Best Clinical Practices in PMS

Alexander Kolevzon, MD
Seaver Autism Center for Research and Treatment
Icahn School of Medicine at Mount Sinai

Icahn School of Medicine at Mount Sinai

seaver autism center for research & treatment @ mount sinai

REVIEW Open Access

Phelan-McDermid syndrome: a review of the literature and practice parameters for medical assessment and monitoring

Alexander Kolevzon[1,2,3,10,11*], Benjamin Angarita[1,2], Lauren Bush[1,2], A Ting Wang[1,2,4,10], Yitzchak Frank[1,2,3,5], Amy Yang[6], Robert Rapaport[3,7], Jeffrey Saland[3], Shubhika Srivastava[3,8], Cristina Farrell[1,3,9], Lisa J Edelmann[6] and Joseph D Buxbaum[1,2,4,6,10,11]

Kolevzon *et al. Journal of Neurodevelopmental Disorders* 2014, **6**:39
http://www.jneurodevdisorders.com/content/6/1/39

Table 3: Summary of Clinical Recommendations for Assessment

Medical Specialty	Common Clinical Features	Assessments
Clinical Genetics	Large fleshy hands	Dysmorphology exam
	Bulbous nose	
	Long eyelashes	
	Prominent/dysplastic ears	
	Hypoplastic/dysplastic nails	
	Dolicocephaly	
Molecular Genetics		Chromosomal Microarray
		Chromosome analysis (to identify ring chromosomes)
		Sanger or next generation sequencing (for mutations)
		Fluorescence in situ hybridization (to identify balanced rearrangements in parents)
Psychiatry	Autism spectrum disorder	Gold standard diagnostic assessments
Psychology	Aberrant behavior	Psychiatric evaluation
	Intellectual disability	Cognitive and adaptive behavior testing
	Absent or delayed speech	Speech and language evaluation
Neurology	Seizures	Overnight video-electroencephalography
	Structural brain abnormalities	Brain imaging and head circumference monitoring
	Feeding difficulties	Feeding therapy evaluation
	Hypotonia	Occupational and physical therapy evaluations
	Motor skill deficits	
Endocrinology	Short/tall stature	Monitor height, weight, and body mass index
	Hypothyroidism	Metabolic work-up, including thyroid function
		Nutritional assessment
Nephrology	Vesicoureteral reflux	Renal and bladder ultrasonography
	Urinary tract infections	voiding cystourethrogram
	Hydronephrosis	Monitoring of blood pressure
	Renal cysts, hypoplasia or agenesis	
Cardiology	Congenital heart defects	Electrocardiography
		Echocardiography
Gastroenterology	Gastroesophageal reflux	Referral for dietary changes and/or medicine
	Constipation/diarrhea	management
	Pica	Bowel regimens
		Referral to behavioral therapy
Primary Care/ Developmental Pediatrics	Upper respiratory tract infections	Careful and consistent monitoring and management Referral to otolaryngology, ophthalmology, physiatry, dental, and orthopedics
	Recurring ear infections	
	Hearing and vision problems	
	Lymphedema	
	Dental problems	
	Decreased perspiration/heat intolerance	

Kolevzon et al., 2014

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ACMG Practice Guidelines

Clinical genetics evaluation in identifying the etiology of autism spectrum disorders

G. Bradley Schaefer, MD[1], Nancy J. Mendelsohn, MD[2], and the Professional Practice and Guidelines Committee

ACMG PRACTICE GUIDELINES | Genetics inMedicine

Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions

G. Bradley Schaefer, MD[1] and Nancy J. Mendelsohn, MD[2]; for the Professional Practice and Guidelines Committee

Phelan-McDermid syndrome/22q13 deletion syndrome

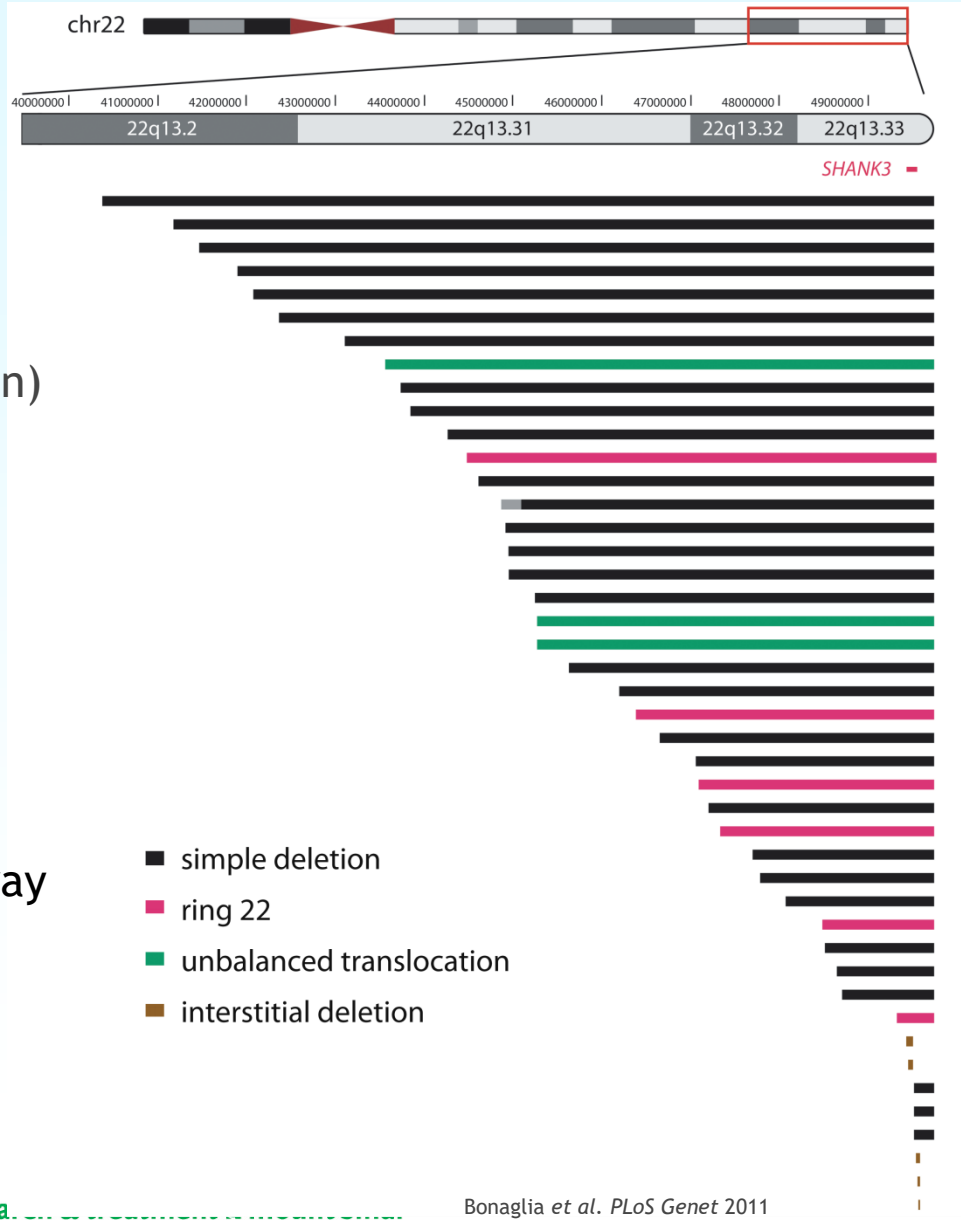
Deletion band 22q13.3:

- simple terminal deletions
- unbalanced rearrangements
- (translocation, ring chromosome, inversion)
- interstitial deletions

~80% *de novo*, ~20% familial translocation

Deletion sizes are highly variable, with no common breakpoints (17 kb - 9 Mb)

Diagnosis: karyotype, FISH, MLPA or microarray

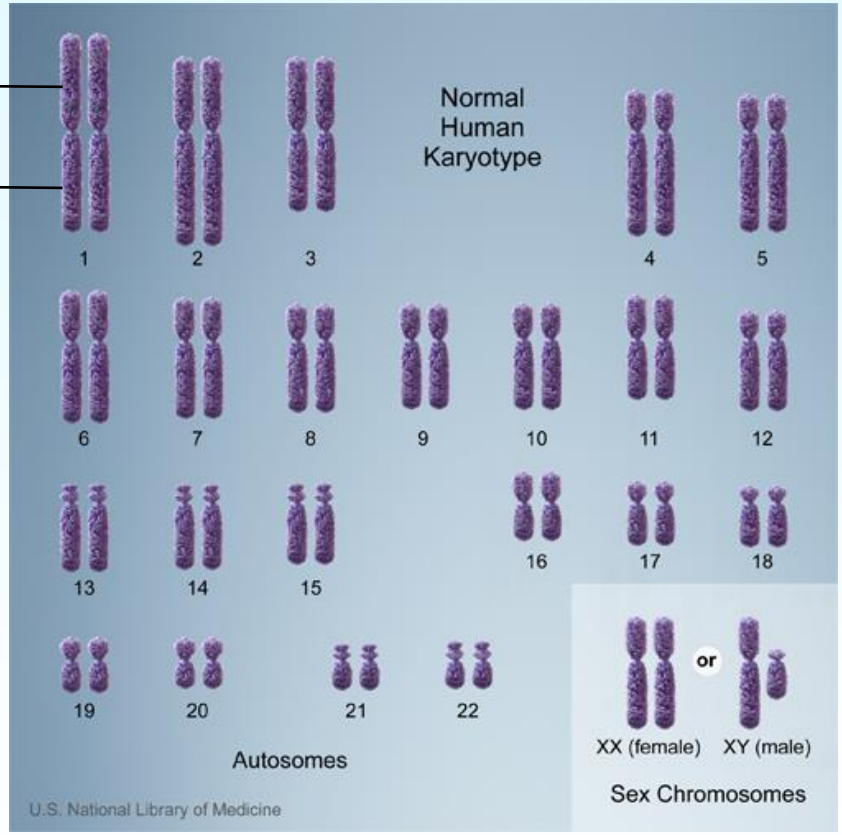


Bonaglia *et al. PLoS Genet* 2011

Chromosomes

p arm

q arm

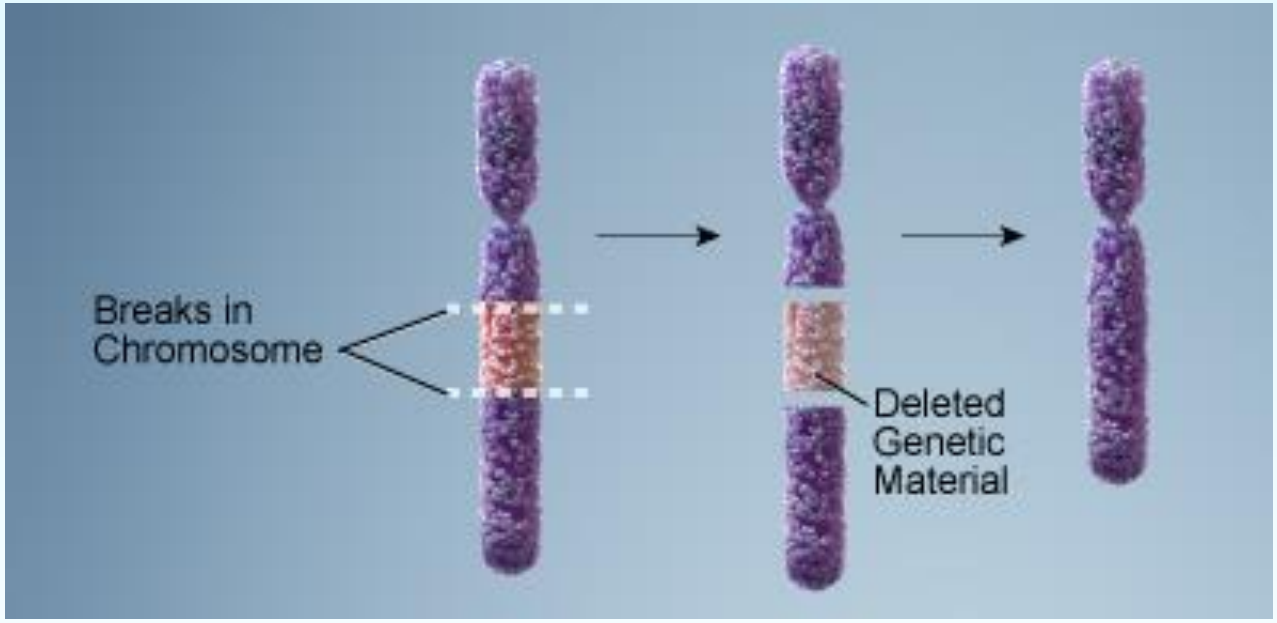


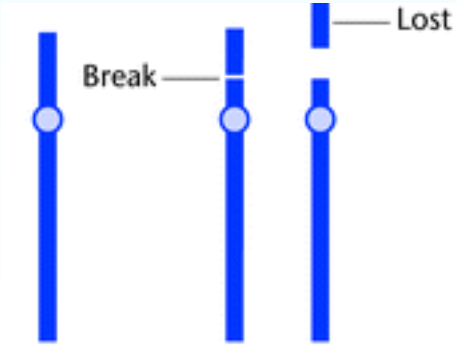
Different types of genetic defects:

→ chromosomal abnormalities

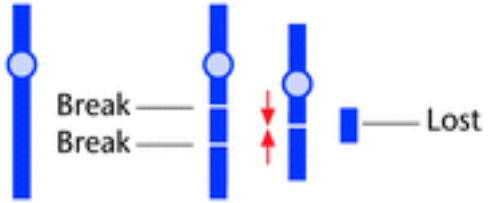
→ DNA sequence mutations

Deletion



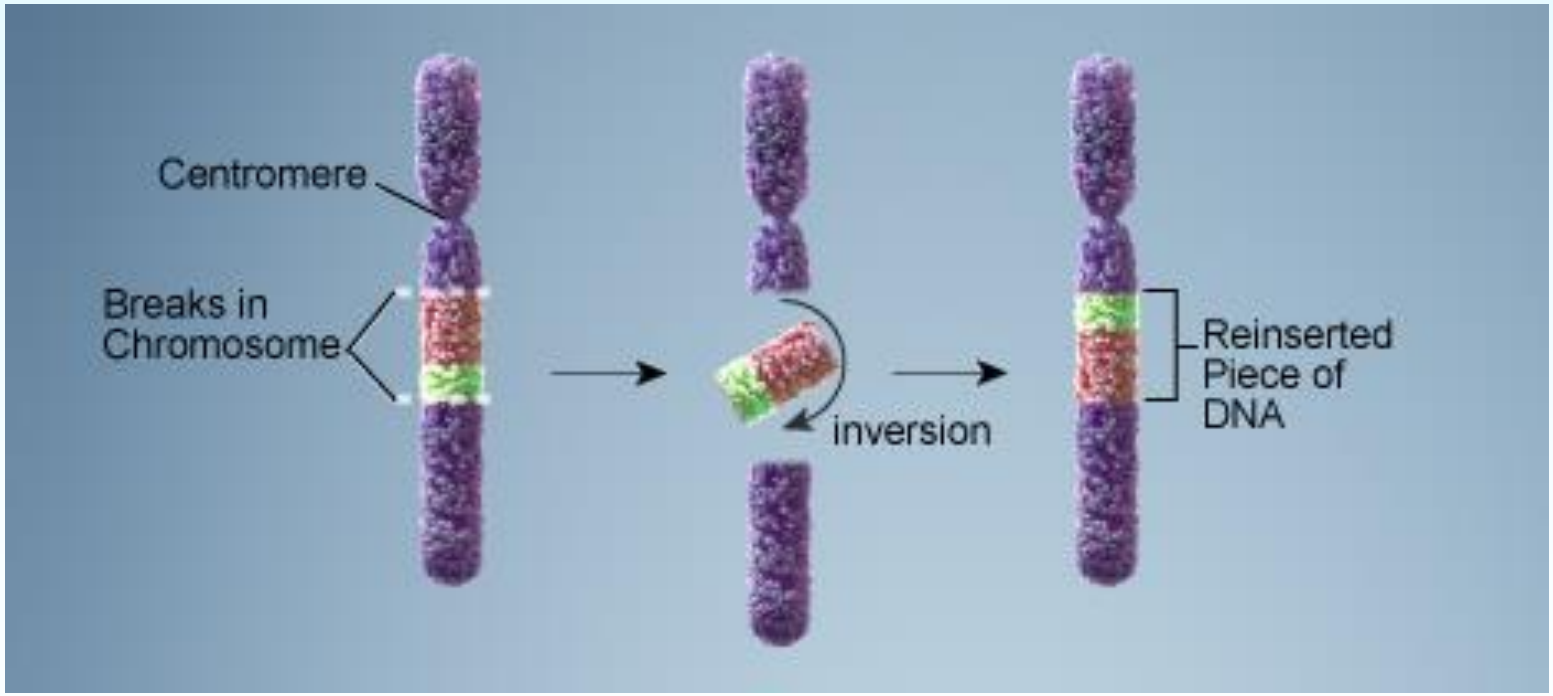


Terminal deletion

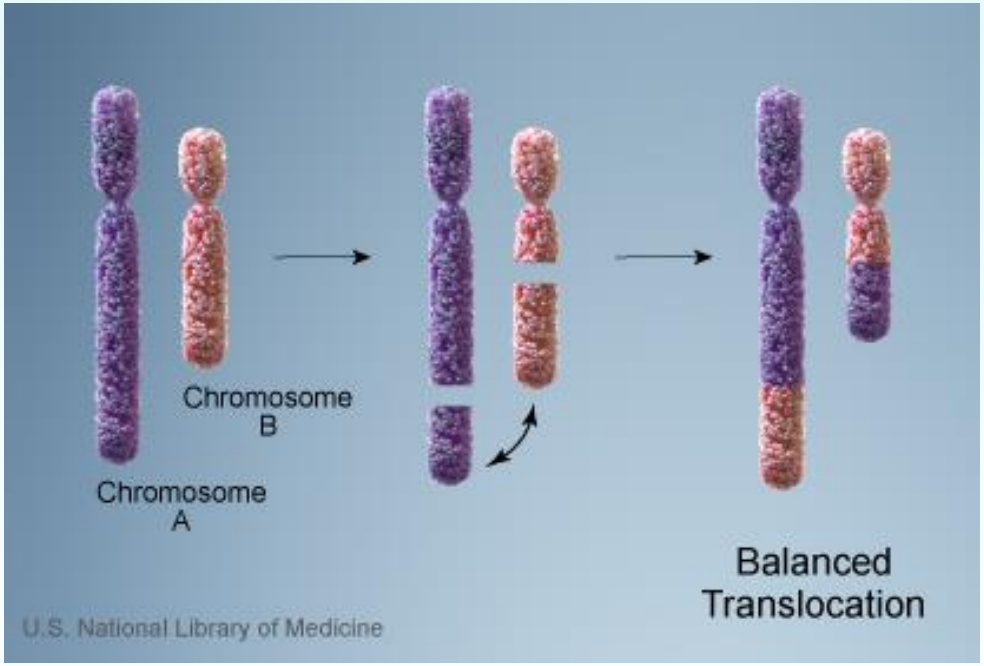


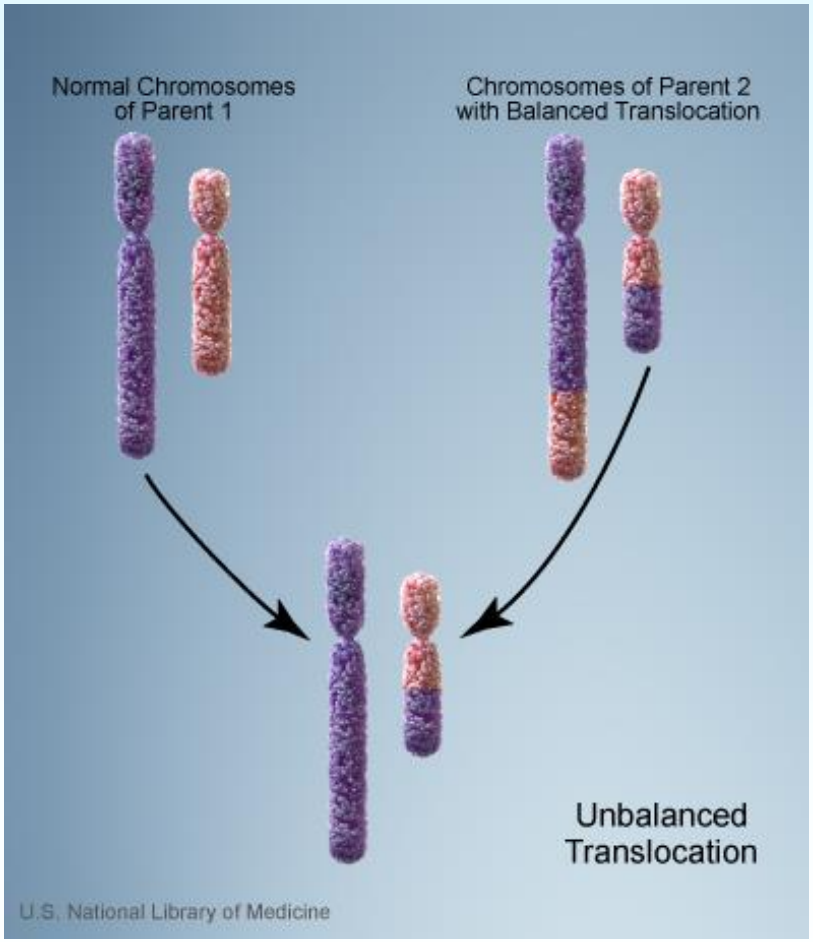
Interstitial deletion

Inversion

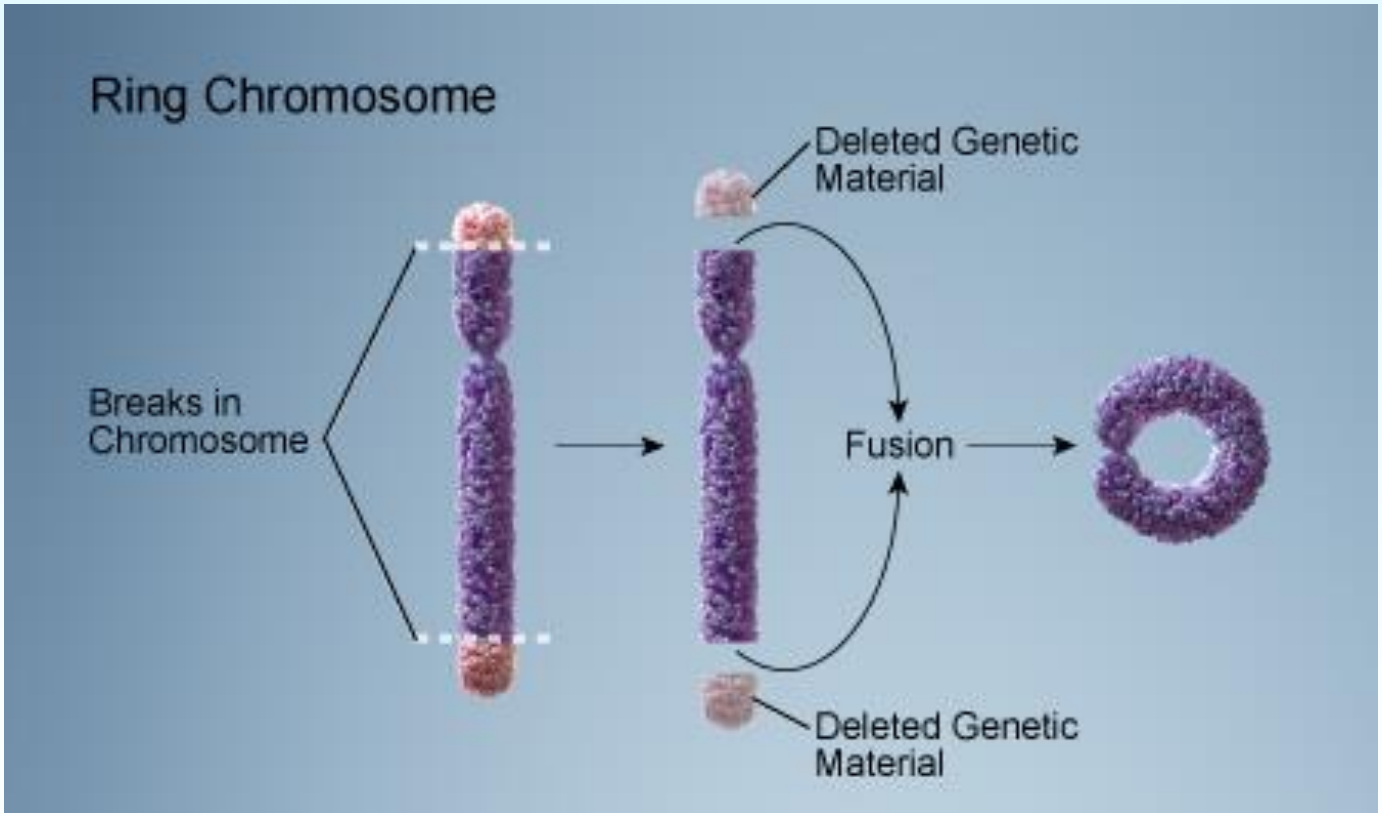

Centromere
Breaks in Chromosome
inversion
Reinserted Piece of DNA

Translocation

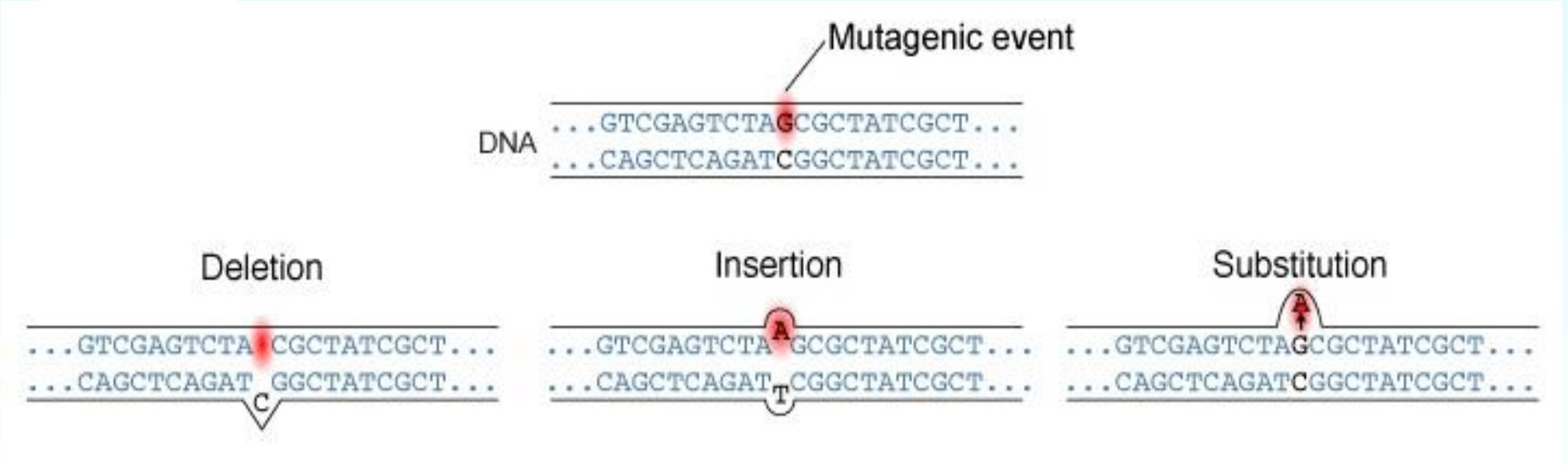




Ring chromosome



DNA sequence mutations



Initial Results

Sample Size	**32**
Male : Female	**18:14**
Age (years)	**1.7- 45.4 (X = 8.8)**
Deletion Size (Mb)	**.058 (point) – 8.5**

Rearrangement	**N**	**%**
Terminal deletion	**21**	**66**
Ring 22	**6**	**19**
Unbalanced translocation	**2**	**6**
Point mutations	**2**	**6**
Interstitial deletion	**1**	**3**

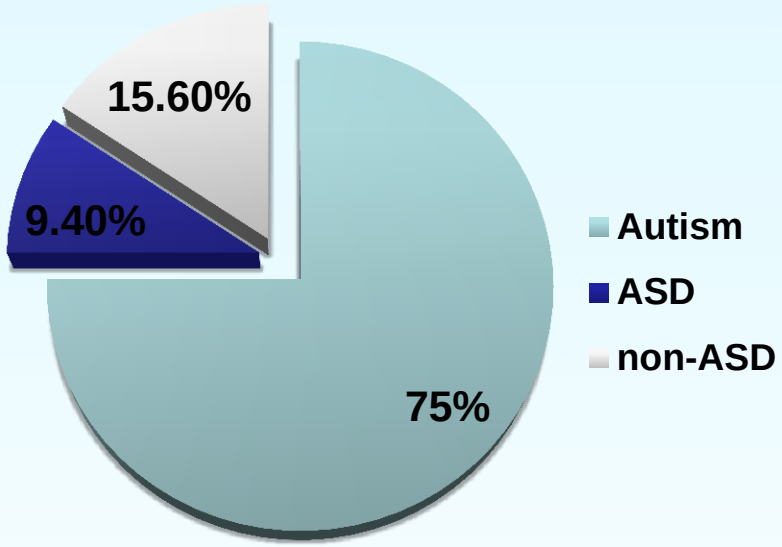
Soorya et al., 2013

Phenotyping

Physical and neurological exam	Renal ultrasound
