The 7q11.23 Microduplication Syndrome: A Clinical Report with Review of Literature

Elham Abbas[1] Devin M. Cox[1,2] Teri Smith[1] Merlin G. Butler[1,2]

[1] Departments of Psychiatry and Behavioral Sciences, University of Kansas Medical Center, Kansas City, Kansas, United States
[2] Department of Pediatrics, University of Kansas Medical Center, Kansas City, Kansas, United States

Address for correspondence Merlin G. Butler, MD, PhD, Department of Psychiatry and Behavioral Sciences, University of Kansas Medical Center, 3901 Rainbow Blvd, MS 4015, Kansas City, Kansas 66160, United States (e-mail: mbutler4@kumc.edu).

J Pediatr Genet 2016;5:129–140.

Abstract

We report a 14-year-old adolescent girl with selective mutism (SM) and a 7q11.23 microduplication detected by chromosomal microarray (CMA) analysis and reviewed the literature from 18 published clinical reports. Our patient had specific phobias, SM, extreme anxiety, obesity, cutis marmorata, and a round appearing face with a short neck and over folded ears. We reviewed the published clinical, cognitive, behavioral, and cytogenetic findings grouped by speech and language delay, growth and development, craniofacial, clinical, and behavior and cognitive features due to the 7q11.23 microduplication. This microduplication syndrome is characterized by speech delay (91%), social anxiety (42%), attention deficit hyperactivity disorder (ADHD, 37%), autism spectrum disorder (29%), and separation anxiety (13%). Other findings include abnormal brain imaging (80%), congenital heart and vascular defects (54%), and mild intellectual disability (38%). We then compared the phenotype with Williams–Beuren syndrome (WBS) which is due to a deletion of the same chromosome region. Both syndromes have abnormal brain imaging, hypotonia, delayed motor development, joint laxity, mild intellectual disability, ADHD, autism, and poor visuospatial skills but opposite or dissimilar findings regarding speech and behavioral patterns, cardiovascular problems, and social interaction. Those with WBS are prone to have hyperverbal speech, lack of stranger anxiety, and supravalvular aortic stenosis while those with the 7q11.23 microduplication have speech delay, SM, social anxiety, and are prone to aortic dilatation.

Keywords

- 7q11.23 microduplication
- selective mutism
- extreme anxiety
- obesity
- round appearing face
- speech delay

Introduction

The 7q11.23 microduplication syndrome has been reported in 18 published studies from the literature due to a duplication of the chromosome 7q11.23 band which contains 28 genes and is the same region deleted in the better studied Williams–Beuren syndrome (WBS).[1–19] WBS is characterized by intellectual disability and cardiovascular disease particularly supravalvular aortic stenosis and elastin arteriopathy, dysmorphic facial features (e.g., broad forehead, periorbital fullness, malar flattening, long philtrum, thick vermillion of lips, and large earlobes), connective tissue abnormalities, intellectual disability, loquacious personality with lack of stranger anxiety, hoarse voice, specific phobias, hyperacusis, strengths in verbal memory or language with extreme weakness in visuospatial skills, hypercalcemia, and endocrine with growth abnormalities.[20–24] The most common features reported in the 7q11.23 microduplication syndrome are speech problems, anxiety disorders, autism, and mild dysmorphic features[3,14] and the prevalence is estimated at 1 in 7,500 to 20,000 individuals.[19] Selective mutism (SM) as an abnormal speech behavior has been reported in the

received
November 18, 2015
accepted after revision
April 11, 2016
published online
June 20, 2016

DOI http://dx.doi.org/10.1055/s-0036-1584361.
ISSN 2146-4596.

7q11.23 microduplication syndrome, for example, Velleman and Mervis[14] described several patients with this cytogenetic anomaly and SM.

Herein, we report a 14-year-old adolescent girl with SM, social anxiety disorder, and the 7q11.23 duplication syndrome which involves the same chromosome region deleted in the WBS, due to a classical deletion of 1.5 to 1.8 Mb in size and usually contains 28 genes [OMIM 194050]. Deletions and duplications within this region occur at a frequent rate due to flanking sections of low copy DNA repeats which can lead to non-allelic homologous recombination as seen in other microdeletion syndromes, such as, Prader–Willi and Angelman syndromes and the 22q11.2 deletion. Several of these deletion syndromes have recognized reciprocal duplications (e.g., dup 15q11-q13, dup 22q11.2) involving the same chromosome regions. Our report is focused on two major aims: a clinical report of a 14-year-old adolescent girl with the 7q11.23 microduplication, and summary of the literature reviewing the clinical, genetic and, behavior findings of this microduplication syndrome and a review of the similarities and differences in behavior and clinical features in relationship to WBS.

Clinical Report

Our patient is a 14-year-old adolescent girl, born at full term from an uncomplicated pregnancy and delivered vaginally. She weighed 4.03 kg (90th percentile) at birth. She met all her motor milestones appropriately with the exception of walking (at 18 mo) and toilet training (at 4 y 6 mo). Her speech was delayed. She had surgical correction of right-sided strabismus at the age of 3 years and developed severe anxiety at about the same time, particularly when separating from her mother. At preschool, she would not speak to her teacher and at the age of 4 years was diagnosed with separation anxiety, social anxiety, and SM. She did not exhibit irritability or outbursts at that time and made good eye contact, but was generally withdrawn, anxious, and mute around unfamiliar people. She was evaluated for autism spectrum disorder (ASD) and ADHD at 4 years of age but did not meet the diagnostic criteria. She was started on Celexa which helped her anxiety, and continued the treatment until the age of 7 years when her behavioral problems decreased. At 10 years of age, her SM symptoms worsened and interfered with daily life. She did not make friends and had difficulty connecting with others. Her parents reported findings of separation anxiety and hoarding behaviors. She preferred to spend time at home and became distressed during interactive social settings. She experienced three episodes of enuresis at the age of 14 years during times of stress. She was anxious in crowded settings or around strangers. She became very clingy. She demonstrated explosiveness, over-reactivity, or low frustration tolerance, and exhibited problems in showing emotions. She lacked empathy. She developed phobia of escalators, needles, and medical procedures. She denied sensory issues, but did not like to shower. She had no repetitive or stereotypic behaviors, but was reevaluated for ASDs with the checklist for autism spectrum disorder; she did not meet the criteria. No learning disabilities were noted, and currently she is enrolled in three advanced classes in the school setting.

She was found to have increased size (edema) of both optic nerves, with a sedated brain magnetic resonance imaging (MRI) indicating mild generalized volume loss with several nonspecific flair hyperintense foci within the hemispheric white matter and mild volume loss. She had increased T2 weighted signals of the optic nerves. She passed both hearing and vision screens and her blood pressure was normal. She had an echocardiogram under sedation that was normal. A referral was made to the genetics clinic at 14 years of age, at this time she would talk to her parents and briefly with acquainted individuals only. She would listen to conversations but would not readily volunteer to participate or answer questions. She appeared anxious and would cling to her father during the clinic visit or spend time drawing multiple detailed pictures of individuals and objects from memory, but would not draw a specific object (e.g., bicycle) when asked.

