University of Colorado
Denver | Anschutz Medical Campus

Children's Hospital Colorado

Triple X Syndrome

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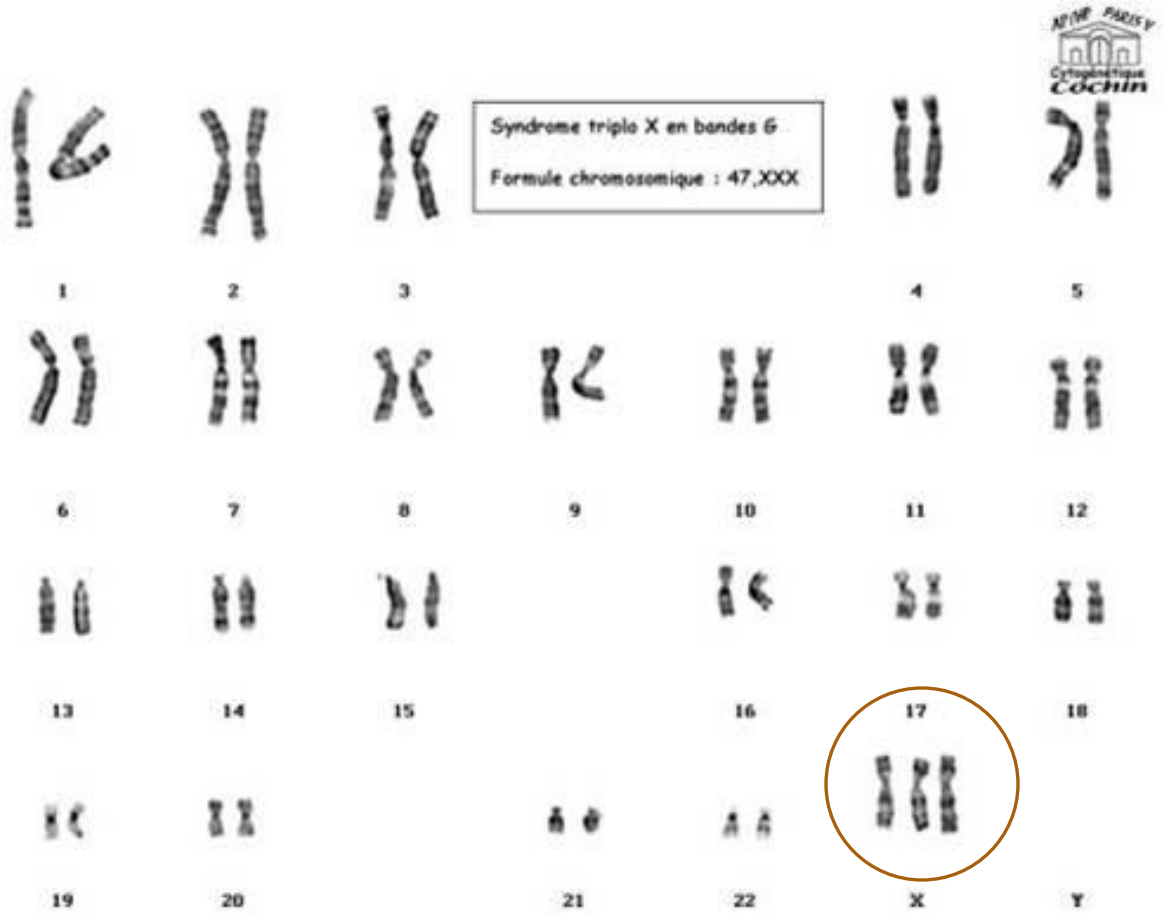
Definition

- 47, XXX; **Triple X syndrome**; Trisomy X; Triplo-X
- Occurs in 1 in 1,000 live female births
  - Only approx. 10% are clinically ascertained
- Timing of ascertainment
  - Prenatal vs Postnatal
- Variable physical and psychological features
- Physical and medical features hypothesized to result from overexpression of genes that escape X-inactivation

Karyotype


Syndrome triplo X en bandes G
Formule chromosomique : 47,XXX
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Background

How does Triple X occur?

- Non-disjunction event
- Most commonly maternal in origin
  - (90% maternal vs. 10% paternal)
- ~60% meiosis I (AMA)
- ~20% during meiosis II
- ~20% post-zygotic mitotic non-disjunction event (Jacobs and Hassold et al, 1988)

Background

Can Triple X be mosaic?

