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NLM Citation: Mervis CB, Morris CA, Klein-Tasman BP, et al. 7q11.23 Duplication Syndrome. 2015 Nov 25 [Updated 2021 Mar 25]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

7q11.23 Duplication Syndrome

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Created: November 25, 2015; Updated: March 25, 2021.

Summary

Clinical characteristics

7q11.23 duplication syndrome is characterized by delayed motor, speech, and social skills in early childhood; neurologic abnormalities (hypotonia, adventitious movements, and abnormal gait and station); speech sound disorders including motor speech disorders (childhood apraxia of speech and/or dysarthria) and phonologic disorders; behavior issues including anxiety disorders (especially social anxiety disorder [social phobia]), selective mutism, attention-deficit/hyperactivity disorder, oppositional disorders, physical aggression, and autism spectrum disorder; and intellectual disability in some individuals. Distinctive facial features are common. Cardiovascular disease includes dilatation of the ascending aorta. Approximately 30% of individuals have one or more congenital anomalies.

Diagnosis/testing

The diagnosis of 7q11.23 duplication syndrome is established by detection of a recurrent 1.5- to 1.8-Mb heterozygous duplication of the Williams-Beuren syndrome critical region.

Management

Treatment of manifestations: Address developmental delays through early intervention programs (including speech-language therapy, physical therapy, and occupational therapy), special education programs, and vocational training. Address childhood apraxia of speech with intensive speech-language therapy to maximize effective oral communication and prevent or limit later language impairment and/or reading disorder. Address emotional and behavioral disorders (aggression, social anxiety, selective mutism, autism spectrum disorder) with cognitive-behavioral therapy, applied behavior analysis behavior modification intervention, and psychotropic medications as needed. Standard treatment for seizures and congenital heart disease. Ventriculo-peritoneal shunt as needed for hydrocephalus. Aortic dilatation is treated with beta-blocker therapy and/or surgery as needed. Feeding therapy and gastrostomy tube placement may be required. Constipation should be

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aggressively managed. Human growth hormone replacement therapy for growth hormone deficiency. Treatment per nephrologist and/or urologist for genitourinary malformations. Standard treatments for vision and hearing issues and recurrent otitis. Casting and treatment per orthopedist for clubfeet. Social work support for families.

Surveillance: Assessment of growth and nutrition at each visit. Annual assessment by occupational and physical therapists and speech-language pathologists until at least age six years. Annual assessment of intellectual ability and academic achievement. Head circumference at every visit in infancy or at least every three months. Assess for new-onset seizures or monitor those with seizures as clinically indicated. Behavior assessment annually. Annual monitoring of aortic diameter (including z scores in children). Annual monitoring for constipation, hearing and vision issues, and kyphoscoliosis. Assess need for additional genetic counseling and family support.

Genetic counseling

7q11.23 duplication syndrome is transmitted in an autosomal dominant manner. About 27% of individuals diagnosed with 7q11.23 duplication syndrome have an affected parent; about 73% of individuals have the disorder as the result of a *de novo* genetic alteration. If one of the parents has the 7q11.23 duplication identified in the proband, the risk to each sib of inheriting the duplication is 50%. It is not possible to reliably predict the phenotype in sibs who inherit a 7q11.23 duplication because manifestations of 7q11.23 duplication syndrome may vary in affected family members. If the 7q11.23 duplication identified in the proband cannot be detected in parental leukocyte DNA and neither parent has a balanced chromosome rearrangement, the recurrence risk to sibs is low but greater than that of the general population because of the possibility of parental germline mosaicism. Once a 7q11.23 duplication has been identified in an affected family member, prenatal and preimplantation genetic testing are possible; however, the manifestations of 7q11.23 duplication syndrome cannot be reliably predicted on the basis of prenatal test results or family history.

Diagnosis

Suggestive Findings

7q11.23 duplication syndrome **should be suspected** in individuals with the following findings:

- **Developmental delay / intellectual disability.** Delayed motor, speech, and social skills in early childhood:
  - Motor. Hypotonia, adventitious movements, abnormalities of gait and station, developmental coordination disorder in children
  - Language. Speech delay, childhood apraxia of speech, dysarthria. Expressive language is usually more delayed than receptive language.
  - Cognitive. About 20% have borderline intellectual ability, approximately 18% have intellectual disability. The majority of school-age children have intellectual ability in the low average-to-average range.
- **Behavior issues.** Anxiety disorders, selective mutism, attention-deficient/hyperactivity disorder, autism spectrum disorder, oppositional disorders, and physical aggression
- **Distinctive craniofacial features.** Macrocephaly, brachycephaly, broad forehead, straight eyebrows, deep-set eyes, long eyelashes, broad nasal tip, low insertion of the columella, short philtrum, thin vermilion of the upper lip, high-arched palate, and minor ear anomalies (overfolded helix, lateral protrusion) are observed at all ages (Figure 1). Facial asymmetry and low-hanging columella become more evident in older children and adults (Figure 2).
- **Cardiovascular disease.** Dilatation of the ascending aorta (46%) is reported at all ages and may be progressive [Morris et al 2015]. Patent ductus arteriosus and septal defects are also reported (>20%).
- **Seizures** (18%)
- **Linear growth** is in the normal range for most individuals; about 17% have short stature.
- **Brain MRI.** Ventriculomegaly, decreased white matter volume, and cerebellar vermis hypoplasia

- **Growth hormone deficiency** (9%)

Establishing the Diagnosis

The diagnosis of 7q11.23 duplication syndrome **is established** in a proband with suggestive findings and a heterozygous 1.5- to 1.8-Mb duplication of the Williams-Beuren syndrome critical region identified on genomic testing (see Table 1).

