' Policy Statement on FXS

- Individuals with intellectual disability, developmental delay, or autism
- Individuals with a family history of FXS or undiagnosed ID who are seeking reproductive counseling
- Prenatal testing of individuals who are known premutation carriers
- Women with reproductive or fertility problems especially if there is a family history of POF, FXS, or undiagnosed ID
- Individuals with late onset tremor or cerebellar ataxia especially if there is a family history of movement disorders, FXS, or undiagnosed ID

PRENATAL SCREENING FOR FXS (YARON ET AL., 2012)

- Detection rate almost 100%; false-positive rate < 0.5%
- Original Southern blotting tests expensive; newer molecular tests much less expensive
- Counseling is complicated by potential health consequences for maternal and fetal carriers



FXS TESTING IN YOUNG CHILDREN

- Few readily identifiable physical characteristics at birth
- Often not detected until delays in development are significant enough to prompt genetic testing
- May go undiagnosed or misdiagnosed

FRAGILE X RELATED DISORDERS

Associated Conditions

- **Language impairment**
- **Cognitive delay**
- **Autism spectrum disorder (30-70%)**
- Middle ear infection
- Gross and fine motor delay
- Seizures (20%)
- Hyperactivity and ADHD (80% males; 30% females)
- Anxiety
- Premature ovarian failure**
- Fragile X-associated tremor/ataxia syndrome (FXTAS)**

GENDER DIFFERENCES

- Females with FXS are typically less impaired than males
- Most males with FXS have moderate to severe intellectual disability; 1/3 of females with full mutation have mild to moderate delays
- Females may exhibit more anxiety and depression
- Females may by identified as having a learning disability

COGNITIVE DEVELOPMENT

- Males typically have IQs in the moderate to severe range of intellectual disability
- Delays/impairments related to language learning:
  - Sequential processing
  - Working memory
    - Auditory and visual-spatial

COGNITIVE DEVELOPMENT

- Significant problems with attention
  - Sustained attention
  - Inhibitory control
- High rate of FXS and ADHD co-morbidity
  - 80% of males
  - 30% of females

DEFINING ASD

DSM-V criteria:

1. Deficits in Social Communication/ Interaction
2. Restricted/repetitive behaviors and interests

Autism Spectrum Disorders

DEFICITS IN SOCIAL COMMUNICATION/ INTERACTION

- 1) Problems reciprocating social or emotional interaction, including difficulty establishing or maintaining back-and-forth conversations and interactions, inability to initiate an interaction, and problems with shared attention or sharing of emotions and interests with others.
- 2) Severe problems maintaining relationships — ranges from lack of interest in other people to difficulties in pretend play and engaging in age-appropriate social activities, and problems adjusting to different social expectations.
- 3) Nonverbal communication problems such as abnormal eye contact, posture, facial expressions, tone of voice and gestures, as well as an inability to understand these.

RESTRICTED AND REPETITIVE BEHAVIORS

1. Stereotyped or repetitive speech, motor movements or use of objects
2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change
3. Highly restricted interests that are abnormal in intensity or focus
4. Hyper or hypo reactivity to sensory input or unusual interest in sensory aspects of the environment

Autism Spectrum Disorders

Severity Level for ASD	Social Communication	Restricted interests & repetitive behaviors
Level 3 'Requiring very substantial support'	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning; very limited initiation of social interactions and minimal response to social overtures from others.	Preoccupations, fixated rituals and/or repetitive behaviors markedly interfere with functioning in all spheres. Marked distress when rituals or routines are interrupted; very difficult to redirect from fixated interest or returns to it quickly.
Level 2 'Requiring substantial support'	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions and reduced or abnormal response to social overtures from others.	RRBs and/or preoccupations or fixated interests appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress or frustration is apparent when RRB's are interrupted; difficult to redirect from fixated interest.
Level 1 'Requiring support'	Without supports in place, deficits in social communication cause noticeable impairments. Has difficulty initiating social interactions and demonstrates clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions.	Rituals and repetitive behaviors (RRB's) cause significant interference with functioning in one or more contexts. Resists attempts by others to interrupt RRB's or to be redirected from fixated interest.