On physical examination, at 14 years of age, she was a pleasant caucasian adolescent girl with a height of 154 cm (18th percentile), weight of 75.84 kg (96th percentile), body mass index (BMI) of 31 (>97 percentile), and a head circumference of 56.5 cm (97th percentile). She had a round appearing face with a relatively short neck and bilaterally overfolded ears. She had generalized cutis marmorata, freckles on her right hand and feet, several vertical striae on her abdomen, a minor crease on the plantar surface of her left foot between the 2nd and 3rd toe and 2 to 3 toe syndactyly. She would not respond to or answer questions and refused to have her picture taken during the clinic visit. The family history indicated that her father suffered from depression and her paternal grandmother suffered from social anxiety and had heart and kidney problems. She had one maternal half-uncle who had strabismus and one maternal first cousin with ADHD.

Results and Discussion

We performed a high-resolution chromosomal microarray (CMA) and fragile X testing on the 14-year-old adolescent girl presenting with SM and behavioral problems. The FirstStepDx PLUS (a CMA service provided commercially by Lineagen Inc., Salt Lake City, Utah, United States) was undertaken to identify a cause of her clinical presentation. The CMA platform that was used included the Affymetrix CytoScanHD array with 88,435 custom probes combined with an existing 2,036,689 oligonucleotides and 748,296 single nucleotide polymorphic (SNP) probes. This microarray analysis showed a 1.47 Mb duplication at 7q11.23 [ISCN: arr[hg19] 7q11.23 (72,664,088–74,142,215)x3] representing 29 genes [27 within the duplication region and 2 that were partially duplicated (see ►**Fig. 1**)]. No further copy number changes were detected in the genome. Paternal testing showed normal CMA findings, the mother was unavailable for testing. Fragile X DNA testing was normal with 30 and 32 CGG triplet repeats detected.

In the review of literature, we found 18 reported studies with clinical and genetic data from individuals with the 7q11.23 microduplication published between 2005 and 2015. The data from the published reports were then organized into four tables. ►**Table 1** described growth/developmental and craniofacial features, while ►**Table 2** included

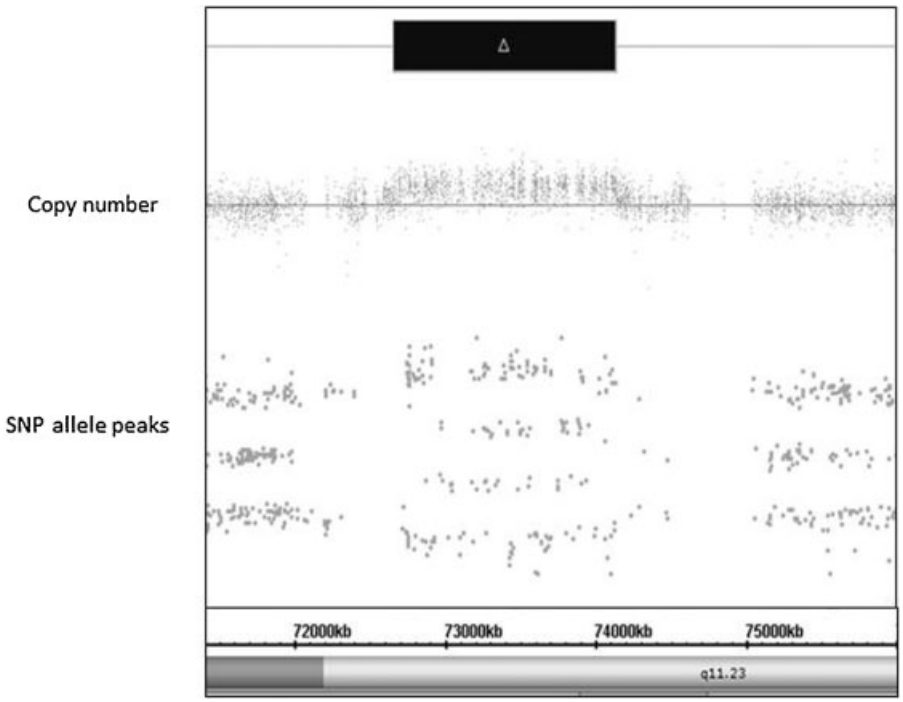

Fig. 1 A 1,478 Mb duplication (black rectangle) was found within the chromosome 7q11.23 band at genomic coordinates 72,664,088–74,142,215 with high resolution microarray analysis (NCBI build 37, Feb 2009, hg 19). The figure shows the duplication via both copy number pattern and single nucleotide probe allele peak patterns. The copy number probes indicating the presence of a duplication are noted above the baseline probes (representing a normal copy number of 2). The single nucleotide probes are present in two separate rows instead of a single row indicating the duplicated region. Genes fully included within this duplication were *NSUN5, TRIM50, FKBP6, FZD9, BAZ1B, BCL7B, TBL2, MLXIPL, VPS37D, DNAJC30, WBSCR22, STX1A, MIR4284, ABHDD11-AS1, ABHD11, CLDN3, CLDN4, WBSCR27, WBSCR28, ELN, LIMK1, EIF4H, MIR590, LAT2, RFC2, CLIP2,* and *GTF2IRD1*. Genes partially included within this duplication were *GTF2IRD2P1* and *GTF2I*.

other clinical features. ►**Table 3** summarized information describing behavioral and cognitive features. ►**Table 4** included the summary of the 7q11.23 chromosomal duplication findings reported in the literature.

Clinical, Behavioral and Genetic Findings

Speech and Language of 7q11.23 Microduplication Syndrome

SM was the chief complaint that led to the genetic evaluation for our patient and now recognized as a feature in this rare microduplication syndrome. SM is an anxiety disorder characterized by lack of speech in settings where speaking is socially expected. Associated features can include shyness, social anxiety with fear of social embarrassment, withdrawal, tantrums, crying, clinging, and compulsive traits[25] with a mean age of onset ranging from 2.7 to 4.1 years.[26,27] Some children outgrow the condition without intervention.[28] The prevalence ranges from 0.03 to 1% and does not vary by sex or race/ethnicity. Social situations are avoided or endured with intense anxiety out of proportion to the actual threat. SM causes significant problems in functioning[25] with some people (i.e., 6–10%) showing comorbid externalizing or oppositional disorders.[29] Speech and language disorders are present in 30 to 38% of children with SM[30] and substantial psychopathology noted among parents including depression, lack of drive, neurotic or personality disorders, alcoholism, withdrawal, shyness, and irritability.[31] SM has been associated with mild intellectual disability, Asperger syndrome,[32] enuresis (in 17% of children), encopresis (7%), and tic disorder (7%).[29,33]