For this *GeneReview*, the 7q11.23 recurrent duplication is defined as the presence of a recurrent 1.5- to 1.8-Mb duplication at the approximate position of chr7:73330452-74728172 in the reference genome (NCBI Build 38).

Note: (1) Since these duplications are recurrent and mediated by segmental duplications, the unique genetic sequence that is duplicated is the same in all individuals with each duplication; however, the reported size of the duplication: (a) may be larger if adjacent segmental duplications are included in the size; and (b) may vary based on the design of the microarray used to detect it (see Molecular Pathogenesis). (2) The phenotype of significantly larger or smaller duplications within this region may be clinically distinct from the 7q11.23 recurrent duplication (see Genetically Related Disorders). (3) Although several genes of interest are within the 1.5- to 1.8-Mb recurrent microduplication, no single gene has been definitively identified as causing individual clinical features (see Molecular Genetics for genes of interest in this region).

Genomic testing methods that determine the copy number of sequences can include **chromosomal microarray (CMA)** or **targeted duplication analysis.** Note: The 7q11.23 duplication cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.

- **CMA** using oligonucleotide or SNP arrays can detect the recurrent duplication in a proband. The ability to size the duplication depends on the type of microarray used and the density of probes in the 7q11.23 region.

  Note: (1) Most individuals with a 7q11.23 recurrent duplication are identified by CMA performed in the context of evaluation for developmental delay, intellectual disability, and/or autism spectrum disorder. (2) This duplication can be detected by BAC arrays.

- **Targeted duplication analysis.** FISH analysis, quantitative PCR (qPCR), multiplex ligation-dependent probe amplification (MLPA), or other targeted quantitative methods may be used to test relatives of a proband who is known to have the 7q11.23 recurrent duplication.

  Note: (1) Targeted duplication testing is not appropriate for an individual in whom the 7q11.23 recurrent duplication was not detected by CMA designed to target this region. (2) It is not possible to size the duplication routinely by use of targeted methods.

Figure 1. Children with characteristic facial features of 7q11.23 duplication syndrome

Top row: Age 1 year, age 2 years, age 2 years, age 2 years, age 4 years

Bottom row: Age 4 years (front and profile), age 7 years, age 7 years, age 8 years

Note the brachycephaly, broad forehead, straight eyebrows, deeply set eyes, long eyelashes, broad nasal tip, low insertion of the columella, short philtrum, thin vermilion of the upper lip, and minor ear anomalies (overfolded helix, protruding ears).

Figure 2. Adolescents and adults with 7q11.23 duplication syndrome

Top row: Age 12 years (front and profile), age 14 years, age 21 years

Bottom row: Age 18 years (front and profile), age 39 years (front and profile)

In addition to the facial features noted in children (Figure 1), facial asymmetry and low-hanging columella become more evident/are more common in older children and adults.

Table 1. Genomic Testing Used in 7q11.23 Duplication Syndrome

Duplication [1]	Method	Sensitivity	
		Proband	At-risk family members
1.5- to 1.8-Mb heterozygous duplication at 7q11.23 ISCN: seq[GRCh38] dup(7)(q11.23) chr7:73,330,452-74,728,172dup [2] ClinGen ID: ISCA-37392	CMA [3]	100%	100%
	Targeted duplication analysis [4]	NA [5]	100% [6]

1. See Molecular Genetics for details of the duplication and genes of interest included in the region.
2. Standardized clinical annotation and interpretation for genomic variants from the Clinical Genome Resource (ClinGen) project (formerly the International Standards for Cytogenomic Arrays [ISCA] Consortium). Genomic coordinates represent the minimum duplication size associated with the 7q11.23 duplication as designated by ClinGen. Duplication coordinates may vary slightly based on array design used by the testing laboratory. Note that the size of the duplication as calculated from these genomic positions may differ from the expected duplication size due to the presence of segmental duplications near breakpoints. The phenotype of significantly larger or smaller duplications within this region may be clinically distinct from the 7q11.23 duplication (see Genetically Related Disorders).
3. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 7q11.23 region.
4. Targeted duplication analysis methods can include FISH, quantitative PCR (qPCR), and multiplex ligation-dependent probe amplification (MLPA) as well as other targeted quantitative methods.
5. Not applicable. Targeted duplication analysis is not appropriate for an individual in whom the 7q11.23 duplication was not detected by CMA designed to target this region.
6. Targeted duplication analysis may be used to test at-risk relatives of a proband who is known to have the 7q11.23 duplication.

Evaluating at-risk relatives. FISH, qPCR, or other quantitative methods of targeted duplication analysis can be used to identify the 7q11.23 recurrent duplication in at-risk relatives of the proband. Testing of parental samples is important for determining recurrence risk (see Genetic Counseling).

Clinical Characteristics

Clinical Description

Among probands with 7q11.23 duplication syndrome, the most common reasons for evaluation were developmental delay and autism spectrum disorder (ASD) [Morris et al 2015]. Developmental delay has been reported in almost all individuals with 7q11.23 duplication syndrome. Speech is significantly delayed. Congenital malformations occur in approximately 30% of individuals and include cleft lip and/or palate, congenital heart disease, diaphragmatic hernia, unilateral renal agenesis, vertebral anomalies, cryptorchidism, and talipes equinovarus [Berg et al 2007, Van der Aa et al 2009, Dixit et al 2013, Morris et al 2015].