HOW IS ASD DIAGNOSED?

- **GOLD Standard:**
- Autism Diagnostic Observation Schedule 2nd edition (ADOS-2)
  - Observe social, communication and play in structured and semi-structured settings
- Autism Diagnostic Interview-Revised (ADI-R)
  - Provides severity score for communication, reciprocal social interaction, & restricted and repetitive behaviors
  - Used with verbal & nonverbal children
  - For children over 3 years of age

ADOS-2

Purpose:
Assess and diagnose ASD across ages, developmental levels, and language skills
Ages / Grade:
Toddlers to adults
Administration Time
30 to 60 minutes
Format:
Standardized behavioral observation and coding
Score: Cutoff scores for ASD and a severity score

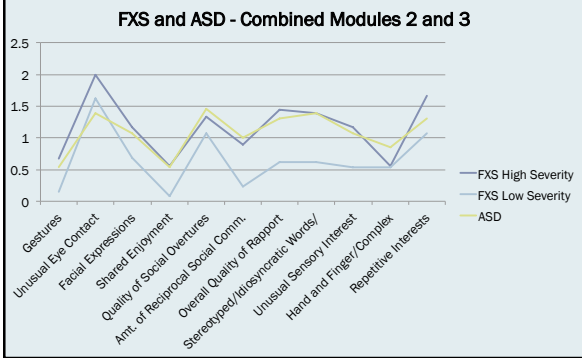
ADI-R

Purpose:
Useful for diagnosing ASD, planning treatment, and distinguishing ASD from other developmental disorders
Ages / Grade:
Children and adults with a mental age above 2.0 years
Administration Time
1 1/2 to 2 1/2 hours, including scoring
Format:
Standardized interview and response coding

RATES OF ASD IN FXS

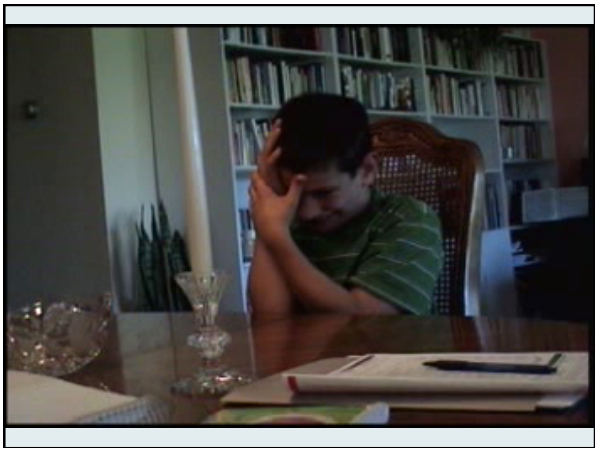
- Generally reported about 50%
- Clinical Rates:
  - Parents reported 46% of boys and 16% of females had received an ASD co-diagnosis
- Research Rates:
  - Studies using ADOS report 50-74% of males meet for ASD
  - Studies using ADOS and ADI-R together have found rates varying from 27-81% meet for ASD
  - Studies using the CARS report rates from 24-30%

HOW DO DIAGNOSTIC SYMPTOMS VARY?



FXS & ASD

- 50-90% reported to have symptoms concurrent with ASD regardless of diagnosis (Bailey et al., 1998; Feinstein & Reiss, 1998)
  - Lack of responsiveness
  - Poor eye contact
  - Perseverative speech
  - Self-agression (e.g., hand biting)
  - Abnormal body use (e.g., rocking, spinning, hand flapping)



IS IT ASD?