- Yes, post-zygotic mitotic nondisjunction is commonly associated with mosaicism, such as 47,XXX/45,X or with 46,XX
- Further medical evaluation and genetic counseling may be indicated, depending on which type of mosaicism is present, especially if there is a 45,X cell line

Background

Why do the features associated with Triple X occur?

- ~5-15% of X chromosome genes escape inactivation and overexpressed in Triple X
- Hypothesized that over expression leads to the phenotypic features
- example, the SHOX gene on the X escapes X-inactivation and over expression is related to tall stature in Triple X (Ottensen et al, 2010).
- Many X chromosome genes are involved in neurodevelopment.

Features of Trisomy X

- Physical Features
- Motor Tone and Coordination
- Renal and Cardiac
- Seizures
- Autoimmune
- Puberty and Fertility
- Other Medical problems…
- Developmental and Psychological Features
- Cognitive/Intellectual
- Psychiatric concerns
- Adaptive, independent daily living skills

Physical Features:

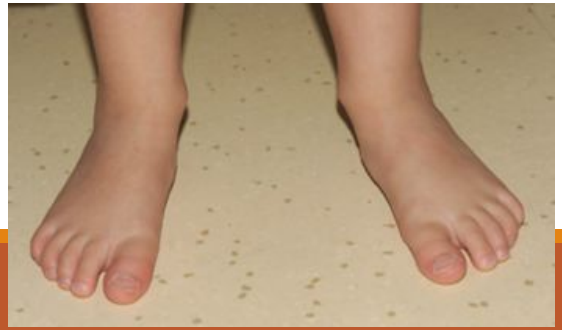
Growth

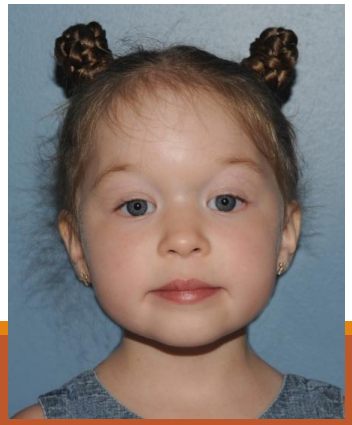
Tall stature with height >75%ile

- 5ft7” - 5ft9”
- Long legs

Subtle Physical features (>40%)

- Epicanthal folds
- Hypertelorism
- Clinodactyly
- Pes planus
- Hypotonia





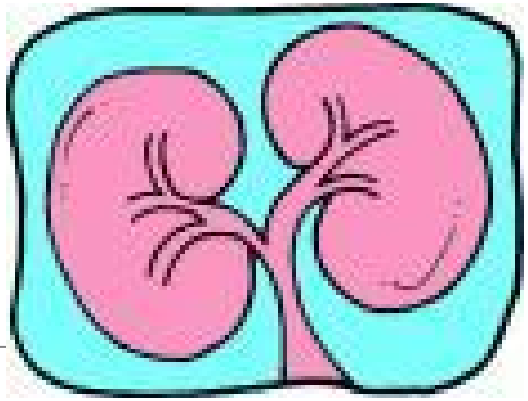
Motor Tone and Coordination:

Low Muscle Tone / Hypotonia

Recommendations:

- Occupational/Physical therapy evaluations and treatments
- Orthotics for flat feet
- School age: Keyboarding/Assistive technology

Kidney Abnormalities



Literature:

- 1/11 Denver Trisomy X sample with atrophic kidney
- At least 6-7 other reports of various kidney malformations in Trisomy X

Our study: 9/74 (12.2%)

- Multicystic/dysplastic kidney
- Bilateral hydronephrosis
- Unilateral kidney
- Vesciculoreteral reflux

Recommendations:

- Renal ultrasound performed for all new diagnoses or by 6 months after birth in a prenatal diagnosis.

Cardiac Abnormalities

Literature:

- Increased risk of congenital heart malformation

Our Study:

- 7/74 with septal defect (9.4%)
  - Ventricular Septal Defect
  - Atrial Septal Defect
  - All closed spontaneously

Recommendation:

- Cardiology consultation or Echocardiogram for all new diagnoses or after birth in a prenatal diagnosis

Seizures

Literature

- Grosso et al, 2004 – 7 girls evaluated by EEG, 4 with complex partial seizures. Lower IQ associated with seizures

Our Sample 12/74 (16.2%)

- No structural brain abnormalities on imaging
- Good response to medication treatment
- Usually started at 5-9 years of age
- Associated with lower cognitive scores, postnatal diagnosis