To date, more than 150 individuals with a 7q11.23 recurrent duplication have been identified [Somerville et al 2005, Berg et al 2007, Depienne et al 2007, Orellana et al 2008, Torniero et al 2008, Van der Aa et al 2009, Değerliyurt et al 2012, Malenfant et al 2012, Dixit et al 2013, Prontera et al 2014, Zarate et al 2014, Morris et al 2015, Parrott et al 2015, Patil et al 2015, Abbas et al 2016, Earhart et al 2017, Castiglia et al 2018, Dentici et al 2020, Lechich et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. 7q11.23 Duplication Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
DD	~95%	
ID	~20%	IQ in borderline range for ~20%; median IQ in low-average range
Speech/language delay	100%	Esp expressive speech delay
Speech sound disorder	83%	
Hypotonia	60%	
Seizures	18%	
Anxiety disorder other than specific phobia	>60%	Social phobia (~50%), selective mutism (~30%), generalized anxiety disorder (~15%), separation anxiety disorder (~10%)
Specific phobia	>50%	
ASD	~19%	Eval requires consideration of role of selective mutism & social anxiety.
ADHD	~35%	
Oppositional disorders	~25%	
Characteristic craniofacial features	100% [1]	Macrocephaly, brachycephaly, broad forehead, straight eyebrows, deep-set eyes, long eyelashes, broad nasal tip, low insertion of columella, short philtrum, thin vermilion of upper lip, high-arched palate, minor ear anomalies
Congenital heart disease	>20%	Patent ductus arteriosus, septal defects
Aortic dilatation	46%	
GI manifestations	>60%	Feeding issues, chronic constipation
Growth hormone deficiency	9%	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
GU tract abnormalities	15%	Hydronephrosis, unilateral renal agenesis, abnormalities of müllerian structures, cryptorchidism
Strabismus	15%	
Hearing loss	~5%	
Musculoskeletal abnormalities	40%	Joint laxity, talipes equinovarus

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DD = developmental delay; GI = gastrointestinal; GU = genitourinary; ID = intellectual disability

1. All individuals reported have had some subset of the listed craniofacial features. However, the overall facial gestalt is not as striking as in Williams syndrome.

Neurodevelopment / motor development. Infants with 7q11.23 duplication syndrome are hypotonic and may have joint laxity, resulting in delayed attainment of motor milestones. Median age of walking based on parent report is age 1.33 years [Morris et al 2015]. Neurologic examination is abnormal in 89% of children; findings include hypotonia (60%), abnormalities in gait and station such as wide-based gait and difficulty with balance (62%), and adventitious movements such as involuntary motor overflow (83% of children age >14 years). Developmental coordination disorder is present in 74% [Morris et al 2015].

Seizures are present in 18% [Berg et al 2007, Torniero et al 2007, Van der Aa et al 2009, Değerliyurt et al 2012, Morris et al 2015, Castiglia et al 2018, Dentici et al 2020].

Hydrocephalus requiring shunting was present in 5.6% in one series [Morris et al 2015].

Neuroimaging. Common MRI findings include varying degrees of ventriculomegaly, thin corpus callosum, increased extra-axial spaces, thin white matter, delayed myelination, posterior fossa cysts, and cerebellar vermis hypoplasia [Berg et al 2007, Depienne et al 2007, Torniero et al 2007, Orellana et al 2008, Torniero et al 2008, Van der Aa et al 2009, Dixit et al 2013, Prontera et al 2014, Morris et al 2015, Castiglia et al 2018, Dentici et al 2020].

Speech and language difficulties. Speech is significantly delayed, with first use of single words at a median age of two years based on parental report [Morris et al 2015].

DSM-V speech sound disorder, present in 83%, includes motor speech disorders (such as childhood apraxia of speech), phonologic disorders (cognitive-linguistic disorders reflecting inaccurate or incomplete phonologic representations or inappropriate phonologic rules), and articulation disorders (persistent distortions of certain sounds). The incidence and severity of speech disorders decrease with age [Mervis et al 2015, Morris et al 2015].

The most common speech sound disorder in children with 7q11.23 duplication is childhood apraxia of speech (a neurologic speech disorder not due to muscle weakness or muscle tone differences but rather due to problems of planning and coordinating the muscle movements needed to pronounce words) or manifestations of this disorder.

Childhood dysarthria or its manifestations (usually resulting from low muscle tone) are also common [Velleman & Mervis 2011, Mervis et al 2015]. "Developmental" articulation problems, such as distortions of /s/ or /r/, may persist past typical ages.

On omnibus tests of language abilities (including receptive and expressive modalities and vocabulary and grammar) overall performance is most commonly in the range of mild-to-moderate language disorder but can range from severe language disorder to average language ability. For most children vocabulary abilities are stronger than grammatical abilities [Velleman & Mervis 2011].

School-age children who received consistent speech-language therapy from late infancy or early toddlerhood had considerably stronger language and literacy skills than children who had not. Children who were taught to read using a systematic phonics approach had better reading skills than children taught with other approaches [Velleman & Mervis 2011].

Cognitive abilities. Median IQ is 85 (low average), with a range from severe intellectual disability to superior ability. On average, verbal, nonverbal reasoning, and spatial abilities are at about the same level, although a variety of patterns of relative strengths and weaknesses occur. Median reading achievement performance is at the bottom of the average range (varying from severe disability to superior ability) and median mathematics achievement performance is at the bottom of the low average range (also varying from severe disability to superior ability) [Mervis et al 2015].

Adaptive behavior. Adaptive skills are more limited than expected for IQ [Mervis et al 2015, Dentici et al 2020]. Median performance is at the mild adaptive deficit-to-borderline level (range: severe adaptive deficit to average). Executive functioning difficulties may also be observed [Mervis et al 2015].

Behavior issues. Anxiety disorders are common, with at least 60% meeting DSM-IV criteria for at least one anxiety disorder other than specific phobia [Mervis et al 2015, Dentici et al 2020]. The most common disorders in children are specific phobia (53%), social anxiety disorder (50%), selective mutism (29%), and separation anxiety disorder (13%) [Mervis et al 2015]. Approximately 35% met DSM-IV criteria for attention-deficit/hyperactivity disorder and about 25% met DSM-IV criteria for oppositional defiant disorder or disruptive behavior disorder – not otherwise specified [Mervis et al 2015]. An elevated rate of physical aggression is also common. High pain tolerance was reported by parents in 25% of children [Morris et al 2015].