Our review of literature revealed that 91% of the 163 reported individuals with the 7q11.23 microduplication had significant speech/language delay (see ►**Table 1**) as a hallmark feature of this syndrome. Expressive language was found to be impaired more than receptive language. For example, Velleman and Mervis[14] reported that 41 of their 42 subjects with the microduplication had detectable ongoing oral, motor or speech sound problems but only a few studies contained details regarding the nature of speech disorders associated with this syndrome. The symptoms were divided into four categories: oral apraxia, verbal apraxia or childhood apraxia of speech, phonological disorder, and dysarthria. Most individuals demonstrated mixed motor speech disorders with symptoms in more than one area with >75% meeting full criteria and exhibited either dysarthria or symptoms of dysarthria. More than 50% of children demonstrated a phonological disorder or phonological symptoms and >50% had oral apraxia or oral apraxia symptoms. Many children demonstrated effortful, choppy speech typically resulting in inappropriate word stress patterns. Velleman and Mervis[14] further reported that most adults learned to compensate with errors made primarily in challenging multisyllabic words (e.g., "aluminum"). Other studies have also reported similar findings with phonological errors, incomplete pronunciations, and use of idiosyncratic words

Table 1 Growth/developmental and craniofacial features of 7q11.23 microduplication syndrome

	Somerville et al[20]	Kriek et al[5]	Torniero et al[12]	Kirchhoff et al[4]	Depienne et al[2]	Berg et al[1]	Torniero et al[12]	Van der Aa et al[13]	Orellana et al[7]	Velleman and Mervis[14]	Malenfant et al[6]	Dixit et al[3]	Prontera et al[9]	Zarate et al[15]	Parrott et al[8]	Morris et al[16]	Patil et al[17]	Present Case	Total	%
Number of cases	1	2	1	1	1	7	2	14	1	42	1	8	1	5	9	64	2	1	163	
Growth and development																				
Delayed speech	1/1	1/2	1/1	1/1	1/1	7/7	2/2	13/13	1/1	41/42	1/1	7/8	1/1	4/5	5/9	NA	2/2	0/1	89/98	**91**
Delayed motor	1/1	0/2	0/1	0/1	1/1	6/7	2/2	11/14	1/1	NA	NA	6/8	1/1	4/5	4/9	NA	1/2	1/1	39/56	**70**
Short stature	1/1	0/2	0/1	0/1	1/1	0/7	0/2	2/14	1/1	NA	1/1	2/8	0/1	1/5	1/9	3/45	0/2	0/1	13/102	**13**
Obesity	0/1	0/2	1/1	0/1	0/1	1/7	0/2	0/14	0/1	NA	0/1	1/8	0/1	0/5	1/9	14/50	0/2	1/1	19/107	**18**
Craniofacial features																				
Cranial																				
Craniosynostosis/ abnormal head shape	1/1	2/2	0/1	0/1	0/1	0/7	1/2	1/14	1/1	NA	1/1	0/8	0/1	0/5	0/9	47/64	1/2	0/1	55/121	**45**
Macrocephaly	0/1	0/2	1/1	0/1	0/1	1/7	0/2	1/14	0/1	NA	0/1	0/8	1/1	0/5	1/9	32/64	1/2	0/1	38/121	**31**
Face/neck																				
Asymmetric face	1/1	1/2	1/1	0/1	0/1	0/7	0/2	0/14	1/1	NA	1/1	0/8	0/1	0/5	0/9	54/64	1/2	0/1	60/121	**50**
Round face	0/1	0/2	1/1	0/1	0/1	0/7	0/2	0/14	0/1	NA	0/1	0/8	0/1	0/5	0/9	0/64	0/2	1/1	2/121	**2**
Short neck	0/1	0/2	1/1	0/1	0/1	0/7	1/2	0/14	0/1	NA	0/1	0/8	0/1	0/5	0/9	0/64	0/2	1/1	3/121	**2**
Forehead																				
Broad	0/1	0/2	0/1	1/1	0/1	0/7	0/2	5/14	1/1	NA	0/1	6/8	0/1	0/5	1/9	40/64	2/2	0/1	56/121	**46**
Straight brow line	0/1	0/2	0/1	0/1	0/1	0/7	0/2	9/14	0/1	NA	0/1	7/8	0/1	0/5	1/9	33/64	2/2	0/1	52/121	**43**
High/prominent	1/1	0/2	0/1	0/1	0/1	4/7	1/2	0/14	0/1	NA	0/1	0/8	0/1	0/5	0/9	13/64	1/2	0/1	20/121	**17**
Eyes																				
Deep set eyes	0/1	0/2	0/1	0/1	0/1	0/7	0/2	6/14	0/1	NA	0/1	4/8	0/1	0/5	0/9	29/64	1/2	0/1	40/121	**33**
Hypertelorism	0/1	0/2	0/1	0/1	0/1	1/7	0/2	4/14	0/1	NA	0/1	5/8	0/1	0/5	1/9	1/64	0/2	0/1	12/121	**10**
Strabismus	0/1	0/2	1/1	0/1	0/1	0/7	1/2	0/14	1/1	NA	0/1	0/8	0/1	0/5	0/9	0/64	0/2	1/1	4/121	**3**
Narrow/short palpebral fissures	0/1	0/2	0/1	1/1	0/1	0/7	0/2	0/14	0/1	NA	0/1	0/8	0/1	0/5	1/9	0/64	0/2	0/1	2/121	**2**
Astigmatism	0/1	0/2	0/1	0/1	0/1	1/7	0/2	0/14	1/1	NA	0/1	0/8	0/1	0/5	0/9	0/64	0/2	0/1	2/121	**2**
Optic disc abnormalities	0/1	0/2	0/1	0/1	0/1	0/7	0/2	1/14	0/1	NA	0/1	0/8	0/1	0/5	0/9	0/64	0/2	1/1	2/121	**2**
Nose																				
High/broad tip	1/1	0/2	0/1	0/1	0/1	4/7	0/2	8/14	1/1	NA	1/1	5/8	0/1	2/5	0/9	49/64	1/2	0/1	72/121	**56**
Ears																				
Abnormal/ overfolded helix	0/1	0/2	0/1	0/1	1/1	3/7	0/2	0/14	1/1	NA	0/1	2/8	0/1	0/5	0/9	27/64	0/2	1/1	35/121	**29**
Posteriorly rotated	0/1	0/2	1/1	0/1	0/1	2/7	2/2	4/14	0/1	NA	0/1	4/8	0/1	0/5	1/9	7/64	0/2	0/1	21/121	**17**
Low set	0/1	0/2	1/1	0/1	0/1	1/7	1/2	3/14	1/1	NA	1/1	3/8	0/1	2/5	1/9	0/64	1/2	0/1	15/121	**12**
Prominent/ protruding	0/1	0/2	0/1	1/1	0/1	0/7	0/2	0/14	0/1	NA	0/1	3/8	0/1	0/5	0/9	11/64	0/2	0/1	15/121	**12**

Table 1 (*Continued*)