- Not "true ASD"
  - Abbeduto and colleagues argue ASD in FXS is not the same underlying psychological and neurobiological impairments (Abbeduto et al., 2014)
- Meaningful clinical group
  - Behaviors and symptoms more closely aligned with idiopathic ASD than FXS-Only (Budimirovic & Kaufmann, 2011; Hernandez et al., 2009)

EARLY LANGUAGE DEVELOPMENT IN FXS

- First indicators
  - Weak gesture use
  - Limited communication reciprocity
  - Poor play skills
  - Late emergence of first words

EARLY LANGUAGE DEVELOPMENT

- In a study 55 mothers of 18- to 36-month old children with FXS with and without ASD, 42 reported that their children were nonverbal or producing very few words (Brady et al., 2006)
  - 29 were nonverbal (average age 26 months)
  - 13 emerging verbal (average age 28 months)
  - 13 verbal (average age 34 months)

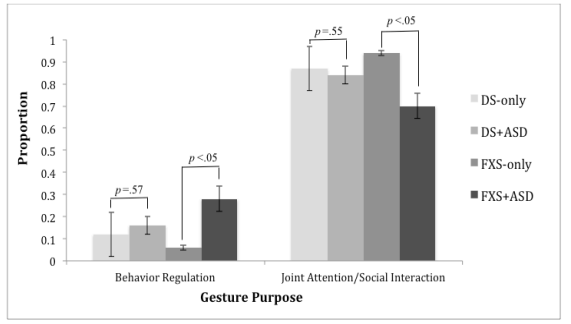
PRELINGUISTIC COMMUNICATION

- Joint attention
  - Based on CSBS scores with boys under the age of 8, relative strengths in:
    - Social affective signaling
    - Gaze shifts
    - Vocalizations and gestures used in conjunction
  - Weakness in:
    - Repair strategies
    - Positive affect

PRELINGUISTIC COMMUNICATION

- Gestures:
  - Weakness in:
    - Conventional gestures (e.g., pushing away)
    - Distal gestures (e.g., pointing at a distance)
    - Complex action schemes

LATER GESTURE DEVELOPMENT (LORANG & STERLING, IN PREP)



EARLY LEXICAL DEVELOPMENT IN FXS

- Delayed first spoken word
  - 28 months
- Delayed expressive language
  - One study reported development at approximately 1/3 rate of typical development
- Expressive more delayed than receptive

ORAL-MOTOR CHARACTERISTICS (HAGERMAN, 1996)

- Children with FXS have a number of oral-motor problems including:
  - High, narrow arched palate
  - Generalized hypotonia
  - Oral tactile defensiveness and drooling
  - Cleft palate reported in 5% of children with FXS

PHONOLOGICAL DEVELOPMENT

- Overall delayed development
- Early-, middle-, and later-developing consonants acquired in same sequence as typical development

Shriberg (1993) Developmental Sound Groups	
Early 8	/m/ /b/ /j/ /n/ /w/ /d/ /p/ /h/
Middle 8	/t/ /ŋ/ /k/ /g/ /f/ /v/ /tʃ/ /dʒ/
Late 8	/ʃ/ /θ/ /s/ /z/ /ð/ /l/ /ʒ/ /r/

LATER DEVELOPMENT

- Speech and language abilities continue to be significantly delayed.
- Speech and language abilities traditionally examined by comparing children and adolescents with FXS to:
  - Children and adolescents with Down syndrome
  - Younger children with typical language and cognitive development

VOCABULARY

- Some children with ASD have an atypical profile of better production than comprehension
- School-age boys with ASD and FXS+ASD
  - Compared PPVT and EVT: Co-normed Vocabulary assessments
  - 36% of boys with ASD had lower PPVT scores compared to EVT scores
  - 14% of boys with FXS+ASD had lower PPVT scores compared to EVT

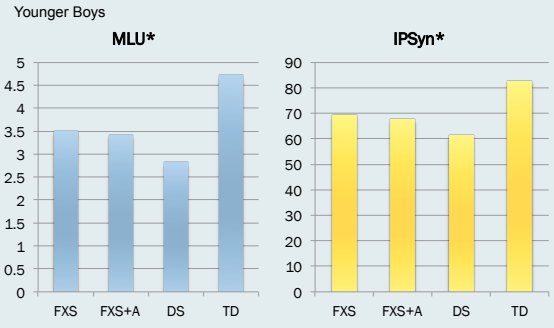
GRAMMATICAL DEVELOPMENT

- Delayed morphosyntax compared to nonverbal mental age matches
- Children use shorter, less complex utterances
  - Less complexity in noun and verb phrases (Price et al., 2008)