Thirty-three percent screened positive for a possible autism spectrum disorder [Mervis et al 2015] and 19% met criteria for an autism spectrum disorder based on a gold-standard assessment (Autism Diagnostic Observation Schedule [ADOS]-2 [Lord et al 2012] and Autism Diagnostic Interview Schedule – Revised [ADI-R] [Lord et al 1994], in addition to clinical judgment) with differential diagnosis taking into account selective mutism and social anxiety [Klein-Tasman & Mervis 2018].

Craniofacial features. The characteristic craniofacial phenotype including macrocephaly, brachycephaly, broad forehead, straight eyebrows, deep-set eyes, long eyelashes, broad nasal tip, low insertion of the columella, short philtrum, thin vermilion of the upper lip, high-arched palate (44%), diastema (31%), micrognathia (30%), and minor ear anomalies (overfolded helix, protruding ears) is observed at all ages (Figure 1). Facial asymmetry and low-hanging columella are more common (or become more evident) in older children and adults (Figure 2) [Morris et al 2015].

Cardiovascular disease. Patent ductus arteriosus is present in 15%-30% [Van der Aa et al 2009, Morris et al 2015, Dentici et al 2020] and septal defects are present in 2% of affected individuals.

The prevalence of aortic dilatation is 46% [Morris et al 2015]. Aortic dilatation may be detected at any age; surgical correction has been required in some adolescents and adults. Some individuals with dilatation of the ascending aorta also have had dilatation of the aortic root [Zarate et al 2014, Morris et al 2015, Parrott et al 2015]. One study demonstrated effacement of the sinotubular junction on echocardiogram in all 21 individuals with 7q11.23 duplication syndrome evaluated [Lechich et al 2020].

Gastrointestinal manifestations. Infants with 7q11.23 duplication syndrome may have feeding problems such as difficulty with latching on, and 7.5% have persistent feeding problems requiring gastrostomy tube feeding. Chronic constipation is a significant problem in 66% of children and 27% of adults. Encopresis occurs in 20% of the children with constipation and 7.5% require hospitalization for disimpaction [Morris et al 2015].

Growth/endocrine. Median birth weight is at the 75th centile, median birth length is at the 80th centile, and median head circumference is at the 75th centile (30% of newborns have an OFC ≥95th centile). Most affected individuals have normal stature. Growth hormone deficiency is found in 9% [Morris et al 2015].

Genitourinary tract abnormalities. Congenital anomalies of the urinary tract occur in 15%-18% of affected individuals, including hydronephrosis and unilateral renal agenesis [Zarate et al 2014, Morris et al 2015]. Females with unilateral renal agenesis may have abnormalities of müllerian structures [Morris et al 2015]. Approximately 15% of males have cryptorchidism [Orellana et al 2008, Van der Aa et al 2009, Morris et al 2015, Dentici et al 2020].

Vison/hearing. Strabismus is present in 15% of affected individuals. Chronic otitis media affects 25% of children; ventilating tubes are placed in 15% and tonsillectomy and adenoidectomy are performed in 15% [Morris et al 2015]. Hearing loss has been reported in approximately 5% of individuals with 7q11.23 duplication syndrome.

Musculoskeletal issues. Joint laxity may be present in young children [Berg et al 2007, Van der Aa et al 2009, Dixit et al 2013, Zarate et al 2014, Morris et al 2015, Dentici et al 2020]. Talipes equinovarus (5%) responds to casting [Morris et al 2015].

Other. Cutis marmorata is present in 45% of children younger than age 14 years [Morris et al 2015].

Genotype/Phenotype Correlations

Based on the limited number of affected individuals identified, there is currently no indication of phenotypic difference between those with the 1.5-Mb duplication and those with the slightly larger 1.8-Mb duplication [Dentici et al 2020].

Penetrance

Penetrance is complete in both males and females.

Prevalence

Prevalence has been estimated at 1:7,500-1:20,000 [Van der Aa et al 2009, Velleman & Mervis 2011].

Genetically Related (Allelic) Disorders

Williams syndrome (WS) is caused by a recurrent 7q11.23 contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) that encompasses the elastin gene (*ELN*). The 7q11.23 recurrent deletions of the WBSCR comprise either 1.55 Mb (90%-95% of individuals with WS) or 1.84 Mb (5%-10% of individuals with WS).

WS is characterized by cardiovascular disease (elastin arteriopathy, peripheral pulmonary stenosis, supravalvar aortic stenosis, hypertension), distinctive facies, connective tissue abnormalities, intellectual disability (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities, and endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, and early puberty). Behaviorally, WS is characterized by overfriendliness, social disinhibition, attention issues, and non-social anxiety, including non-social specific phobias. WS is also associated with difficulty with sensory modulation and emotional regulation.

Duplications larger than 1.84 Mb that include *HIP1* have been reported [Berg et al 2007, Dixit et al 2013, Zarate et al 2014]. Berg et al [2007] and Dixit et al [2013] noted that these individuals did not appear to differ phenotypically from those with the recurrent 7q11.23 duplication. However, systematic comparisons to a large group of individuals with the recurrent 7q11.23 duplication are needed to determine if larger duplications are

associated with a more severe phenotype, considering that larger deletions of 7q11.23 including *HIP1* are associated with more severe intellectual disability than is typical for individuals with WBSCR deletions [Stock et al 2003].