	Somerville et al[20]	Kriek et al[5]	Torniero et al[12]	Kirchhoff et al[4]	Depienne et al[2]	Berg et al[1]	Torniero et al[12]	Van der Aa et al[13]	Orellana et al[7]	Velleman and Mervis[14]	Malenfant et al[6]	Dixit et al[3]	Prontera et al[9]	Zarate et al[15]	Parrott et al[8]	Morris et al[16]	Patil et al[17]	Present Case	Total	%
Mouth/jaw																				
Columella anomaly	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	50/64	NA	NA	50/64	**78**
Thin upper lip	0/1	0/2	1/1	0/1	0/1	4/7	1/2	12/14	0/1	NA	1/1	5/8	0/1	0/5	0/9	52/64	1/2	0/1	77/121	**64**
Short philtrum	1/1	0/2	1/1	0/1	0/1	3/7	1/2	6/14	0/1	NA	1/1	6/8	0/1	2/5	0/9	37/64	2/2	0/1	60/121	**50**
High arched palate	1/1	0/2	0/1	0/1	0/1	1/7	0/2	0/14	1/1	NA	0/1	0/8	0/1	0/5	0/9	28/64	0/2	0/1	31/121	**26**
Retrognathia/ micrognathia	1/1	0/2	0/1	0/1	1/1	0/7	1/2	0/14	1/1	NA	0/1	0/8	1/1	0/5	0/9	19/64	1/2	0/1	25/121	**21**
Cleft lip/cleft palate	0/1	0/2	0/1	0/1	0/1	2/7	0/2	0/14	1/1	NA	0/1	1/8	0/1	0/5	0/9	0/64	0/2	0/1	4/121	**3**
Dental malocclusion/overcrowding	1/1	0/2	0/1	0/1	0/1	1/7	0/2	0/14	1/1	NA	0/1	0/8	0/1	0/5	0/9	0/64	0/2	0/1	3/121	**2**

or unintelligible speech in individuals with the 7q11.23 microduplication syndrome.[2,11] Most individuals were found to have nonverbal communication via gestures, signs, pointing, drawings or writings.[1–3,6,12,14,20] Consistent with the reported literature, our patient had delayed speech development but did not have identified communication, speech, or articulation problems.

Behavioral and Cognitive Features of 7q11.23 Microduplication Syndrome

Several psychiatric disorders are associated with the 7q11.23 microduplication syndrome with social anxiety reported in 42% of cases followed by ADHD (in 37% of individuals), SM (in 28%), autism (in 29%), specific phobias (in 36%), and separation anxiety (in 13%). Velleman and Mervis[14] further reported that >75% of children with this microduplication had at least one anxiety disorder and current findings are consistent with these observations. Aggression, temper outbursts, and oppositional defiant disorders were reported in 22% of cases. Other behavioral problems included repetitive or stereotypical behaviors (11%), poor social skills (8%), sensory issues (7%), sleep problems (4%), self-injurious behaviors (4%), and hoarding (2%). Thirty-eight percent of the individuals with the 7q11.23 microduplication syndrome evaluated for cognition were reported to have mild intellectual disability with 21% having moderate and 6% with severe intellectual disability (see ►**Table 3**). Although our patient's chief complaint was SM and behavioral problems with normal cognition, she had social and separation anxiety, aggression/temper tantrums, specific phobias of escalators, needles and medical procedures, hoarding behavior, and poor social skills in selective settings.

In addition, Mulle et al[34] reported that this reciprocal duplication of the 7q11.23 band is seen in a deletion form in WBS which confers an approximate ten-fold increased risk for schizophrenia. They reported duplications at the 7q11.23 band seen in 11 of 14,387 cases of schizophrenia but only 1 in 28,139 controls. Three of the schizophrenic duplication carriers with available detailed retrospective data showed social anxiety and language delay prior to the onset of schizophrenia.

Growth and Development of 7q11.23 Microduplication Syndrome

Of individuals reported with the 7q11.23 microduplication in the literature, 70% had delayed motor development (see ►**Table 1**). Thirteen percent were found to have short stature and 18% were obese. Our patient also had delayed motor milestones and walked at 18 months of age. At the age of 14 years, her weight was at the 96th percentile, height was at the 18th percentile, and her BMI was 31 or in the obese range.

Craniofacial Features of 7q11.23 Microduplication Syndrome

The review of literature revealed that the 7q11.23 microduplication syndrome is associated with recognizable craniofacial features (see ►**Table 1**). The most common features were a thin upper lip (64%), high broad nose (56%), short philtrum (50%), asymmetric face (50%), craniosynostosis/abnormal head shape (45%), straight brow line (43%), macrocephaly (31%),

Table 2 Clinical features of 7q11.23 microduplication syndrome

	Somerville et al[20]	Kriek et al[5]	Torniero et al[12]	Kirchhoff et al[4]	Depienne et al[2]	Berg et al[1]	Torniero et al[12]	Van der Aa et al[13]	Orellana et al[7]	Malenfant et al[6]	Dixit et al[3]	Prontera et al[9]	Zarate et al[15]	Parrott et al[8]	Morris et al[16]	Patil et al[17]	Present Case	Total	%
Number of cases	1	2	1	1	1	7	2	14	1	1	8	1	5	9	64	2	1	121	
Cutaneous																			
Cutis marmorata	0/1	0/2	0/1	0/1	0/1	0/7	0/2	1/14	0/1	0/1	0/8	0/1	0/5	0/9	21/47	0/2	1/1	23/95	**24**
Café au lait spots	0/1	0/2	1/1	0/1	0/1	1/7	0/2	0/14	0/1	0/1	0/8	0/1	0/5	0/9	0/64	0/2	0/1	2/121	**2**
Musculoskeletal																			
Joint laxity	0/1	0/2	0/1	0/1	0/1	1/7	0/2	5/14	0/1	0/1	7/8	0/1	3/5	0/9	5/53	0/2	0/1	21/110	**19**
Cubitus valgus	0/1	0/2	1/1	0/1	0/1	1/7	0/2	0/14	0/1	0/1	0/8	0/1	0/5	0/9	1/53	0/2	0/1	3/110	**3**
Long thin fingers/ toes	0/1	0/2	0/1	0/1	0/1	1/7	0/2	0/14	1/1	0/1	0/8	0/1	0/5	0/9	0/64	0/2	0/1	2/121	**2**
Cardiovascular																			
Aortic dilation	0/1	0/2	0/1	NA	0/1	0/7	0/2	0/14	0/1	0/1	0/8	0/1	3/5	9/9[d]	12/26	0/2	NA	24/81	**30**
Patent ductus arteriosus	0/1	0/2	0/1	NA	0/1	0/7	0/2	3/14	0/1	0/1	0/8	0/1	0/5	1/9	4/53	0/2	NA	8/108	**7**
Ventricular septal defect	0/1	1/2	0/1	NA	0/1	0/7	0/2	0/14	0/1	0/1	0/8	0/1	1/5	0/9	1/53	1/2	NA	4/108	**4**
Atrial septal defect	0/1	0/2	0/1	NA	0/1	0/7	0/2	1/14	0/1	0/1	0/8	0/1	1/5	0/9	1/53	0/2	NA	3/108	**3**
Other	0/1	1/2[a]	0/1	NA	0/1	1/7[b]	0/2	0/14	1/1[c]	0/1	0/8	0/1	2/5[e]	4/9[f]	1/53[g]	1/2[h]	NA	11/108	**10**
Neurological[1]																			
Abnormal brain imaging	NA	NA	1/1	NA	1/1	3/4	1/2	5/7	1/1	0/1	2/2	1/1	NA	2/2	31/38	[i]1/1	NA	49/61	**80**
Hypotonia	1/1	0/2	0/1	0/1	1/1	3/7	1/2	8/14	0/1	0/1	5/8	1/1	1/5	1/9	31/53	0/2	0/1	53/110	**48**
Poor visuospatial skills	0/1	NA	1/1	NA	1/1	0/3	NA	NA	1/1	0/1	NA	0/1	NA	NA	NA	NA	0/1	3/10	**30**
Seizures	0/1	0/2	1/1	0/1	0/1	2/7	1/2	2/14	0/1	0/1	0/8	0/1	0/5	3/9	10/53	0/2	0/1	19/110	**17**
Urogenital																			
Cryptorchidism	0/1	0/2	0/1	0/1	0/1	0/7	1/2	3/14	1/1	0/1	1/8	0/1	1/5	1/9	3/53	0/2	0/1	11/110	**10**
Enuresis	0/1	0/2	0/1	0/1	1/1	0/7	0/2	0/14	0/1	1/1	0/8	0/1	0/5	0/9	0/64	0/2	1/1	3/121	**2**