Clinical Genetics Evaluation	Electroencephalography
Medical and Psychiatric History	Laboratory bloodwork
Echocardiography	Height and weight measurement
Electrocardiography	Head circumference

Domain	Measure
Global Cognitive Ability	Mullen Scales for Early Learning or Stanford Binet-5
Adaptive Behavior	Vineland Adaptive Behavior Scales
Language	Mullen and Vineland Subscales Macarthur Bates Communication Developmental Inventory Peabody Picture Vocabulary Test-4 Expressive Vocabulary Test-2
Motor Functioning	Mullen and Vineland Subscales Developmental Coordination Disorder Questionnaire
Autism Symptoms	Autism Diagnostic Observation Schedule Social Responsiveness Scale Repetitive Behavior Scales-Revised
Other Symptoms	Child Behavior Checklist Aberrant Behavior Checklist Sensory Profile Questionnaire- Short Form

ASD and IQ diagnostic classifications



	N	%
Nonverbal IQ classification (n=30)		
Average (IQ 100-110)	1	3.3
Mild intellectual disability (IQ 50-55 to 70)	3	10
Moderate intellectual disability (IQ 35-40 to 50-55)	3	10
Severe intellectual disability (IQ 20-25 to 35-40)	7	23.3
Profound intellectual disability (IQ < 20-25	16	53.3

Soorya et al., 2013

Table 5 Medical comorbidities identified from clinical interviews and medical record reviews (n = 32)

Medical comorbidity	N	%	Estimated frequency from previous reports *
Increased pain tolerance	28	88	>50%
Hypotonia	24	75	>75%
Recurring upper respiratory tract infections	17	53	
Gastroesophageal reflux	14	44	>25%
Sleep disturbance	13	41	
Seizures (febrile and/or non-febrile)	13	41	>25%
Constipation and/or diarrhea	12	38	
Renal abnormalities	12	38	>25%
Lymphedema	7	22	>25%
Seasonal allergies	6	19	
Food allergies	5	16	
Asthma	3	9	
Strabismus	2	6	>25%
Cardiac abnormalities	1	3	>25%
Hypothyroidism	1	3	5%
Hypertrichosis	1	3	
Vitiligo	1	3	