7q11.23 duplications smaller than 1.55 Mb have also been reported [Zarate et al 2014, Parrott et al 2015]. Systematic comparisons to a large group of individuals with the recurrent 7q11.23 duplication are needed to determine phenotypic similarities and differences as a function of the specific genes duplicated. However, a recent report found three family members with duplication of only *GTF2I* and mild intellectual disability, compared to average intellectual ability in a family member without the duplication [Pinelli et al 2020].

7q11.23 triplication. Given the small number of individuals identified with a 7q11.23 triplication and the variable size of the triplication, it is not yet known if the phenotype associated with the triplication is more severe than that associated with the duplication.

- A child age 38 months with a 7q11.23 triplication including almost all of the genes in the WBSCR has been reported [Beunders et al 2010]. The child had gross motor delay, severe language delay, anxiety, and aggressive behavior.
- A child who has a triplication of four genes in the WBSCR plus a duplication of the remaining genes in the WBSCR has been reported [Zarate et al 2014].
- A large family including 11 individuals in three generations who had a triplication of *ELN* and *LIMK1* has been identified [Guemann et al 2015]; ten of the 11 had a supravalvar aortic aneurysm.

Differential Diagnosis

7q11.23 duplication syndrome should be distinguished from other syndromes that include developmental delay, macrocephaly, hypotonia, distinctive craniofacial features, and behavior issues. Examples include fragile X syndrome (see *FMR1* Disorders) and Sotos syndrome.

7q11.23 duplication syndrome should be added to the list of syndromes that are associated with aortic dilatation: Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndromes (EDS) (see Classic EDS, Hypermobility EDS, *PLOD1*-Related Kyphoscoliotic EDS, and Vascular EDS), and thoracic aortic disease. The distinctive facial features and developmental and behavioral phenotype of 7q11.23 duplication syndrome distinguish it from these conditions.

Management

Suggestions for evaluation, health surveillance, and treatment have been published [Morris et al 2015].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with 7q11.23 duplication syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with 7q11.23 Duplication Syndrome

System/Concern	Evaluation	Comment
Development	Multidisciplinary developmental assessment to incl motor, adaptive, cognitive, & speech-language eval	• Speech-language eval preferably by examiner experienced in evaluating childhood apraxia of speech • PT eval • OT eval (incl assessment for sensory integration difficulties) • Eval for early intervention / special education, incl learning disability services

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• Consider EEG if seizures are a concern. • Consider brain MRI in those w/macrocephaly &/or abnormal neurologic exam to evaluate for ventriculomegaly/hydrocephalus, cerebellar vermis hypoplasia, &/or white matter abnormalities. [1]
Psychiatric/ Behavioral	Neuropsychiatric eval	Age >12 mos: screening for behavior concerns (preferably by licensed psychologist) incl: • Anxiety (e.g., social anxiety disorder, selective mutism, separation anxiety, generalized anxiety disorder) • Attention issues • ASD. If indicated, refer for gold-standard autism assessment (ADOS-2 and ADI-R, + clinical judgment) [2] – preferably by examiner experienced w/persons w/social anxiety &/or selective mutism. • Oppositional behavior/aggression. If indicated, refer for functional behavioral assessment, preferably by board-certified behavior analyst.
Cardiologic	Cardiologic eval	Incl echocardiogram, w/measurement of aortic root & ascending aorta w/ computation of z scores to evaluate for aortic dilatation
GI/Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/dysphagia &/or aspiration risk.
Growth/ Endocrine	Plotting of growth parameters	Evaluate those w/short stature for growth hormone deficiency.
Genitourinary	Renal ultrasound	Also: • Males: physical exam for cryptorchidism • Females w/unilateral renal agenesis: eval of müllerian structures
Eyes	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular movement, strabismus
Hearing	Audiologic eval	Assess for hearing loss.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, kyphoscoliosis • Mobility, ADL, need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of 7q11.23 duplication syndrome to facilitate medical & personal decision making

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Social work	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing or respite care referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ADI-R = Autism Diagnostic Interview Schedule – Revised; ADOS = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder; GI = gastrointestinal; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Because sedation is likely to be necessary for brain MRI, this should be weighed carefully and may not be necessary in every individual.

2. Lord et al [1994], Lord et al [2012]

3. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with 7q11.23 Duplication Syndrome

Manifestation/Concern	Treatment	Considerations/Other
DD	• Early intervention programs, special education programs, vocational training • Speech-language therapy, PT, OT	Hippotherapy should be considered, esp for children who have difficulty w/balance & children who have ASD.
Childhood apraxia of speech or other significant speech delay/disorder	Intensive speech-language therapy (preferably by a speech-language pathologist who has specific training in treating motor speech disorders)	To maximize effective oral communication & prevent or limit later language impairment &/or reading disorder
Anxiety / Selective mutism	• Cognitive-behavioral intervention for anxiety (preferably by licensed clinical psychologist) • Psychotropic medication if indicated	For children who have selective mutism, co-treatment by speech-language therapist & psychologist should be strongly considered.
ASD	Applied behavior analysis (preferably conducted by a board-certified behavior analyst) or other empirically supported intervention for ASD	
ADHD	• Behavioral modifications in home & school settings • Psychotropic medication if indicated	
Aggression	• Applied behavior analysis intervention • Psychotropic medication if indicated	Physical aggression should be assessed & treated immediately to prevent development of a long-standing pattern of aggression.
Oppositionality	• Behavioral interventions w/emphasis on reinforcing positive behaviors • Psychotropic medication if indicated	Maintain awareness of potential role of anxiety & speech &/or language difficulties.
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Hydrocephalus	Ventriculo-peritoneal shunting as needed	
Congenital heart disease	Treatment per cardiologist	
Aortic dilatation	Beta-blocker therapy in some affected persons per cardiologist	Some w/severe aortic dilatation have required surgery. [2]