[a]Subvalvular pulmonic stenosis.
[b]II/IV cardiac murmur.
[c]Bradycardia, supravalvular aortic stenosis with poststenotic dilation.
[d]Dilation of ascending aorta - 8/9 cases; dilation of aortic root - 4/9 cases; dilation of sinotubular junction - 2/9 cases.
[e]Mild aortic insufficiency – 1/5 cases; mildly dilated right atrium – 1/5 cases.
[f]Patent foramen ovale - 1/9 cases, ventricular trabeculations - 2/9 cases, dilated cardiomyopathy+ left ventricular noncompaction - 1/9 cases.
[g]Subvalvular aortic stenosis.
[h]Mild aortic regurgitation.
[i]Other neurological/neurodevelopmental abnormalities reported by Morris et al (2015)[16] include – abnormalities of gait and station (33/53 = 62.3%), involuntary overflow movements (83% of children,14 years), departmental coordination disorder (38/46 = 82.6%).

Table 3 Behavioral and cognitive features of 7q11.23 microduplication syndrome

	Somerville et al[20]	Torniero et al[12]	Kirchhoff et al[4]	Depienne et al[2]	Berg et al[1]	Van der Aa et al[13]	Orellana et al[7]	Velleman and Mervis[14]	Malenfant et al[6]	Dixit et al[3]	Prontera et al[9]	Parrott et al[8]	Mervis et al[19]	Present case	Total	%
Number of cases	1	1	1	1	7	14	1	30[a]	1	8	1	9	72[#]	1	148	
Psychiatric/behavioral features																
Social anxiety	0/1	0/1	0/1	0/1	4/7	0/14	0/1	15/30	1/1	3/8	0/1	1/9	37/72	1/1	62/148	**42**
Attention-deficit/ hyperactivity disorder	1/1	0/1	0/1	1/1	3/7	4/14	1/1	15/30	0/1	2/8	0/1	2/9	22/62	0/1	51/138	**37**
Selective mutism	0/1	0/1	0/1	0/1	0/7	0/14	0/1	NA[c]	0/1	0/8	0/1	0/9	29/62	1/1	30/108	**28**
Autism	0/1	0/1	1/1[*]	1/1	2/7	6/14	0/1	0/30	1/1	7/8	1/1	1/9	14/42	0/1	34/118	**29**
Specific phobias	0/1	0/1	0/1	0/1	0/7	0/14	0/1	15/30	0/1	0/8	0/1	0/9	37/72	1/1	53/148	**36**
Aggression/ temper outbursts/ODD	0/1	0/1	0/1	1/1	3/7	1/14	1/1	6/30	0/1	2/8	0/1	0/9	15/62	1/1	30/138	**22**
Separation anxiety	0/1	0/1	0/1	0/1	1/7	0/14	0/1	8/30	0/1	0/8	0/1	0/9	8/62	1/1	18/138	**13**
Repetitive/ stereotypical behaviors	0/1	0/1	0/1	1/1	3/7	1/14	0/1	NA[d]	0/1	0/8	0/1	0/9	NA	0/1	5/46	**11**
Poor social skills	0/1	0/1	1/1	0/1	0/7	2/14	0/1[**]	0/30	1/1	0/8	0/1	1/9	NA	1/1	6/76	**8**
Sensory issues	0/1	0/1	0/1	1/1[***]	1/7	0/14	0/1	NA[e]	1/1[***]	0/8	0/1	0/9	NA	0/1	3/46	**7**
Sleep problems	1/1	0/1	0/1	0/1	1/7	0/14	0/1	NA	0/1	0/8	0/1	0/9	NA	0/1	2/46	**4**
Self-injurious behaviors	0/1	0/1	0/1	0/1	2/7	0/14	0/1	NA	0/1	0/8	0/1	0/9	NA	0/1	2/46	**4**
Hoarding	0/1	0/1	0/1	0/1	0/7	0/14	0/1	NA	0/1	0/8	0/1	0/9	NA	1/1	1/46	**2**
Cognition																
Mild disability	1/1	–	–	–	5/7	6/12[b]	–	NA	1/1	1/4	0/1	2/3	0/12	0/1	16/42	**38**
Moderate disability	–	1/1	–	–	2/7	4/12[b]	1/1	NA	–	0/4	0/1	1/3	0/12	0/1	9/42	**21**
Severe disability	–	–	1/1	1/1	–	0/12	–	NA	–	0/4	0/1	0/3	0/12	0/1	2/35	**6**

[*]Asperger syndrome suspected [**]Hypersociable [***]Hyperacusis.
[a]Exact number of cases with specific features not provided. Only approximate percentage provided.
[b]Two patients were too young to be evaluated for intellectual disability.
[c]Exact percentage/number of cases not provided but study reports that 'several' patients had selective mutism.
[d]Exact percentage/number of cases not provided but study reports 'most' children had repetitive behaviors.
[e]Exact percentage/number of cases not provided but study reports 'most' children had sensory modulation difficulties.
[f]ODD: oppositional defiant disorder.
[#]75 subjects were studied and psychiatric behavior analysis performed on 72 individuals (62 children and 10 adults).

