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16p11.2 Recurrent Deletion

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Summary

Clinical characteristics

The 16p11.2 recurrent deletion phenotype is characterized by motor speech disorder, language disorder, motor coordination difficulties, psychiatric conditions, and autistic features. While most, if not all, individuals with the 16p11.2 recurrent deletion experience some degree of developmental delay, the severity varies significantly. Most affected individuals do not have intellectual disability (defined as an IQ of <70), but many have below average cognition and learning disabilities in both verbal and nonverbal domains. Obesity is a feature of this disorder and generally emerges in childhood; BMI in individuals with the 16p11.2 recurrent deletion is significantly higher than in the general population by age five years. Seizures are observed in approximately 25% of individuals with the recurrent deletion. Vertebral anomalies, hearing impairment, macrocephaly, and cardiovascular malformation have each been observed in some individuals. Clinical follow-up data from adults suggests that the greatest medical challenges are obesity and related comorbidities that can be exacerbated by medications used to treat behavioral and psychiatric problems.

Diagnosis/testing

The diagnosis of 16p11.2 recurrent deletion is established by detection of a heterozygous ~593-kb recurrent deletion at the approximate position of chr16:29638676-30188531 in the reference genome (NCBI Build 38).

Management

Treatment of manifestations: Treatment should be targeted to the specific deficits identified. Full developmental assessment, including neuropsychological testing by a clinical psychologist, is strongly suggested to establish neurodevelopmental needs and treatment recommendations. Standard treatment by a neurologist for seizures or movement disorders. Because of the high risk of obesity beginning in adolescence, encourage healthy eating

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habits with attention to portion size and an active lifestyle from a young age. Routine management of vertebral anomalies, hearing loss, and congenital heart defects.

Surveillance: Routine surveillance of growth parameters and calculation of BMI after age two years. Monitor developmental progress and educational needs and provide behavioral assessment at each visit. Monitor those with seizures as clinically indicated and monitor for any new neurologic changes, scoliosis, or hearing loss. For those with obesity, monitor blood pressure and fasting blood glucose.

Genetic counseling

The 16p11.2 recurrent deletion is *de novo* in most probands. Less commonly, the deletion is transmitted from a parent to a child in an autosomal dominant manner.

Once a 16p11.2 recurrent deletion has been identified in a family member, prenatal and preimplantation genetic testing are possible. Interpretation of results from prenatal testing is challenging given the inherent difficulty in accurately predicting the phenotype.

Diagnosis

Suggestive Findings

The 16p11.2 recurrent deletion **should be considered** in individuals with the following clinical findings:

- Motor speech disorder, especially childhood apraxia of speech
- Language disorder
- Learning difficulties / intellectual disability
- Social impairments with or without a diagnosis of autism spectrum disorder (ASD)
- Macrocephaly
- Chiari I malformation / cerebellar tonsillar ectopia
- Seizures/epilepsy
- Vertebral anomalies
- Obesity starting in adolescence, and in the setting of developmental delay

Family history. Because the 16p11.2 recurrent deletion is most often caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of the 16p11.2 recurrent deletion **is established** by identification of a heterozygous ~593-kb deletion at the approximate position of chr16:29638676-30188531 in the reference genome (GRCh38) (sometimes referred to as between BP4 and BP5) (see Table 1 and Molecular Genetics).

Of note, an adjacent (distal) recurrent 16p11.2 deletion (GRCh38 chr16:28811314-29035178), which is also associated with variable features, is not discussed further, as this *GeneReview* addresses the more proximal chr16:29638676-30188531 recurrent deletion only.

Molecular methods that determine the copy number of sequences can include **chromosomal microarray (CMA)**, **exome/genome sequencing with copy number variant calling**, or **targeted deletion analysis**. Note: The 16p11.2 deletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.

- **Chromosomal microarray (CMA)** using oligonucleotide arrays or SNP genotyping arrays can detect the recurrent deletion in a proband. The ability to size the deletion depends on the type of microarray used and the density of probes in the 16p11.2 region.