Soorya *et al. Molecular Autism* 2013, **4**:18

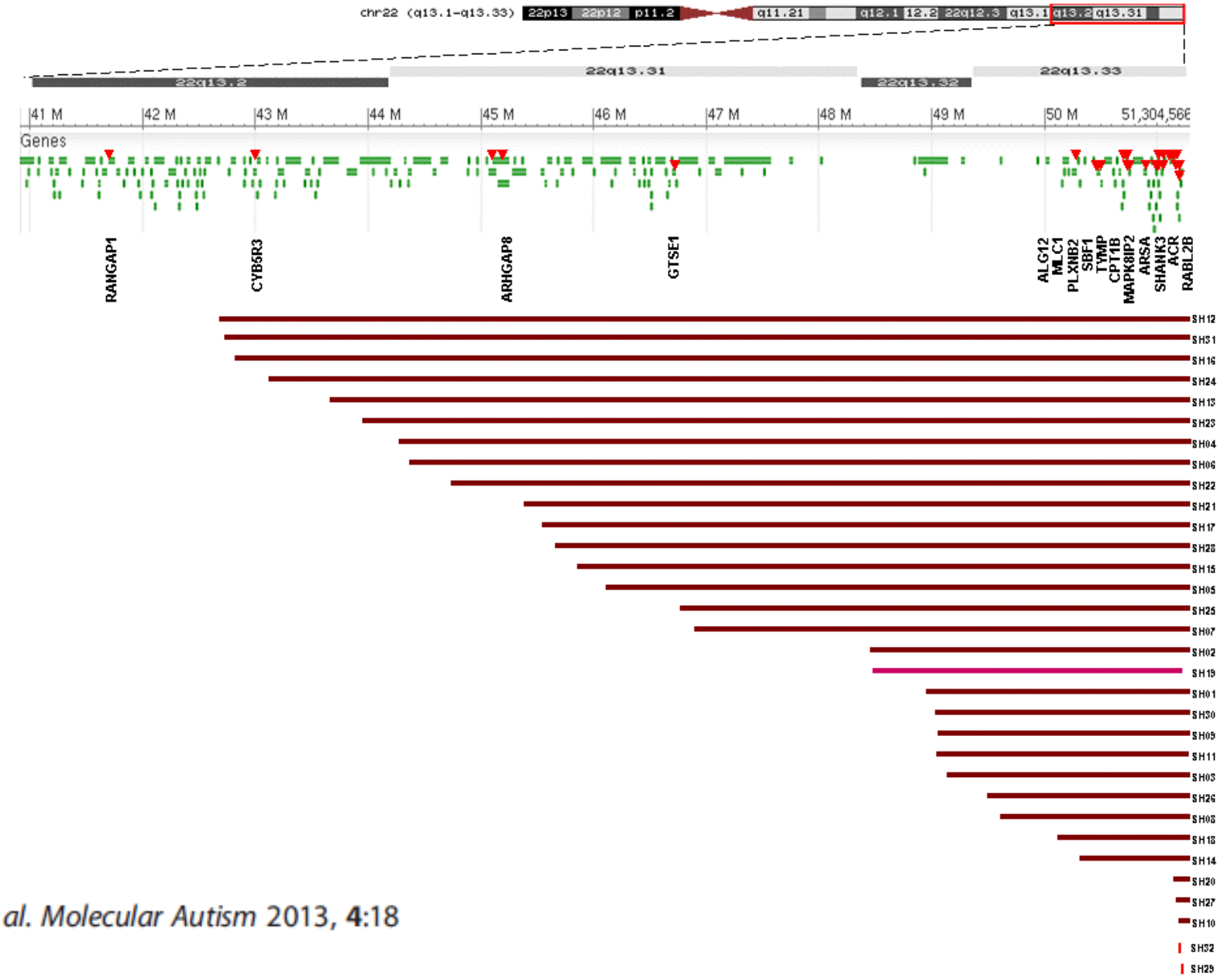
*Phelan & McDermid, 2012

Table 4 Dysmorphic features identified in the clinical genetic evaluation (N = 32)

Dysmorphic features	N	%	Estimated frequency from previous reports [50] *
Large, fleshy hands	17	53	>50%
Bulbous nose	15	47	>50%
Long eyelashes	14	44	>50%
Ear anomalies	13	41	>50%
Hypoplastic/dysplastic nails	11	34	>50%
Full lips	10	31	
Epicanthal folds	10	31	>25%
Macrocephaly[a]	10	31	
Dolichocephaly	8	25	>50%
High arched palate	8	25	>25%
Hyperextensibility	8	25	
Full cheeks	8	25	>50%
Periorbital fullness	8	25	>50%
Pointed chin	7	22	>50%
Abnormal spine curvature	7	22	
Wide nasal bridge	5	16	>50%
Long philtrum	5	16	>25%
Sparse hair/abnormal whorl	5	16	
Malocclusion/widely spaced teeth	6	19	>25%
Micrognathia	4	13	
Hypertelorism	4	13	
Short stature[b]	4	13	
Sacral dimple	4	13	>50%
Syndactyly of toes 2 and 3	3	9	
Malar hypoplasia	3	9	
Fifth finger clinodactyly	3	9	<14%
Microcephaly[c]	2	6	
Deep set eyes	2	6	>50%
Accelerated growth[d]	1	3	
Flat midface	1	3	>50%
Ptosis	1	3	>25%
Low set ears	1	3	

Soorya *et al. Molecular Autism* 2013, **4**:18

*Phelan & McDermid, 2012



Soorya *et al. Molecular Autism* 2013, **4**:18

Association between deletion size and phenotypic variables

Phenotypic variable	N	Deletion size	BCa confidence interval[#]	
			Lower	Upper
Number of dysmorphic features	32	**.474***	.145	.738
Number of medical comorbidities	32	**.386***	.022	.640
Nonverbal IQ estimate	29	**-.332**	-.640	.112
Gross motor skills (Vineland)	31	**-.402**[†]	-.728	.036
Fine motor skills (Vineland)	31	**-.123**	-.473	.254
Expressive language skills (Vineland)	32	**-.184**	-.531	.199
Receptive language skills (Vineland)	32	**-.231**	-.553	.154
Qualitative abnormalities in reciprocal social interactions (ADI-R)	30	**.466***	.073	.723
Qualitative abnormalities in communication (ADI-R)	30	**.498***	.091	.740
Restricted, repetitive, and stereotyped patterns of behavior (ADI-R)	30	**-.229**	-.592	.214

*significant at .05 level (two-tailed test)
[†]approached significance at .05 level