Table 4 Reported chromosome findings in 7q11.23 microduplication syndrome from 187 unique subjects

Patient	Genetic testing and/or genomic coordinates	De novo/parent of origin	Duplication size
Somerville et al[20]			
pt 1	FISH	NA	NA
Kriek et al[5]			
pt 1	MLPA, FISH	paternal	1.4–1.7 Mb
pt 2	Karyotype, MLPA	maternal	0.3–0.4 Mb
Kirchhoff et al[4]			
pt 1	MRS-MLPA	NA	
Torniero et al[12]			
pt 1	Array CGH, FISH	De novo	~1.44 Mb
Depienne et al[2]			
pt 1	MLPA, FISH	De novo	NA
Berg et al[1]			
pt 1, 3	CMA, FISH	De novo	~1.55 Mb
pt 2	CMA, FISH	NA	~1.55 Mb
pt 4	72,214,530–75,760,667 (hg 17)[a]	De novo	3.55 Mb
pt 5,6	CMA, FISH	Maternal	~1.55 Mb
pt 5m[b]	CMA, FISH	NA	~1.55 Mb
pt 6m[c], 7	CMA, FISH	NA	~1.55 Mb
Torniero et al[12]			
pt 1	Array CGH	Maternal	1.288 Mb
van der Aa et al[13]			
pt 1,8,11	Array based MLPA	Paternal	1.4–1.5 Mb
pt 2,3,6,7,14	Array based MLPA	De novo	1.4–1.5 Mb
pt 4,5,9,10,12,13	Array based MLPA	Maternal	1.4–1.5 Mb
Orellana et al[7]			
pt 1	Array CGH, FISH	NA	~1.55 Mb
Sanders et al[10]			
pt 1,2,3,4	72,773,570–74,144,177 (hg 19)	De novo	1.37 Mb
Malenfant et al[6]			
pt 1	Array CGH	NA	~1.4 Mb
Dixit et al[3]			
pt 1	Oligonucleotide/SNP array	NA	1.5 Mb
pt 2	Oligonucleotide/SNP array	De novo	1.2 Mb
pt 3	Oligonucleotide/SNP array	De novo	1.4 Mb
pt 4	MLPA	De novo	NA
pt 5	MLPA	NA	NA
pt 6	Oligonucleotide/SNP array	De novo	2.55 Mb
pt 7	Oligonucleotide/SNP array	Maternal	4 Mb

Table 4 (*Continued*)

Patient	Genetic testing and/or genomic coordinates	De novo/parent of origin	Duplication size
Prontera et al[9]			
pt 1	Array CGH	De novo	~1.2 Mb
Parrott et al[8]			
pt 1	72,722,981–74,144,177 (hg 19)	Maternal	1.42 Mb
pt 2,4,5	FISH	Maternal	~1.42 Mb
pt 3	72,662,415–74,115,258 (hg 19)	maternal	1.45 Mb
pt 7	72,876,647–73,987,171 (hg 19)	NA	~1.1 Mb
pt 8	72,772,522–74,339–044 (hg 19)	De novo	~1.5 Mb
Mervis et al[19]			
pt ($N = 75$)	FISH, qPCR, microarray	**Children ($N = 63$):** 38 de novo, 10 maternal, 10 NA, 5 paternal	Microarray size range from 472 kb to 1.4 Mb
		Adults ($N = 12$; relatives—6 mothers, 5 fathers, 1 grandmother): 1 de novo, 2 maternal, 1 paternal, 8 NA	
Morris et al[16,d]			
Pt ($N = 64$; 39 single cases; 25 subjects from 9 families)	FISH, qPCR	29 de novo	NA
		25 familial	
		10 NA	
Zarate et al[15]			
pt 1	Array CGH		2.53 Mb
pt 2m[e]	72,351,461–74,899,935 (hg 18)	NA	2.53 Mb
pt 3	72,472,922–74,259–176 (hg 19)	NA	1.80 Mb
pt 4m[f]	72,828,948–73,040,891 (hg 19)	NA	2.53 Mb
pt 5	72,382,457–73,776,177 (hg 18)	NA	1.40 Mb
Our patient			
pt 1	72,664,088–74,142,215 (hg 19)	NA	1.47 Mb

Abbreviation: NA, not available.
[a]Partially deleted in hg 19 build.
[b]Mother of patient 5.
[c]Mother of patient 6.
[d]Subjects were previously included in Mervis et al[19] and 1 subject was described previously by Sommerville et al.[20]
[e]Mother of patient 1.
[f]Mother of patient 3.

abnormal/overfolded helices (29%), high arched palate (26%), and retrognathia/micrognathia (21%). Other craniofacial features seen in less than 20% of reported individuals arranged in descending frequency were high and prominent forehead (17%), posteriorly rotated ears (17%), low set ears (12%), prominent/protruding ears (12%), hypertelorism (10%), strabismus (3%), cleft lip/palate (3%), and 2% for a round face, short neck and dental problems. She had surgical correction of

right-sided strabismus at 3 years of age and swelling of both optic nerves. She had a normal blood pressure and no history of headaches.

Other Clinical Features of 7q11.23 Microduplication Syndrome

The 7q11.23 microduplication syndrome is associated with several cardiovascular, neurological, musculoskeletal, urogenital, and cutaneous abnormalities. Abnormal brain imaging results were reported in 80% of individuals studied with the 7q11.23 microduplication but no consistent abnormal finding was observed. The anomalies included an abnormal left cerebral temporal lobe,[11] mild dilatation of the left temporal horn and a small arachnoid cyst in the temporal fossa,[2] mild cerebral atrophy, mild prominence of the lateral and third ventricle and gliosis,[1] pachygyria, migration abnormality, and hypoplastic cerebellar vermis,[12] metopic craniosynostosis, supratentorial ventriculomegaly, external benign hydrocephaly, multiple intense focal nodules in the frontal lobe and less intense nodules in the parietal and occipital lobes,[7] and benign hydrocephalus with prominent Virchow–robin spaces.[3] Furthermore, Prontera et al[9] reported functional MRI findings in a patient with the 7q11.23 microduplication syndrome and found that the amygdala, cingulum, and the orbital frontal cortex (corresponding to the social brain) appeared silent. Our subjects' brain MRI showed mild generalized volume loss with the ventricles and subarachnoid spaces mildly prominent in size and configuration. Several nonspecific flair hyperintense foci within the hemispheric white matter were noted with mild volume loss and increased T2 weighted signals of the optic nerves.

Forty-eight percent of cases reported had hypotonia with poor visuospatial skills in 30% of individuals with the 7q11.23 microduplication syndrome. Seventeen percent had seizures. These findings were not present in our patient. Various cardiovascular abnormalities are reported in patients with the 7q11.23 microduplication syndrome with aortic dilation being the most common at 30%. The ascending aorta was reported to be the most common site of dilation with the aortic root and sinotubular junction being less frequently involved.[8] Other reported cardiac abnormalities occurred in 10% of cases and included patent ductus arteriosus (7%), ventricular septal defect (4%), and atrial septal defect (3%). To date, our patient had a normal echocardiogram with no dilatation or abnormalities noted.