  Note: (1) Most individuals with the 16p11.2 recurrent deletion are identified by CMA performed in the context of evaluation of developmental delay, intellectual disability, or ASD. (2) Prior to 2008 many CMA platforms did not include coverage for this region and thus may not have detected this deletion.

- **Exome and genome sequencing analyses** are next-generation sequencing technologies that generate DNA sequence either for all coding regions (exome) or the entire genome. Copy number variant-calling algorithms need to be utilized to detect the 16p11.2 recurrent deletion.

- **Targeted deletion analysis.** Fluorescent in situ hybridization (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 known to have the 16p11.2 recurrent deletion.

  Note: (1) Targeted deletion testing is not appropriate for an individual in whom the 16p11.2 recurrent deletion was not detected by CMA designed to target this region. (2) It is not possible to size the deletion routinely by use of targeted methods.

Table 1. Genomic Testing Used in the 16p11.2 Recurrent Deletion

Deletion [1]	Method	Sensitivity	
		Proband	At-risk family members
~593-kb heterozygous deletion at 16p11.2 ISCN: seq[GRCh38] del(16)(p11.2) chr16:29,638,676-30,188,531 [2] ISCA-37400	CMA [3]	100%	100%
	Targeted deletion analysis [4]	NA [5]	100% [6]

1. See Molecular Genetics for details of the deletion and genes of interest.
2. Standardized ISCN 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 deletion size associated with the 16p11.2 recurrent deletion as designated by ClinGen. Deletion coordinates may vary slightly based on array design used by the testing laboratory. Note that the size of the deletion as calculated from these genomic positions may differ from the expected deletion size due to the presence of segmental duplications near breakpoints. The phenotype of significantly larger or smaller deletions within this region may be clinically distinct from the recurrent 16p11.2 deletion (see Genetically Related Disorders).
3. Chromosome microarray analysis (CMA) using oligonucleotide or SNP arrays. CMA designs in current clinical use target the 16p11.2 region. Note: The 16p11.2 recurrent deletion may not have been detectable by older oligonucleotide or BAC platforms.
4. Targeted deletion analysis methods can include FISH, quantitative PCR, and multiplex ligation-dependent probe amplification (MLPA) as well as other targeted quantitative methods.
5. Targeted deletion analysis is not appropriate for an individual in whom the 16q11.2 recurrent deletion was not detected by CMA designed to target this region.
6. Targeted deletion analysis may be used to test at-risk relatives of a proband known to have the 16q11.2 recurrent deletion.

Clinical Characteristics

Clinical Description

The 16p11.2 recurrent deletion is one of the most common known genetic causes of neurodevelopmental disorders [Männik et al 2015, Chung et al 2021]. Common clinical features include motor speech disorder, language disorder, motor coordination difficulties, psychiatric conditions, and autistic features. Clinical follow-up data from adults suggest that the greatest medical challenges are obesity and related comorbidities that can be exacerbated by medications used to treat behavioral and psychiatric problems.

Table 2. Select Features of the 16p11.2 Recurrent Deletion

Feature	% of Persons w/Feature	Comment
Developmental delay	Most (if not all)	Degree varies significantly.
Psychiatric/behavioral issues	>90%	50% have ≥1 psychiatric/behavioral diagnoses. Most report symptoms of behavioral conditions.
Motor speech disorders	80%	Incl apraxia, dysarthria; majority mild-to-moderate, some minimally verbal
Language disorder	80%-90%	Broadly impaired receptive, expressive, pragmatic domains
Obesity	75%	Onset in early adolescence through adulthood
Motor coordination difficulties	60%	
Autistic features / autism	20%-25%	
Seizures	25%	
Vertebral anomalies	21%	May be assoc w/scoliosis
Hearing loss	<11%	Both sensorineural & conductive reported
Paroxysmal kinesigenic dyskinesia (PKD)	≤9%	Incl benign familial infantile seizures, PKD, & PKD w/infantile convulsions
Cardiac malformations	6%	