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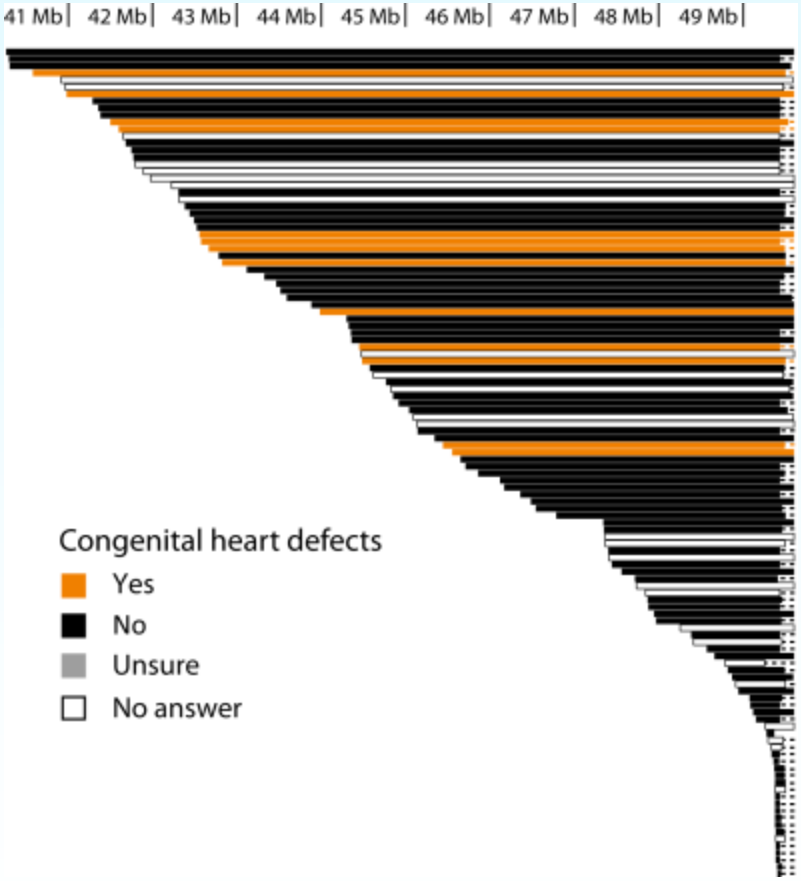
Soorya et al., 2013

Genotype-Phenotype



Relationship between presence of congenital heart defects and deletion size in the PMS International Registry

Betancur, C

The spectrum of epilepsy and electroencephalographic abnormalities due to *SHANK3* loss-of-function mutations

J. Lloyd Holder, Jr. and Michael M. Quach

Epilepsia, 57(10):1651–1659, 2016

Summary

Objective: The coincidence o
intellectual disability.[1] Indivi
intellectual disability, autism,
ologies and electroencephalog
in detail. With the recent repo
2% of individuals with modera
with autism, determining the
abnormalities will be critical
families of patients with *SHAN*

Methods: A retrospective chart review was performed of all individuals treated at the Blue Bird Circle Clinic for Child Neurology who have been identified as having either a chromosome 22q13 microdeletion encompassing *SHANK3* or a loss-of-function mutation in *SHANK3* identified through whole-exome sequencing. For each subject, the presence or absence of seizures, seizure semiology, frequency, age of onset, and efficacy of therapy were determined. Electroencephalography studies were reviewed by a board certified neurophysiologist. Neuroimaging was reviewed by both a board certified pediatric neuroradiologist and child neurologist.

Results: There is a wide spectrum of seizure semiologies, frequencies, and severity in individuals with *SHANK3* mutations. There are no specific EEG abnormalities found in our cohort, and EEG abnormalities were present in individuals diagnosed with epilepsy and those without history of a clinical seizure.

Significance: All individuals with a mutation in *SHANK3* should be evaluated for epilepsy due to the high prevalence of seizures in this population. The most common semiology is atypical absence seizure, which can be challenging to identify due to comorbid intellectual disability in individuals with *SHANK3* mutations; however, no consistent seizure semiology, neuroimaging findings, or EEG findings were present in the majority of individuals with *SHANK3* mutations.

Significance: All individuals with a mutation in *SHANK3* should be evaluated for epilepsy due to the high prevalence of seizures in this population. The most common semiology is atypical absence seizure, which can be challenging to identify due to comorbid intellectual disability in individuals with *SHANK3* mutations; however, no consistent seizure semiology, neuroimaging findings, or EEG findings were present in the majority of individuals with *SHANK3* mutations.

Jimmy Holder, MD

research & treatment @ mount sinai

Neurobehavioral Profile and Brain Imaging Study of the 22q13.3 Deletion Syndrome in Childhood

Anne Philippe, MD, PhD[a], Nathalie Boddaert, MD, PhD[b], Laurence Vaivre-Douret, PhD[c,d], Laurence Robel, MD, PhD[c], Laurent Danon-Boileau, PhD[e], Valérie Malan, MD[a], Marie-Christine de Blois, MD[a], Delphine Heron, MD[f], Laurence Colleaux, PhD[a], Bernard Golse, MD[c], Monica Zilbovicius, MD, PhD[b], Arnold Munnich, MD, PhD[a]

Pediatrics 2008;122:e376–e382

Cerebellar and posterior fossa malformations in patients with autism-associated chromosome 22q13 terminal deletion

Kimberly A. Aldinger[1,10], **Jillene Kogan**[2,11], **Virginia Kimonis**[3], **Bridget Fernandez**[4], **Denise Horn**[5], **Eva Klopocki**[5], **Brian Chung**[6], **Annick Toutain**[7], **Rosanna Weksberg**[6], **Kathleen J. Millen**[8], **A. James Barkovich**[9], and **William B. Dobyns**[8]

Am J Med Genet A. 2013 January

Neural selectivity for communicative auditory signals in Phelan-McDermid syndrome

A. Ting Wang[1,2,3,4*], Teresa Lim[5], Jesslyn Jamison[1,2], Lauren Bush[6], Latha V. Soorya[7], Teresa Tavassoli[1,2], Paige M. Siper[1,2], Joseph D. Buxbaum[1,2,3,4,8,9] and Alexander Kolevzon[1,2,4,9,10]

Journal of Neurodevelopmental Disorders (2016) 8:5

Neuroimaging Findings

- Most descriptions of PMS (n=~70) report higher than expected rates of structural brain changes (~70%):
  - thinning or hypoplasia of the corpus callosum;
  - white matter changes (e.g., delayed myelination, generalized white matter atrophy);
  - ventricular dilatation;
  - cysts;
  - cerebellar malformations (e.g., hypoplasia).