Urogenital problems reported in patients with the 7q11.23 microduplication syndrome included cryptorchidism (10%) and enuresis (2%). Our patient was reported to have delayed toilet training and enuresis in social situations. Cutaneous manifestations in this syndrome include cutis marmorata (24%) and café au lait spots (2%). Our patient was found to have cutis marmorata but no other cutaneous manifestations.

Cytogenetic Findings of the 7q11.23 Microduplication Syndrome

The review of literature showed that the majority of microduplications were between 1 and 2 Mb in size (see ►**Table 4**). There were reported individuals whose duplications were smaller (0.3–0.4 Mb in Kriek et al.[5]) than average and some were larger (3.55 Mb in Berg et al.[1]). A list of the 7q11.23 microduplications reported in the literature and their sizes and descriptions can be found in ►**Table 4**.

The majority of reports did not provide breakpoints for the duplication and more research is needed to determine if phenotype–genotype implications exist for the 7q11.23 microduplication syndrome or specific genes that may be involved. However, 187 unique subjects were recorded and analyzed (see ►**Table 4**). Where parent of origin information was available, it was estimated that 8% were paternal in origin, 22% were maternal in origin and 70% were de novo. Our patient's duplication was 1.48 Mb in size and included 27 genes with 2 additional genes being partially involved.

Williams–Beuren Syndrome

The 7q11.23 microduplication seen in our patient was ~1.5 Mb in size and represented a chromosome region that is well characterized but usually involved in a recurrent reciprocal deletion causing the Williams–Beuren syndrome (WBS). These two chromosomal rearrangements can arise de novo or be inherited but present with clinical similarities and differences. Individuals with WBS typically have a mean intelligence quotient (IQ) in the mild to severe intellectual disability range (IQ, 51–70)[35] and with significant deficits in conceptual reasoning, spatial organization, and problem solving, while rated in the borderline range for verbal and nonverbal reasoning and verbal short term memory.[14,35] Language development in WBS is typically delayed with acquisition, resembling that of learning a second language.[14,35] Once speech develops, concrete vocabulary and phonological memory are areas of strength while conceptual and relational vocabularies are areas of weakness.[14] Reading ability ranges from not able to read to comprehending at the grade school level but with greater decoding and comprehension abilities.[14]

Individuals with WBS typically exhibit hyperacusis with an exaggerated emotional response to noise with either aversion or attraction.[35] Facial processing skills with increased recognition of components or features versus configural or holistic processes used to distinguish faces are normal as seen in typically developing individuals.[35] The behaviors seen in WBS are characterized by overfriendliness, charismatic and hyperverbal speech, lack of stranger anxiety, nonsocial anxiety (general anxiety), specific phobias typically of loud noises, people (e.g., doctors) or medical procedures involving blood or injections, and ADHD.[14,24,35] The personality profile for individuals with WBS shows high levels of sociability, empathy, tension, and sensitivity with an eagerness to interact with others.[36] Speech in individuals with WBS is typically overfamiliar, perseverative in responses, and introduces irrelevant experiences.

Conclusion

In summary, this clinical report and review of published data generated a better delineation of the clinical presentation and findings seen in the 7q11.23 microduplication syndrome.

Table 5 Comparison of features seen in the 7q11.23 microduplication and the reciprocal deletion causing Williams-Beuren Syndrome (WBS)

Feature	7q11.23 microduplication	7q11.23 microdeletion
Craniofacial	Broad forehead (46%)	Broad forehead
	Deep set eyes (33%)	Periorbital fullness
	High, broad nose (56%)	Low nasal root
	Low-set (12%), posteriorly rotated ears (17%)	Large ear lobes
	Thin upper lip (64%)	Full lips
	Short philtrum (50%)	Long philtrum
Growth and development	Delayed speech (91%)	Speech initially delayed, then relative strength
	Delayed motor development (70%)	Delayed motor development
	Normal growth or stature	Delayed growth, short stature, failure to thrive
Endocrine	Normal calcium levels	Hypercalcemia
Musculoskeletal	Joint laxity (19%)	Joint laxity
Cardiovascular	Aortic dilation (30%)	Supravalvular aortic stenosis
	Congenital heart defects (13%)	VSD[a], ASD[b]
Neurological	Abnormal brain imaging (80%)	Abnormal brain imaging
	Hypotonia (48%)	Hypotonia
	Poor visuospatial skills (30%)	Poor visuospatial skills
	Mild intellectual disability (38%)	Mild intellectual disability
Psychiatric/behavior	ADHD[c] (37%)	ADHD
	Social anxiety (42%)	Lack of stranger anxiety
	Autism (29%)	Autism
	Specific phobias (36%)	Specific phobias
	Aggression/temper outbursts (22%)	No aggression
	No hearing issues	Hyperacusis

[a]Ventricular septal defect.
[b]Atrial septal defect.
[c]Attention deficit hyperactivity disorder.

Those with the 7q11.23 microduplicaton have a broad forehead and high broad nose, low-set posteriorly rotated ears, a thin upper lip, a short philtrum, aortic root dilatation, and congenital heart disease. Other 7q11.23 clinical features include anxieties, particularly social and specific phobias, speech delay, and aggression (see ►**Table 5**). The 7q11.23 microduplication and the reciprocal microdeletion causing WBS share similar findings such as abnormal brain imaging, hypotonia, delayed motor development, mild intellectual disability, ADHD, autism, poor visuospatial skills, and joint laxity. Hyperverbal speech and lack of stranger anxiety are more commonly seen in those with WBS and opposite findings of SM, and extreme anxiety are more common in the 7q11.23 microduplication syndrome. The opposite presentation in clinical findings have been reported in other reciprocal deletion and duplication cytogenetic syndromes, including 9p trisomy and 9p monosomy[37] and the 21q22 duplication and 21q22 deletion syndromes.[38] The authors encourage further research regarding the 7q11.23 microduplication as additional information would be useful to provide better medical care and more accurate genetic counseling for family members.

Conflict of Interest
None.

Acknowledgment
The authors acknowledge the National Institute of Child Health and Human Development (NICHD) HD02528 grant.