Recommendations

- Neurology consultation and/or EEG if concerns
- Anticonvulsant medication(s) if indicated

Autoimmune Disorders

Increased risk for autoimmune disorders

- Goswami et al, 2003: Increased risk for thyroid disorders: 2/52 (3.8%) POF attributed to thyroid disorders
- Liu et al, 2016 identified 47,XXX in 1 in 404 women with Systemic Lupus Erythematosus (total: 7/2826) and 1 in 344 women with Sjogren's syndrome (total: 3/1033) had 47,XXX

Recommendations:

- Thyroid screening every 1-2 yrs starting in adolescence, or sooner if concerning symptoms
- Discussion and monitoring of other autoimmune symptoms with primary care provider

Puberty and Fertility

Puberty early, normal, or delayed?

- Stagi 2016: 15 XXX vs. 30 controls – early activation of HPA axis even without signs of puberty, higher LH/FSH, lower estrogen and ovarian volume

Premature ovarian failure (POF)

- POF: loss of ovarian function (production of estrogen/progesterone, ovulation) before age 40
- 47,XXX identified in 1-4% of POF population.
  - Goswami et al, 2003. Trisomy X in 2/52 (3.8%) of women w/secondary amenorrhea/POF

Fertility

- Many w/normal fertility and normal children (8 of 11 Denver girls got pregnant, 1 SIDS baby)
- Various reports of women w/abnormal ovaries, lack/decreased numbers of oocytes (eggs) in ovaries
- Some reports of increased chance of medical problems/malformations in children of XXX moms (Fryns et al, 1983)

Puberty and Fertility (cont)

Recommendations:

- Endocrine evaluation if early or late puberty
- Endocrine or GYN evaluation if abnormal/irregular periods
- Genetic counseling and gynecologic evaluation prior to pregnancy
- Referral to reproductive endocrinologist for infertility concerns
- Close monitoring during pregnancies for malformations or other problems in babies

Other Medical Problems

Our study (n=74):

Medical Feature	Total Number	%
Constipation	34/74	45.9%
Significant Dental Problems (4+ caries/fillings, significant malocclusion, current or previous orthodontia)	32/72	44.4%
Allergies (Food or Environmental)	21/74	28.4%
Asthma	16/71	22.5%
Recurrent Otitis Media	15/72	21.1%
Abdominal Pains	14/74	18.9%
Headaches	13/73	17.8%
Hospitalized for Respiratory Infection or Asthma	12/74	16.2%
Strabismus	11/74	14.9%
Cleft Palate/Velopharyngeal Insufficiency	3/73	4.1%
Congenital hip dysplasia	7/74	9%
Club foot	2/74	2.7%

Developmental & Psychological Features

Neurodevelopmental and Psychological Risks in SCA Conditions	
Developmental Delay:	Executive Functioning Deficits
Speech-Language delay	Slow Processing Speed
Motor skills delay	Attention Deficit Hyperactivity Disorder (ADHD)
Cognitive Impairments / Intellectual Disability	Adaptive Functioning Deficits
Learning Disabilities:	Sensory Processing Differences
Language-Based Learning Disability (Dyslexia)	Social Difficulties:
Speech and Language Disorders:	Social Cognitive Deficits
Receptive Expressive Language Disorder	Social-Emotional Immaturity
Apraxia/Dyspraxia of Speech	Autism Spectrum Disorders
Pragmatic / Social Communication	Emotional / Psychological Disorders:
Motor Skills Disorders:	Anxiety disorder
Motor coordination problems	Depression
Hypotonia	Mood disorders / Bipolar Disorder
Graphomotor deficits	Psychotic features / Schizophrenia

Development

Speech / language delays

- Expressive delays > receptive delays
- Apraxia / Dyspraxia
- Our study: Avg age at first word was 13.9 months
  - SD 4.3 months, range 7-24 months

Motor Delays / Hypotonia

- Delayed age of walking
- Our research sample 28/39 (72%) had motor delays
- Our study: Average age of first steps 15.3 months
  - SD= 3.2 months, range 10-25 months