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	Aggressive mgmt at all ages to prevent encopresis & impaction
Growth hormone deficiency	Human growth hormone replacement therapy	
Genitourinary malformations	Treatment per nephrologist &/or urologist	
Abnormal vision &/or strabismus	Standard treatment(s) per ophthalmologist	Community vision services through early intervention or school district
Hearing / Recurrent otitis	• Standard treatment of otitis • Hearing aids may be helpful per ENT.	Community hearing services through early intervention or school district
Clubfeet	Casting & treatment per orthopedist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ASM = anti-seizure medication; DD = developmental delay; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
2. Zarate et al [2014], Morris et al [2015], Parrott et al [2015]

Surveillance

Table 5. Recommended Surveillance for Individuals with 7q11.23 Duplication Syndrome

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Development	OT & PT assessment	Annually at least until age 6 yrs
	Speech-language assessment	Annually at least until age 6 yrs; beyond age 6 yrs if moderate or severe speech-language disorder
	Assessment of intellectual abilities & academic achievement	Annually
Neurologic	Measurement of head circumference	In infancy at every visit or at least every 3 mos
	• Assess for new-onset seizures. • Monitor those w/seizures as clinically indicated.	At each visit
Psychiatric/ Behavioral	• Behavior assessment (e.g., attention, anxiety, opposition, aggression) • Educators should be made aware of signs/symptoms of social anxiety disorder & selective mutism, & of appropriate educational interventions & support for children w/these disorders.	Annually

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Cardiovascular	• Cardiologic eval • Echocardiogram to measure aortic root & ascending aorta w/calculation of z scores to monitor for progressive aortic dilatation	• Annually • Significant dilatation may require more frequent monitoring &/or CT angiography or MR angiography.
GI	Monitor for constipation.	Annually
Eyes	Vision screening to monitor for refractive errors & strabismus	
Hearing	Audiologic eval	In infancy & then annually
Musculoskeletal	Monitor for kyphoscoliosis.	At each visit
Genetic counseling	Assess need for additional counseling.	As needed in adolescence or adulthood
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

Based on Mervis et al [2015], Morris et al [2015], and Parrott et al [2015]
GI = gastrointestinal; OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

7q11.23 duplication syndrome is transmitted in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 27% of individuals diagnosed with 7q11.23 duplication syndrome have an affected parent [Morris et al 2015].
- About 73% of individuals diagnosed with 7q11.23 duplication syndrome have the disorder as the result of a *de novo* genetic alteration.
- Genomic testing that will detect the 7q11.23 duplication present in the proband is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment. Testing for a balanced chromosome rearrangement in the parents is also recommended.

- If the 7q11.23 duplication identified in the proband is not identified in either confirmed biological parent and neither parent has a balanced chromosome rearrangement, the following possibilities should be considered:
  - The proband has a *de novo* duplication.
  - The proband inherited a duplication from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- Parental mosaicism has been reported in one family [Castiglia et al 2018].

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the parents:

- If one of the parents has the 7q11.23 duplication identified in the proband, the risk to each sib of inheriting the duplication is 50%. It is not possible to reliably predict the phenotype in sibs who inherit a 7q11.23 duplication because manifestations of 7q11.23 duplication syndrome may vary in affected family members.
- If the 7q11.23 duplication identified in the proband cannot be detected in parental leukocyte DNA and neither parent has a balanced chromosome rearrangement, the recurrence risk to sibs is low (presumed to be <1%) but greater than that of the general population because of the possibility of parental germline mosaicism.
- If one of the parents has a balanced chromosome rearrangement, the risk to sibs of having the 7q11.23 duplication is increased and depends on the specific chromosome rearrangement and the possibility of other variables.

Offspring of a proband. Each child of an individual with 7q11.23 duplication syndrome has a 50% chance of inheriting the duplication.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the 7q11.23 duplication or a balanced chromosome rearrangement, the parent's family members may also have the duplication or the chromosome rearrangement.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk of having a child with 7q11.23 duplication syndrome. Note: If a parent is known to have a balanced chromosome rearrangement, genetic counseling should also address reproductive risks associated with balanced chromosome rearrangements.

Prenatal Testing and Preimplantation Genetic Testing

Pregnancies known to be at increased risk for the 7q11.23 duplication. Once a 7q11.23 duplication has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Pregnancies not known to be at increased risk for the 7q11.23 duplication. CMA performed in a pregnancy not known to be at increased risk may detect the 7q11.23 recurrent duplication.

Note: The manifestations of 7q11.23 duplication syndrome cannot be reliably predicted on the basis of prenatal test results or family history.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Apraxia Kids**
  Phone: 412-785-7072
  Email: info@apraxia-kids.org
  apraxia-kids.org
- **Duplication Cares**
  Phone: 440-853-7023
  Fax: 425-642-2514
  Email: info@DuplicationCares.org
  www.duplicationcares.org
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  rarechromo.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. 7q11.23 Duplication Syndrome: Genes and Databases

Critical Region	Gene	Chromosome Locus	Protein	ClinVar
WBSCR	*Not applicable*	7q11.23	Not applicable	

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for 7q11.23 Duplication Syndrome (View All in OMIM)

609757	WILLIAMS-BEUREN REGION DUPLICATION SYNDROME

Molecular Pathogenesis

Duplication mechanism. Both the duplication of the Williams-Beuren syndrome critical region (WBSCR) that causes 7q11.23 duplication syndrome and the deletion of the WBSCR that causes Williams syndrome are mediated by the genomic structure of the region. The WBSCR is flanked by low copy repeats (LCRs) with high nucleotide sequence similarity that predisposes the region to nonallelic homologous recombination.