References
1 Berg JS, Brunetti-Pierri N, Peters SU, et al. Speech delay and autism spectrum behaviors are frequently associated with duplication of the 7q11.23 Williams-Beuren syndrome region. Genet Med 2007; 9(7):427–441
2 Depienne C, Heron D, Betancur C, et al. Autism, language delay and mental retardation in a patient with 7q11 duplication. J Med Genet 2007;44(7):452–458

3 Dixit A, McKee S, Mansour S, et al. 7q11.23 Microduplication: a recognizable phenotype. Clin Genet 2013;83(2):155–161
4 Kirchhoff M, Bisgaard AM, Bryndorf T, Gerdes T. MLPA analysis for a panel of syndromes with mental retardation reveals imbalances in 5.8% of patients with mental retardation and dysmorphic features, including duplications of the Sotos syndrome and Williams-Beuren syndrome regions. Eur J Med Genet 2007;50(1): 33–42
5 Kriek M, White SJ, Szuhai K, et al. Copy number variation in regions flanked (or unflanked) by duplicons among patients with developmental delay and/or congenital malformations; detection of reciprocal and partial Williams-Beuren duplications. Eur J Hum Genet 2006;14(2):180–189
6 Malenfant P, Liu X, Hudson ML, et al. Association of GTF2i in the Williams-Beuren syndrome critical region with autism spectrum disorders. J Autism Dev Disord 2012;42(7):1459–1469
7 Orellana C, Bernabeu J, Monfort S, et al. Duplication of the Williams-Beuren critical region: Case report and further delineation of the phenotypic spectrum. J Med Genet 2008;45:187–189
8 Parrott A, James J, Goldenberg P, et al. Aortopathy in the 7q11.23 microduplication syndrome. Am J Med Genet A 2015;167A(2): 363–370
9 Prontera P, Serino D, Caldini B, et al. Brief report: functional MRI of a patient with 7q11.23 duplication syndrome and autism spectrum disorder. J Autism Dev Disord 2014;44(10):2608–2613
10 Sanders SJ, Ercan-Sencicek AG, Hus V, et al. Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. Neuron 2011; 70(5):863–885
11 Torniero C, dalla Bernardina B, Novara F, et al. Cortical dysplasia of the left temporal lobe might explain severe expressive-language delay in patients with duplication of the Williams-Beuren locus. Eur J Hum Genet 2007;15(1):62–67
12 Torniero C, Dalla Bernardina B, Novara F, et al. Dysmorphic features, simplified gyral pattern and 7q11.23 duplication reciprocal to the Williams-Beuren deletion. Eur J Hum Genet 2008; 16(8):880–887
13 Van der Aa N, Rooms L, Vandeweyer G, et al. Fourteen new cases contribute to the characterization of the 7q11.23 microduplication syndrome. Eur J Med Genet 2009;52(2–3):94–100
14 Velleman SL, Mervis CB. Children with 7q11.23 duplication syndrome: Speech, language, cognitive and behavioral characteristics and their implications for intervention. Perspect Lang Learn Educ 2011;18(3):108–116
15 Zarate YA, Lepard T, Sellars E, et al. Cardiovascular and genitourinary anomalies in patients with duplications within the Williams syndrome critical region: phenotypic expansion and review of the literature. Am J Med Genet A 2014;164A(8):1998–2002
16 Morris CA, Mervis CB, Paciorkowski AP, et al. 7q11.23 Duplication syndrome: Physical characteristics and natural history. Am J Med Genet A 2015;167(12):2916–2935
17 Patil SJ, Salian S, Bhat V, et al. Familial 7q11.23 duplication with variable phenotype. Am J Med Genet A 2015;167A(11): 2727–2730
18 Mervis CB, Klein-Tasman BP, Huffman MJ, et al. Children with 7q11.23 duplication syndrome: psychological characteristics. Am J Med Genet A 2015;167(7):1436–1450
19 Mervis CB, Morris CA, Klein-Tasman BP, et al. 7q11.23 Duplication Syndrome. In: Pagon RA, Adam MP, Ardinger HH et al., eds. GeneReviews (Internet). Seattle, WA: University of Washington, Seattle; 2015
20 Somerville MJ, Mervis CB, Young EJ, et al. Severe expressive-language delay related to duplication of the Williams-Beuren locus. N Engl J Med 2005;353(16):1694–1701
21 Jones KL. Williams syndrome. In: K.L Jones, ed. Smith's Recognizable Patterns of Human Malformation. Philadelphia, PA: Elsevier Saunders; 2006:120–123
22 Morris CA. Williams Syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LIH, Bird TD, Dolan CR, Fong CT, Smith RJH, Stephens K, eds. GeneReviews (online). Seattle, WA: University of Washington, Seattle; 2013
23 Pober BR. Williams-Beuren syndrome. N Engl J Med 2010;362(3): 239–252
24 Ng R, Järvinen A, Bellugi U. Characterizing associations and dissociations between anxiety, social, and cognitive phenotypes of Williams syndrome. Res Dev Disabil 2014;35(10):2403–2415
25 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed.; 2013:195–197
26 Ford MA, Sladeczek IE, Carlson J, et al. Selective mutism: phenomenological characteristics. School Psychology Quarterly 1998; 13(3):192–227
27 Kristensen H. Selective mutism and comorbidity with developmental disorder/delay, anxiety disorder, and elimination disorder. J Am Acad Child Adolesc Psychiatry 2000;39(2):249–256
28 Viana AG, Beidel DC, Rabian B. Selective mutism: a review and integration of the last 15 years. Clin Psychol Rev 2009;29(1):57–67
29 Black B, Uhde TW. Elective mutism as a variant of social phobia. J Am Acad Child Adolesc Psychiatry 1992;31(6):1090–1094
30 Steinhausen HC, Wachter M, Laimböck K, Metzke CW. A long-term outcome study of selective mutism in childhood. J Child Psychol Psychiatry 2006;47(7):751–756
31 Remschmidt H, Poller M, Herpertz-Dahlmann B, Hennighausen K, Gutenbrunner C. A follow-up study of 45 patients with elective mutism. Eur Arch Psychiatry Clin Neurosci 2001;251(6):284–296
32 Kristensen H, Torgersen S. A case-control study of EAS child and parental temperaments in selectively mute children with and without a co-morbid communication disorder. Nord J Psychiatry 2002;56(5):347–353
33 Arie M, Henkin Y, Lamy D, et al. Reduced auditory processing capacity during vocalization in children with Selective Mutism. Biol Psychiatry 2007;61(3):419–421
34 Mulle JG, Pulver AE, McGrath JA, et al; Molecular Genetics of Schizophrenia Consortium. Reciprocal duplication of the Williams-Beuren syndrome deletion on chromosome 7q11.23 is associated with schizophrenia. Biol Psychiatry 2014;75(5):371–377
35 Tassabehji M. Williams-Beuren syndrome: a challenge for genotype-phenotype correlations. Hum Mol Genet 2003;12(Spec No 2):R229–R237
36 Klein-Tasman BP, Mervis CB. Distinctive personality characteristics of 8-, 9-, and 10-year-olds with Williams syndrome. Dev Neuropsychol 2003;23(1–2):269–290
37 De Grouchy J, Turleau C. Chromosome 9. In: J de Grouchy, C Turleau , eds. Clinical Atlas of Human Chromosomes. 2nd ed. New York, NY: Wiley Medical Publication; 1984:146–173
38 Izumi K, Brooks SS, Feret HA, Zackai EH. 1.9 Mb microdeletion of 21q22.11 within Braddock-Carey contiguous gene deletion syndrome region: dissecting the phenotype. Am J Med Genet A 2012; 158A(7):1535–1541