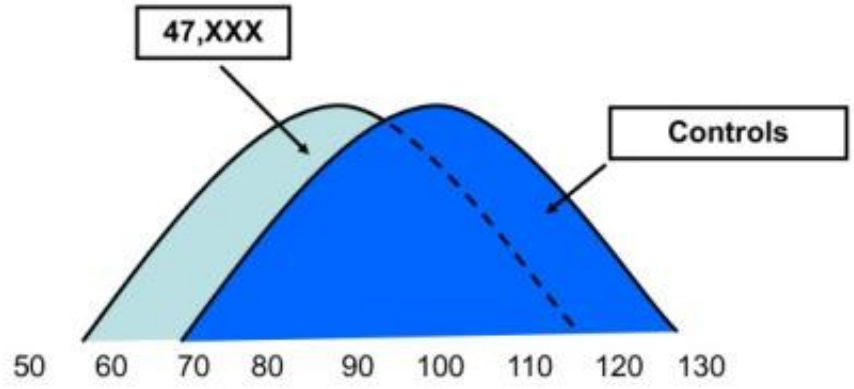
Cognitive / Learning Functioning

Cognitive

- FSIQ in normal ranges but scores 10-20 points less than sibling matched controls

Learning

- Despite normal IQ, high rates of learning disabilities
- 75% special education supports in school



Tartaglia et al. 2010. Orphanet J Rare Diseases 5:8

Neurodevelopmental & Psychiatric Diagnoses

Preliminary analysis in a clinical sample (n=33):

Neurodevelopmental / Psychiatric Feature	Total Number	%
ADHD	20/33	60.6%
Language Disorder		
-Current Dx	10/33	30.3%
-Prior Dx	12/33	36.4%
Learning Disabilities	13/33	39.4%
Intellectual Disability	3/33	9.1%
Autism Spectrum Disorder	6/33	18.2%
Anxiety Disorder	10/33	30.3%
-Anxiety symptoms	10/33	30.3%
Depression	6/33	18.2%
Bipolar Disorder or Psychotic Disorder	2/33	6%

XXX Syndrome

	PRENATAL DX (n=22)	POSTNATAL DX (n=17)
Normal IQ	90% (20/22) 8/20 borderline	71% (12/17) 6/12 borderline
FSIQ	91.6	86.2
Special Ed	68%	76%
Speech delay	36%	88%
Motor delay	36%	76%
PDD	0%	0%
ADHD (>6yo)	n=10, 30%	n=12, 50%

ADHD in Triple X

30-60% of patients

Usually predominantly Inattentive Symptoms

- Difficulty sustaining attention in tasks or play activities
- Difficulty organizing tasks or activities
- Easily distracted
- Loses things necessary for activities (toys, school assignments, pencils)
- Does not follow through on instructions

Recommendations:

- Diagnosis of ADHD by professional
- Consideration of other comorbid diagnoses (i.e. learning disability, anxiety)
- Treatments for ADHD: medications, educational strategies, behavioral interventions

Anxiety in Triple X

30-60% of patients

Symptoms:

- Social withdrawal
- Selective mutism
- Fear, panic, avoidance, tantrums
- Separation anxiety

Recommendations

- Psychological Evaluation
- Therapy – with consideration of learning/language deficits
- Medication Treatment (SSRI)

Social Difficulties

Social-emotional immaturity

Higher level language skills deficits

Social Anxiety

Autism Spectrum Disorders (10-15%)