An inversion polymorphism at 7q11.23 in one parent has been detected in 20% of children with a classic *de novo* 7q11.23 duplication [Morris et al 2015]. In approximately 25% of individuals with a classic Williams syndrome

deletion, the unaffected parent in whom the chromosome deletion originated has the inversion [Osborne et al 2001, Bayés et al 2003, Hobart et al 2010]. Approximately 6% of the general population also has this inversion polymorphism [Hobart et al 2010], which does not cause clinical symptoms [Tam et al 2008]. Presence of the inversion polymorphism confers an increased risk for both 7q11.23 duplication and deletion, likely through increased difficulty in meiotic pairing between chromosomes with the 7q11.23 region in opposite orientations [Osborne et al 2001].

Genes of interest in this region. A number of genes have been mapped within the 7q11.23 duplication region. Of note:

- ***ELN*,** encoding the structural protein elastin, a major component of elastic fibers found in many tissues [Debelle & Tamburro 1999]. Duplication of *ELN* is likely related to the increased risk for aortic dilatation in 7q11.23 duplication syndrome [Zarate et al 2014, Morris et al 2015, Parrott et al 2015]. Deletion of *ELN* is responsible for supravalvar aortic stenosis in Williams syndrome [Ewart et al 1993]. *ELN* pathogenic variants typically result in autosomal dominant supravalvar aortic stenosis [Li et al 1997], and also have been reported in congenital cutis laxa [Tassabehji et al 1998, Zhang et al 1999].
- ***GTF2I*,** encoding general transcription factor 2 I (Gtf2i) (OMIM 601679) [Pérez Jurado et al 1998]. Gtf2i acts as an inducible multifunctional transcription factor in the nucleus [Roy 2012] and a regulator of agonist-induced calcium entry in the cytoplasm [Caraveo et al 2006], which can affect neuronal morphology in the brain [Deurloo et al 2019]. Duplication of *GTF2I* is associated with separation anxiety [Mervis et al 2012]. Mapping of families with atypical CNV of the 7q11.23 region has suggested that deletion and duplication of this gene have a negative effect on IQ [Morris et al 2003, Pinelli et al 2020]. *GTF2I* haplotypes have been associated with severity of manifestations in autism spectrum disorders [Malenfant et al 2012], with low social anxiety and reduced social communication abilities in the general population [Crespi & Hurd 2014], and with influencing the relation between trait anxiety and brain response to aversive social cues [Jabbi et al 2015]. Recently, Gtf2i has been shown to have a role in neuronal myelination [Barak et al 2019] and the generation and maturation of erythrocytes and megakaryocytes [Gurumurthy et al 2020]. Overexpression of GTF2I in neurons that were differentiated from 7q11.23 duplication-induced pluripotent stem cells was able to be modulated back to control levels using histone deacetylase inhibitors [Cavallo et al 2020].

The contribution of the remaining genes within the 7q11.23 duplicated region to the phenotype is unknown. Note: Genes marked with an * in the following list lie entirely within the LCR regions of 7q11.23.

- ***ABHD11*,** encoding abhydrolase domain-containing protein 11 [Merla et al 2002]. This protein has been shown to regulate lipid metabolism and stem cell renewal [Escoubet et al 2020, Liu at al 2020].
- ***ABHD11-AS1*,** encoding ABHD11 antisense RNA 1, tail-to-tail (OMIM 612545) [Brochier et al 2008]. This long noncoding RNA (lncRNA) has been shown to be neuroprotective in a mouse model of Huntington disease [Francelle et al 2015]. It is also upregulated in several cancers [Wu et al 2017, Liu et al 2018, Zhang et al 2021].
- ***BAZ1B*,** encoding bromodomain adjacent to zinc finger domain 1B (OMIM 605681) [Meng et al 1998, Peoples et al 1998]. The BAZ1B protein is part of the WICH chromatin remodeling complex [Bozhenok et al 2002] and has been shown to play a pivotal role in neural crest stem cell induction and migration through regulation of enhancers [Zanella et al 2019]. It was identified as a major human gene patterning the modern human face.
- ***BCL7B*,** encoding B-cell CLL/lymphoma 7B (OMIM 605846) [Jadayel et al 1998, Meng et al 1998]. The BCL7B protein is a subunit of mammalian SWI/SNF tumor suppressor complexes [Kadoch et al 2013].
- ***CLDN3*,** encoding claudin 3 (OMIM 602910) and ***CLDN4*,** encoding claudin 4 (OMIM 602909) [Paperna et al 1998]