pii: zsw062 http://dx.doi.org/10.1093/sleep/zsw062

ORIGINAL ARTICLE

Sleep Disturbances in Individuals With Phelan-McDermid Syndrome: Correlation With Caregivers' Sleep Quality and Daytime Functioning

Della Bro, MS, CGC[1]; Ruth O'Hara, PhD[2]; Michelle Primeau, MD[2,3]; Andrea Hanson-Kahn, MS, LCGC[4,5]; Joachim Hallmayer, MD[2]; Jonathan A. Bernstein, MD, PhD[5]

[1]Virginia Piper Cancer Institute, Allina Health, Minneapolis, MN; [2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA; [3]Department of Sleep Medicine, Palo Alto Medical Foundation, Sunnyvale, CA; [4]Department of Genetics, Stanford University School of Medicine, Stanford, CA; [5]Department of Pediatrics, Stanford University School of Medicine, Stanford, CA

- Clinically significant sleep problems appear prevalent in children with PMS (90% in this sample);
- Disordered child sleep correlates with disordered caregiver sleep;
- Most children with PMS have not been formally evaluated for sleep disorders;
- Addressing sleep problems in children with PMS may improve the well-being of the entire family.

Table 3: Summary of Clinical Recommendations for Assessment

Medical Specialty	Common Clinical Features	Assessments
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	Motor skill deficits	
Endocrinology	Short/tall stature	Monitor height, weight, and body mass index
	Hypothyroidism	Metabolic work-up, including thyroid function
		Nutritional assessment
Nephrology	Vesicoureteral reflux	Renal and bladder ultrasonography
	Urinary tract infections	voiding cystourethrogram
	Hydronephrosis	Monitoring of blood pressure
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	Pica	Bowel regimens
		Referral to behavioral therapy
Primary Care/ Developmental Pediatrics	Upper respiratory tract infections	Careful and consistent monitoring and management Referral to otolaryngology, ophthalmology, physiatry, dental, and orthopedics
	Recurring ear infections	
	Hearing and vision problems	
	Lymphedema	
	Dental problems	
	Decreased perspiration/heat intolerance	

Kolevzon et al., 2014

Practice Parameters for Medical Assessment and Monitoring of Phelan-McDermid Syndrome

What families and doctors should talk about

Psychiatry & Psychology

- Autism spectrum disorder	☐ Gold standard diagnostic assessments
- Aberrant behavior	☐ Psychiatric evaluation
- Intellectual disability	☐ Cognitive and adaptive behavior testing
- Absent or delayed speech	☐ Speech and language evaluation

Endocrinology

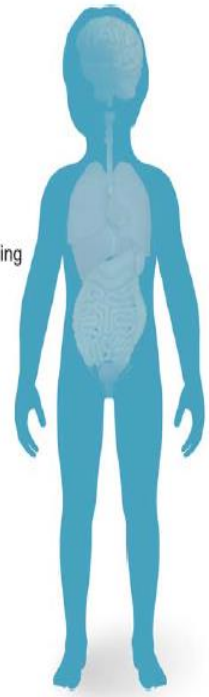
- Short/tall stature	☐ Monitor height, weight, and body mass index
- Hypothyroidism	☐ Metabolic work-up, including thyroid function
	☐ Nutritional assessment

Cardiology

- Congenital heart defects	☐ Electrocardiography
	☐ Echocardiography

Gastroenterology

- Gastroesophageal reflux	☐ Referral for dietary changes and/or medication
- Constipation/ diarrhea	☐ Bowel regimens
- Pica	☐ Referral to behavioral therapy



Neurology

- Seizures	☐ Overnight video electroencephalography
- Structural brain abnormalities	☐ Brain imaging and head circumference monitoring
- Feeding difficulties	☐ Feedling therapy evaluation
- Hypotonia	☐ Occupational and physical therapy evaluations
- Motor skills deficits	

Nephrology

- Vesicoureteral reflux	☐ Renal and bladder ultrasonography
- Urinary tract infections	☐ Voiding cystourethrogram
- Hydronephrosis	☐ Monitoring of blood pressure
- Renal cysts, hypoplasia, or agenesis	

Primary care/ developmental pediatrics

- Upper respiratory tract infections	☐ Careful and consistent monitoring and management
- Recurring ear infections	☐ Referral to otolaryngology, ophthalmology, physiatry, dental and orthopedics
- Hearing and vision problems	
- Lymphedema	
- Decreased perspiration/ heat intolerance	

pmsf

Phelan-McDermid Syndrome Foundation

This document is meant as a guide. Not all patients need all tests.

www.pmsf.org | v1, June, 2016

Adapted from Kolevzon et al. (2014), Journal of Neurodevelopmental Disorders (www.jneurodevdisorders.com/content/6/1/39)

Recommendations for Clinical Assessment in Phelan McDermid Syndrome

Medical Specialty	Assessment Recommended	Performed prior to your visit	Completed during your visit	Recommendation for follow-up
Primary Care/Development Pediatrics	Careful and routine monitoring	X		Age specific
	Hearing Assessment	X		
	Visual Assessment	X		
	Monitoring of height, weight and BMI	X	X	Ongoing
	Otolaryngology (ENT)	X		
	Pediatric dentistry	X		Every six months
	Physiatrist/physical therapy	X		Ongoing
Psychiatric and Psychology	Psychiatric evaluation with focus on autism spectrum disorder	X	X	Every year
	Autism Diagnostic Observation Schedule (ADOS)	X	X	As indicated
	Cognitive or Developmental Assessment	X	X	Every year
	Speech and Language Evaluation/Therapy	X		Ongoing
	Adaptive Function Testing	X		Every year
	Educational Assessment	X		Ongoing
	Occupational Therapy	X		Ongoing
Neurology	Motor development, coordination and gait monitoring, as well as conditions that might be associated with hypotonia, like neuromuscular scoliosis and feeding problems	X	X	Ongoing
	Overnight video EEG	X		As clinically indicated
	Structural brain MRI	X		As clinically indicated
	Head circumference up to 36 months	X		
Nephrology	Renal and bladder ultrasonography	X		As clinically indicated
Cardiology	Echocardiogram	X		As clinically indicated
	Electrocardiogram	X		As clinically indicated
Endocrinology	Thyroid function	X		As clinically indicated
	Nutritional assessment	X		As clinically indicated

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*Dr. Buxbaum and Mount Sinai hold a shared patent for the use of IGF-1 in PMS

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- Craig Powell
- Matt Mosconi
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Icahn School of Medicine at Mount Sinai

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