Attention

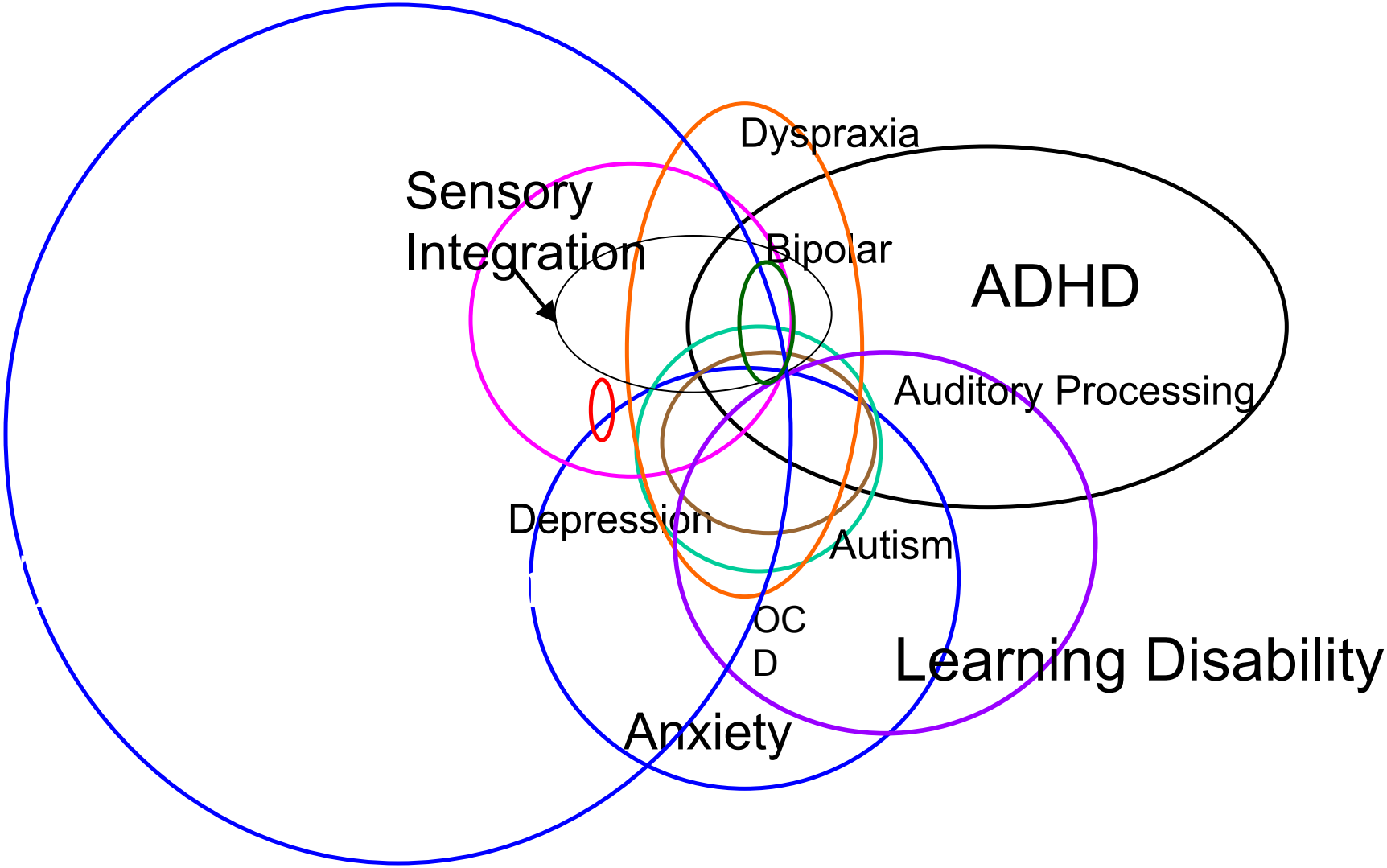
Language disorders

Cognitive/ Executive functioning

Social Skills

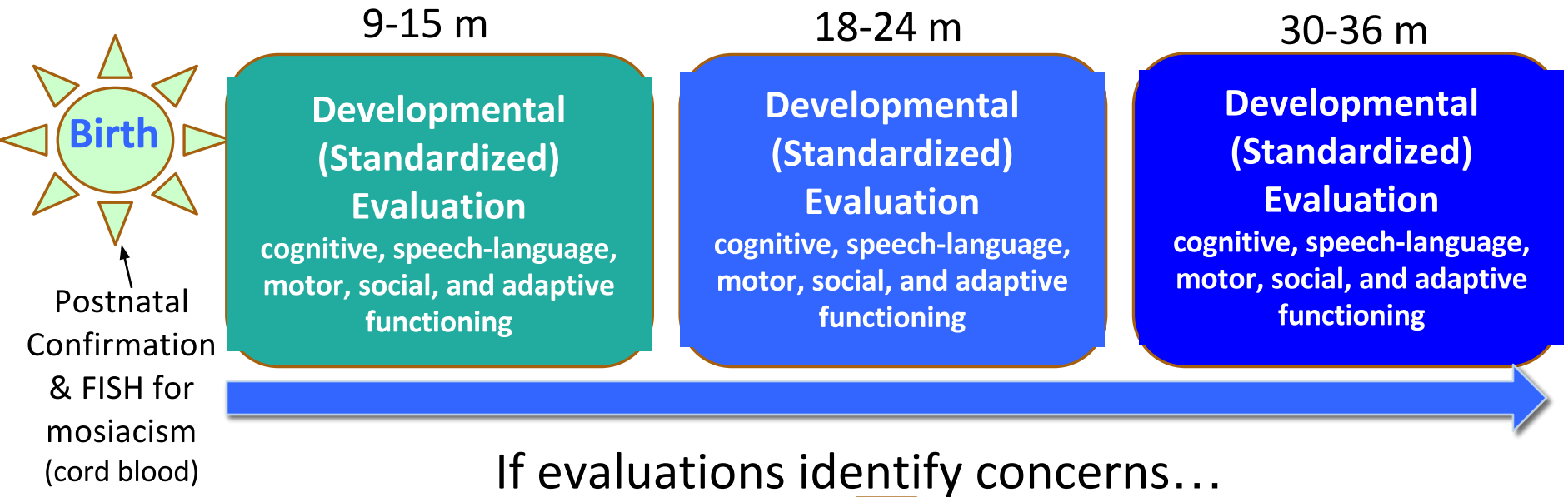
Anxiety

Adaptive Functioning



Adapted from Randy Ross, M.D

Birth to Three Developmental Evaluations



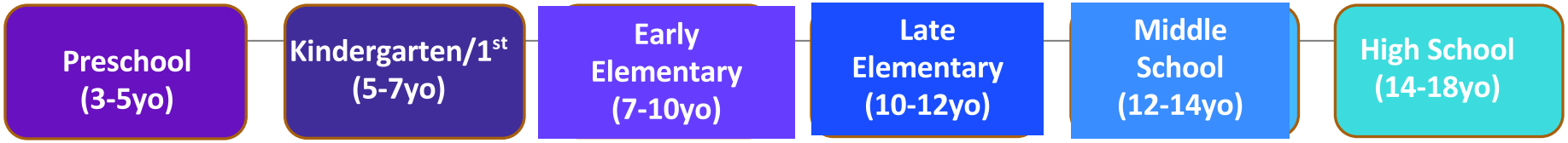
If evaluations identify concerns…

Seek Early Intervention / private therapy

- Developmental, speech, occupational, or physical therapies

Closely monitor developmental progress

Neurodevelopmental Evaluations



1. Neuropsychology
   - Learning disabilities, Academics, Dyslexia / Reading disabilities, ADHD, Executive Functioning
   - Interventions: 504 / IEP, Evidence-based interventions, educational strategies / supports for EF and ADHD, medication
2. Speech LanguageTherapy
   - Expressive-receptive language abilities, higher-order language skills, pragmatic / social use of language, and disorders of speech production (developmental dyspraxia / apraxia) or hypernasality due to possible VPI
   - Interventions: Speech-language therapy (early intervention, school system and/or privately), referral to ENT
3. Clinical Psychology
   - Adaptive Functioning , anxiety, social functioning, autism spectrum disorder and behavioral or emotional concerns