- ***CLIP2*,** encoding CAP-GLY domain-containing linker protein 2 (OMIM 603432) [Hoogenraad et al 2004]. A study of two healthy adult sibs with heterozygous deletion of only *CLIP2* suggested that copy number variants for this gene do not result in a clinical or psychological phenotype [Vandeweyer et al 2012]. The CLIP2 protein product is highly expressed in the nervous system and regulates the growth of membrane microtubules [Akhmanova et al 2001].
- ***DNAJC30*,** encoding DnaJ homolog, subfamily C, member 30 (OMIM 618202) [Merla et al 2002]. DNAJC30 is a mitochondrial protein enriched in neurons, and mice lacking *Dnajc30* had perturbed mitochondrial function, changes in cortical dendrite morphology, and increased sociability and anxiety [Tebbenkamp et al 2018].
- ***EIF4H*,** encoding eukaryotic translation initiation factor 4H (EIF4H) (OMIM 603431) [Osborne et al 1996, Richter-Cook et al 1998], a regulatory subunit within the protein translation initiation complex. It regulates the eIF4A RNA helicase [Marintchev et al 2009].
- ***ELN-AS1*,** encoding ELN antisense RNA 1, an uncharacterized lncRNA
- ***FKBP6*,** encoding FKBP prolyl isomerase family member 6 (OMIM 604839). The FKBP6 protein is essential for proper pairing of homologous chromosomes during meiosis [Crackower et al 2003].
- ***FZD9*,** encoding homolog of *Drosophila* frizzled 9 (OMIM 601766) [Wang et al 1997]. FZD9 is a transmembrane cell surface receptor that binds to Wnt proteins to alter the beta catenin pathway [Karasawa et al 2002].
- ***GTF2IRD1*,** encoding GTF2I repeat domain containing 1, WBSCR11, BEN, MUSTRD1 (OMIM 604318) [O'Mahoney et al 1998, Tassabehji et al 1998, Franke et al 1999, Osborne et al 1999]. GTF2IRD1 is a member of the TFII-I transcription factor family [Tipney et al 2004]. *GTF2IRD1* deletion has been implicated in the craniofacial features of Williams syndrome [Tassabehji et al 2005]. Structural variants in *Gtf2ird1* have been shown to contribute to extreme sociability in domestic dogs [vonHoldt et al 2018]. Overexpression of *GTF2IRD1* in neurons that were differentiated from 7q11.23 duplication-induced pluripotent stem cells was able to be modulated back to control levels using histone deacetylase inhibitors [Cavallo et al 2020].
- * ***GTF2IRD2*,** encoding GTF2I repeat domain containing 2 (OMIM 608899) [Makeyev et al 2004, Tipney et al 2004]. Sometimes duplicated in 7q11.23 duplication syndrome, GTF2IRD2 is a member of the TFII-I transcription factor family [Tipney et al 2004].
- ***LAT2*,** encoding linker for activation of T cells, family member 2 (OMIM 605719) [Doyle et al 2000, Martindale et al 2000]. LAT2 is a transmembrane adaptor protein controlling mast cell activation and survival [Roget et al 2008].
- ***LIMK1*,** encoding lim kinase 1 (OMIM 601329). LIMK1 protein is involved in remodeling of the cytoskeleton in neurons through regulation of actin polymerization and is thought to be important for neuronal plasticity [Arber et al 1998]. Deletion of *LIMK1* has been implicated in the abnormality of visuospatial constructive cognition in Williams syndrome [Frangiskakis et al 1996, Morris et al 2003, Hoogenraad et al 2004].
- ***MIR590*,** encoding microRNA 590 (OMIM 615070), an uncharacterized microRNA that was identified in a screen for human microRNAs that promoted neonatal cardiomyocyte proliferation [Eulalio et al 2012]
- ***MLXIPL*,** encoding MLX-interacting protein-like (OMIM 605678) [Meng et al 1998, Cairo et al 2001]. This protein is involved in lipid and glucose metabolism in the liver and in adipose tissue [Iizuka 2013] and in insulin sensitivity [Morigny et al 2019].
- * ***NCF1*,** encoding neutrophil cytosolic factor 1 (OMIM 608512) [Chanock et al 2000]. Sometimes duplicated in 7q11.23 duplication syndrome, NCF1 is the cytosolic subunit of the NADPH oxidase complex [Volpp et al 1989]. Dosage of this gene has been shown to affect the risk of hypertension in Williams syndrome [Del Campo et al 2006]
- * ***NSUN5*,** encoding NOP2/SUN domain family member 5 (OMIM 615732) [Doll & Grzeschik 2001, Merla et al 2002], a ribosomal RNA methyltransferase that has been linked to stress response and life span in model organisms [Schosserer et al 2015] and to global protein synthesis [Heissenberger et al 2019]

- ***RFC2*,** encoding replication factor C, subunit 2 (OMIM 600404) [Osborne et al 1996, Peoples et al 1996], a subunit of the RFC complex that is required for DNA replication [Tsurimoto & Stillman 1989] and is overexpressed in some in cancers [Li et al 2018]
- ***STX1A*,** encoding syntaxin 1A (OMIM 186590) [Osborne et al 1997], a key component in neurotransmitter release and insulin secretion [Gerber & Südhof 2002]
- ***TBL2*,** encoding transducin-beta-like 2 (OMIM 605842) [Meng et al 1998, Pérez Jurado et al 1999]. Located in the endoplasmic reticulum, the TBL2 protein is involved in the cellular stress response [Tsukumo et al 2014].
- * ***TRIM50*,** encoding tripartate motif-containing protein 50 (OMIM 612548) [Meng et al 1998], an E3 ubiquitin ligase [Micale et al 2008]
- ***VPS37D*,** encoding homolog of yeast vacuolar protein sorting 37 (OMIM 610039) [Micale et al 2008]
- ***BUD23*,** encoding rRNA methyltransferase and ribosome maturation factor (OMIM 615733) [Doll & Grzeschik 2001]. BUD23 is involved in ribosome biogenesis [Õunap et al 2013] and promotes efficient translation of mRNA transcripts with low 5'UTR GC content in cardiomyocytes [Baxter et al 2020].
- ***METTL27*,** encoding methyltransferase like 27 (OMIM 612546) [Micale et al 2008]
- ***TMEM270*,** encoding transmembrane protein 270 (OMIM 612547) [Micale et al 2008]

Chapter Notes

Acknowledgments

The authors' research was supported by grant SFARI 328896 from the Simons Foundation, grant R01 NS35102 from the National Institute of Neurological Disorders and Stroke, grant R37 HD29957 from the National Institute of Child Health and Human Development, and the Las Vegas Pediatric Research Fund of the University of Nevada School of Medicine. We are very grateful to the individuals with 7q11.23 duplication syndrome and their families who have participated in our research for their commitment to the research and for giving so generously of their time.

Revision History

- 25 March 2021 (sw) Comprehensive updated posted live
- 25 November 2015 (me) Review posted live
- 10 July 2015 (cbm) Original submission

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