GRAMMATICAL DEVELOPMENT

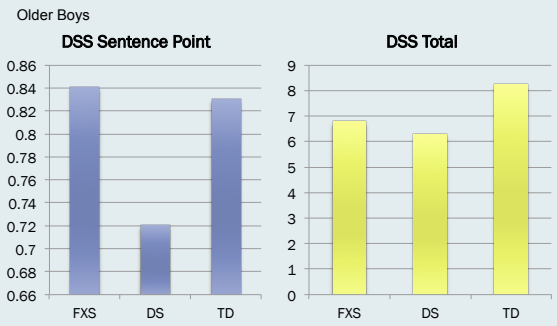
- Impact of ASD
  - Boys with FXS-only use questions and negations more than boys with FXS+ASD (Price et al., 2008)
- Impact of context
  - Grammatical use in conversation appears to be weaker than in narrative context

GRAMMATICAL COMPLEXITY (PRICE ET. AL. 2008)



*Controlling for Leiter-R mental age and maternal education

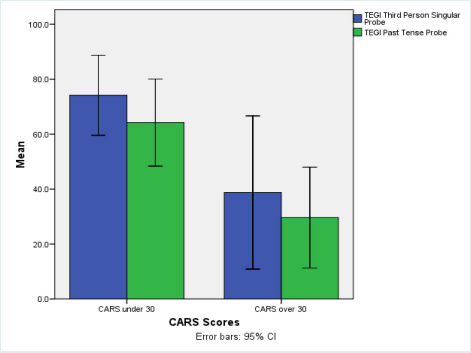
GRAMMATICAL COMPLEXITY (FINESTACK & ABBEDUTO, 2011)



GRAMMATICAL DEVELOPMENT (STERLING ET AL., 2009)

- Tense and agreement markers
  - Third person singular –s (e.g., paints, digs) and past tense (e.g., paint*ed*, d*ug*)
  - 26 boys with FXS between the ages of 8-16
  - Grouped by severity of autistic behaviors (CARS scores)
  - Test of Early Grammatical Impairment (TEGI: Rice & Wexler, 2001)

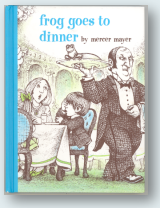
GRAMMATICAL DEVELOPMENT



NARRATIVE LANGUAGE

- Macrostructure Level (Keller-Bell & Abbeduto, 2007)
  - Density and diversity of Evaluation Devices
    - Character names
    - Character dialogues
    - Use of repetition
    - Onomatopoeia, sound effects
    - Fantasy or exaggeration
  - No different than younger TD children, but less than DS

NARRATIVE LANGUAGE



13-year-old boy

HOW DOES THE STORY START?

- AT FIRST HE'S GETTING DRESSED FOR DINNER.
- THE DOG IS ON THE CHAIR.
- PATTING HIS DOG.
- AND SAY GOODBYE TO HIS DOG AND THE TURTLE.
- AND HIS FROG WITH HIM TO DINNER.
- (GET) THEY GET THERE.
- HE GO TO THE RESTAURANT.
- THEY ORDER.
- THEY GO.
- AND THEN THEY GET THE MENUS AND STUFF LIKE THAT.
- THEY WALK IN THE RESTAURANT.

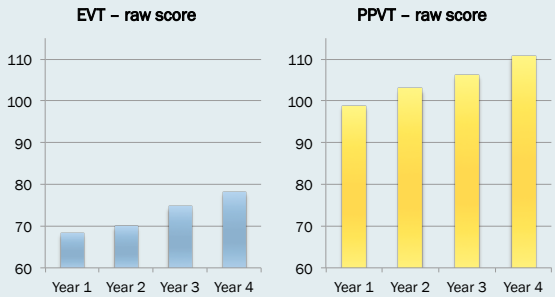
NARRATIVE LANGUAGE

16-year-old girl

HOW DOES THE STORY START?