   - Interventions: Therapy/counseling, school supports and/or medication treatment, referral to developmental pediatrician or psychiatrist, occupational therapy to address self-care
4. Occupational Therapy
   - Fine and gross motor skills, balance, coordination, motor planning
   - Interventions: Occupational and/or physical therapy interventions if motor deficits causing difficulties with handwriting, play or recreational activities, dressing, eating or other self-care skills

Genetic Counseling Considerations

Low ascertainment rates (approx 10%) vs. incidence (1:1000)

Evaluation and treatment recommendations (based on current age)

Diagnosis disclosure

Resources for support and information

Genetic Counseling Challenges

Biggest counseling challenge: understanding significant variability and uncertainty for their daughter

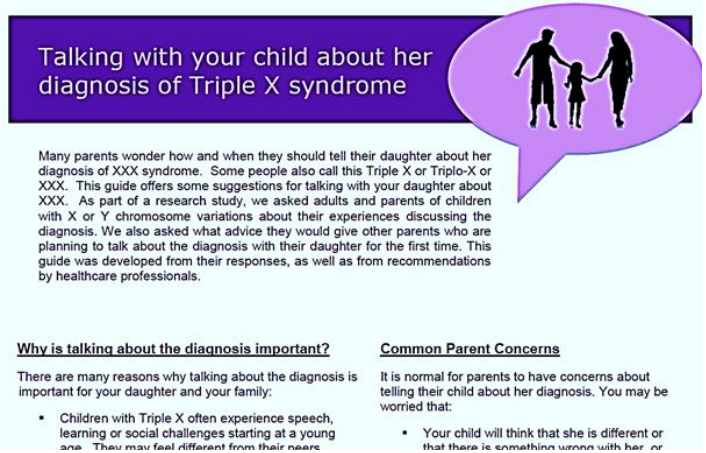
Significant role of family background genes & environment

- child's prognosis relative to entire genetic makeup
- impact of home environment, educational supports, etc.

Resources:

AXYS- parent advocacy organization for Triple X, (**www.genetic.org**)

- Helpline, educational materials, family conferences, social media sites, and regional support group.



Talking with your child about her diagnosis of Triple X syndrome

Many parents wonder how and when they should tell their daughter about her diagnosis of XXX syndrome. Some people also call this Triple X or Triplo-X or XXX. This guide offers some suggestions for talking with your daughter about XXX. As part of a research study, we asked adults and parents of children with X or Y chromosome variations about their experiences discussing the diagnosis. We also asked what advice they would give other parents who are planning to talk about the diagnosis with their daughter for the first time. This guide was developed from their responses, as well as from recommendations by healthcare professionals.

Why is talking about the diagnosis important?

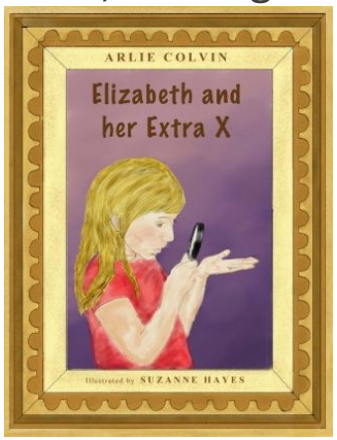
There are many reasons why talking about the diagnosis is important for your daughter and your family:

- Children with Triple X often experience speech, learning or social challenges starting at a young age. They may feel different from their peers

Common Parent Concerns

It is normal for parents to have concerns about telling their child about her diagnosis. You may be worried that:

- Your child will think that she is different or that there is something wrong with her, or



Available at Createspace.com or Amazon.com

Available at eXtraordinarY Kids Clinic and soon to be online (4 pgs)

AXYS Clinic and Research Consortium (ACRC)

A growing clinic consortium that operates as independent dedicated clinics committed to collaborating with one another, sharing informational resources, and exploring opportunities to participate in joint research projects.

X&Y Clinic with access to patients with Trisomy X

Publications

Tartaglia *et al. Orphanet Journal of Rare Diseases* 2010, **5**:8
http://www.ojrd.com/content/5/1/8

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

A review of trisomy X (47,XXX)

Nicole R Tartaglia*[1,2], Susan Howell[1,2], Ashley Sutherland[1], Rebecca Wilson[2] and Lennie Wilson[3]

Tartaglia et al., 2010 (open access).

European Journal of Human Genetics (2009), 1–7

www.nature.com/ejhg

PRACTICAL GENETICS

In association with orphanet

Triple X syndrome: a review of the literature

Otter et al,. 2009

American Journal of Medical Genetics 110:3–10 (2002)

Genetic Counseling for Sex Chromosome Abnormalities

Mary G. Linden,[1]* Bruce G. Bender,[1,2] and Arthur Robinson[1,3]
[1]*Department of Pediatrics, National Jewish Medical and Research Center, Denver, Colorado*
[2]*Department of Psychiatry, University of Colorado Health Sciences Center, Denver, Colorado*
[3]*Department of Biochemistry and Molecular Genetics, University of Colorado Health Sciences Center, Denver, Colorado*

Linden et al, 2002

J Genet Counsel
DOI 10.1007/s10897-014-9741-4

ORIGINAL RESEARCH

"How Should I Tell my Child?" Disclosing the Diagnosis of Sex Chromosome Aneuploidies

Anna Dennis · Susan Howell · Lisa Cordeiro · Nicole Tartaglia

Dennis et al, 2015

Physical & Medical Findings

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Expanding the Phenotype of Triple X Syndrome: A Comparison of Prenatal Versus Postnatal Diagnosis

Kristen Wigby,[1,2] Cheryl D'Epagnier,[1] Susan Howell,[1,3] Amy Reicks,[4] Rebecca Wilson,[3] Lisa Cordeiro,[1] and Nicole Tartaglia[1,3]*

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Manuscript Received: 20 July 2015; Manuscript Accepted: 1 April 2016

Wigby et al, 2016

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Expanding the Phenotype of Triple X Syndrome: A Comparison of Prenatal Versus Postnatal Diagnosis

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[1]Department of Pediatrics, Developmental Pediatrics, University of Colorado School of Medicine, Aurora, Colorado
[2]Division of Genetics, Department of Pediatrics, University of California San Diego, La Jolla, California
[3]eXtraordinarY Kids Clinic, Developmental Pediatrics, Children's Hospital Colorado, Aurora, Colorado
[4]Genetic Counseling Program, University of Colorado Denver, Colorado