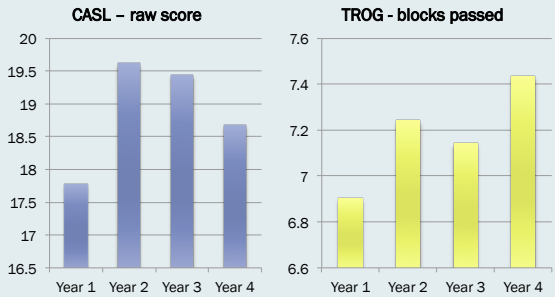
- AS GEORGE GETS READY FOR DINNER, HE TELLS HIS PET FROG THAT HE MUST STAY HOME BECAUSE IT'S SUCH A FANCY RESTAURANT.
- HE SAYS GOODBYE TO HIS DOG AND HIS TURTLE.
- BUT MEANWHILE HIS FROG JUMPS INTO HIS POCKET.
- HE SAYS SEE YOU LATER AS THE FROG WAVES BYE QUIETLY.
- GEORGE LOOKS AT THE SIGN AND TRYS TO READ WHAT IT SAYS.
- BUT HE CAN'T UNDERSTAND IT BECAUSE HE DOESN'T KNOW HOW TO READ IT.

LANGUAGE GROWTH – VOCABULARY



Boys and girls with FXS 10-16 years at Year 1
(Finestack & Abbeduto, in progress)

LANGUAGE GROWTH - GRAMMAR



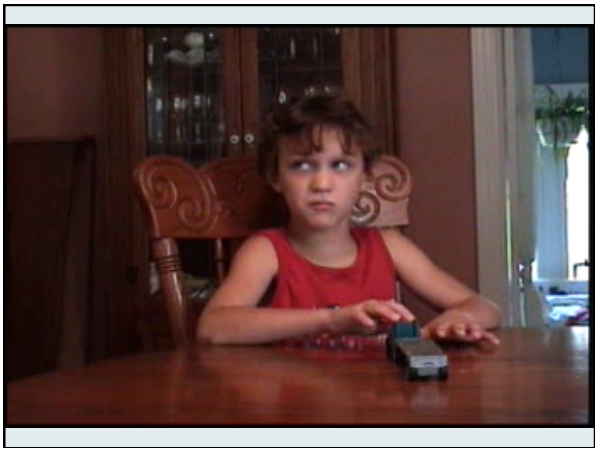
Boys and girls with FXS 10-16 years at Year 1
(Finestack & Abbeduto, in progress)

PRAGMATICS

- Perseverative/repetitive language argued to be a defining characteristic of FXS regardless of ASD co-diagnosis (Sudhalter et al., 1990)
  - Phoneme
  - Word
  - Phrase & Utterance
  - Topic
  - Conversational device repetitions (e.g., "that's a wrap,""right on")

PRAGMATICS

- Other difficulties in pragmatics:
  - Atypical turn-taking
  - Poor topic maintenance
  - Tangential language
  - Difficulty repairing communication breakdowns



PRAGMATICS (FREUND, REISS, & ABRAMS, 1993; LESNIAK-KARPIAK ET AL., 2003)

- Impact of Gender
  - Compared to unaffected females, girls with FXS have:
    - Difficulty initiating and sustaining conversation
    - Longer to initiate interactions
    - Parents report more social problems related to language

PRAGMATICS

- Impact of ASD
  - Boys with FXS-Autism
    - Greater use of tangential language compared to boys with FXS-only
    - More topic changes
    - Perseveration: same rates regardless of autism co-diagnosis

SPEECH INTELLIGIBILITY

- FXS associated with speech intelligibility problems
  - Rapid rate of speech
  - Decreased range and precision of tongue movements
  - Dysfluencies in speech
    - Associated with increases in anxiety

THANK YOU!

- Questions and comments?