Manuscript Received: 20 July 2015; Manuscript Accepted: 1 April 2016

Wigby et al, 2016

Management Recommendations

Medical or Psychological Feature	Recommendation for Follow-Up and Further Evaluation
Developmental delay (Age 0-3)	Comprehensive developmental assessments should be performed for all children, with evaluation of cognitive, speech-language, motor, social, and adaptive functioning domains using standardized measures. If indicated, initiation of early interventions including developmental, speech, occupational or physical therapies. If prenatal diagnosis: Evaluations at 9-15 months, 18-24 months, and 30-36 months. Sooner or more frequent if any developmental concerns. If postnatal diagnosis: Evaluation at diagnosis, and then at ages recommended above.
Learning Disabilities	Monitor learning and academic performance from preschool throughout education. Psychological evaluations to assess cognitive functioning, learning disabilities at key times during education: early elementary, late elementary, middle school, high school, transition to post-secondary programming. Special education supports (504 plans or Individual Education Plans) as needed. Evidence-based interventions for learning disabilities if identified.
ADHD / Executive functioning problems	Education of parents/caretakers about executive functioning (EF) and symptoms of EF deficits. Screening of ADHD symptoms by school system and primary care provider with input from family and school as presentation may vary in different environments. Formal evaluation of executive functioning by psychologist or neuropsychologist beginning at 7-8 years of age, and at key times during education: late elementary, middle school, high school, transition to post-secondary programming. Implementation of educational strategies and supports for EF and ADHD symptoms at school and home if present. Consideration of medication treatment for attentional disorders / ADHD if present.
Speech-Language disorders	Assessment with an experienced pediatric speech and language pathologist with evaluation of expressive-receptive language abilities, higher-order language skills, pragmatic / social use of language, and disorders of speech production (developmental dyspraxia / apraxia) or hypernasality due to possible VPI. Recommended yearly evaluation of speech from birth to 4 years, then every 2-3 years depending on presence or severity of impairment. Speech-language therapy through early intervention, school system and/or privately if indicated.
Motor skills	After age 3 years, monitor fine and gross motor skills, balance, coordination, motor planning. Occupational and/or physical therapy interventions if motor deficits causing difficulties with handwriting, play or recreational activities, dressing, eating or other self-care skills.
Social/Emotional problems	Evaluation by developmental pediatrician, child psychiatrist and/or psychologist related to behavioral difficulties, anxiety, social functioning, autism spectrum disorder and other behavioral or emotional concerns. Therapy/counseling, school supports and/or medication treatment if indicated.
Adaptive functioning problems	Evaluation of adaptive functioning using standardized measures including domains of self-care, communication, social, community use, safety and self-direction should be included as part of the psychological or educational evaluations recommended above. Occupational therapy to address self care and other adaptive domains as needed.
Cardiac anomalies	Cardiology consultation or Echocardiogram / EKG for all new diagnoses or after birth in a prenatal diagnosis.
Abdominal pain or Constipation	Evaluation and treatment with primary care provider if present. Referral to gastroenterology if needed.
Seizures	Neurologic history, including questions about staring spells or atypical movements. Neurology consultation and/or EEG may be indicated. Anticonvulsant medication(s) if indicated.
Ovarian function / Fertility	Evaluation by endocrinologist or gynecologist for abnormal pubertal development, irregular menses, or fertility concerns.
Autoimmune problems	Thyroid screening every 1-2 yrs starting around age 10, or sooner if concerning symptoms. Discussion and monitoring of other autoimmune symptoms with primary care provider.
Renal anomalies	Renal ultrasound should be performed for all new diagnoses or by 6 months after birth in a prenatal diagnosis.
Genetics	In a prenatal diagnosis, postnatal confirmatory genetic testing is recommended, including FISH testing for mosaicism. Consultation with genetic counselor and/or clinical genetics.

Current Research Opportunities

(see www.genetic.org for more information)

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1. **AXYON registry**- self-reported registry led by AXYS (www.genetic.org), all ages
2. **TriXY Study** (International study of development and neuropsychology)
   - Birth to 5yo, PI: Sophie van Rijn, PhD, Denver site PI: Dr. Nicole Tartaglia
   - Enrollment begins July 2017 at Denver Clinic
3. **The OXYGEN Study**: The impact of genetic diagnosis of sex chromosome aneuploidies on life course quality of life.
   - Birth-21yo, Mayo Clinic (Rochester, MN), PI: Dr. Megan Allyse and Dr. Sean Phelan
4. **The Clinical Study of Patients with Sex Chromosome Variants**
   - Ages 18+, NIH study (Bethesda, MD), PI: Dr. Maximilian Muenke and Dr. David Page

Longitudinal and prospective research in Triple X is needed!

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