Developmental Delay

Most if not all individuals with the 16p11.2 recurrent deletion experience some degree of developmental delay, although the severity varies. Developmental coordination (motor) disorder is one of the most common diagnoses in individuals with the 16p11.2 recurrent deletion, followed by phonologic processing disorder, language disorders, and autism spectrum disorder (ASD) [Hanson et al 2015]. Individuals with the 16p11.2 recurrent deletion have been found to perform worse on functional motor tasks and have lower endurance than sibs without the deletion. These individuals generally walked and ran slower than sibs and had worse balance [Goldman et al 2019].

Cognitive Impact

Most affected individuals do not have intellectual disability (defined as an IQ of <70), but many have below average cognition and learning disabilities in both verbal and nonverbal domains. On average, the IQ of individuals with the 16p11.2 recurrent deletion is approximately 2 SD lower than other family members without the deletion. Average IQ was 82.7, representing a 26.8-point (1.8 SD) shift downward compared to the full scale IQ average of 109.5 of familial controls [Hanson et al 2015, Hippolyte et al 2016].

Psychiatric Disease and Behavioral Issues

Individuals with the 16p11.2 recurrent deletion are at increased risk for psychiatric diagnoses, with most individuals with the deletion having at least one psychiatric diagnosis [Chawner et al 2019]. Attention-deficit/hyperactivity disorder (ADHD) is common and reported in approximately 35% of individuals with the deletion. Other psychiatric diagnoses such as anxiety disorders, obsessive compulsive disorder (OCD), oppositional defiant disorder, conduct disorder, and schizophrenia are present in those with the 16p11.2 recurrent deletion, but have not been reported to exceed population controls [Niarchou et al 2019].

Motor Speech Disorders

The majority of children (~80%) with the 16p11.2 recurrent deletion present with a motor speech disorder, such as childhood apraxia of speech (CAS) and dysarthria [Steinman et al 2016, Mei et al 2018]. CAS is particularly prevalent (found in 77% of affected children) and often co-occurs with other speech sound disorders, such as articulation and phonologic disorders [Mei et al 2018]. Most motor speech disorders are classified as mild to moderate in severity, but features of CAS may persist into adulthood. A minority of individuals remain minimally verbal [Fedorenko et al 2016].

CAS appears to occur independently of other neuropsychiatric diagnoses such as ASD [Mei et al 2018], and may result from impaired speech motor control [Demopoulos et al 2018].

Language Disorder

More than 80% of children and adults exhibit some degree of language impairment, with the majority demonstrating both receptive and expressive deficits [Mei et al 2018]. There does not appear to be a pattern of specific strengths and weaknesses among language subdomains; rather, broad deficits are often present across areas of semantics and morphosyntax. Pragmatic language impairment is also common, even among individuals without an autism spectrum diagnosis [Kim et al 2020].

Obesity

The 16p11.2 recurrent deletion is a predisposing factor for overweight (defined as sex-specific BMI for age 85-95th centile) and obesity (defined as sex-specific BMI for age >95th centile).

Overall, several studies show that obesity is a feature of the 16p11.2 recurrent deletion, with the prevalence of overweight and obesity in individuals with the 16p11.2 recurrent deletion higher than in the general population [Jacquemont et al 2011, Gill et al 2014, Kostopoulou et al 2019]. Obesity generally emerges in childhood; BMI in individuals with the 16p11.2 recurrent deletion is significantly higher than in the general population by age five years [Gill et al 2014, D'Angelo et al 2016].

Autistic Features

Individuals with the 16p11.2 recurrent deletion identified in the earliest reported research studies were ascertained primarily through cohorts of individuals with an ASD. Although not all individuals with the 16p11.2 recurrent deletion meet diagnostic criteria for ASD, almost all have some behavioral traits shared with ASD including insistence on sameness, reduced scope of interest, repetitive behaviors, and problems with social communication [Zufferey et al 2012, Hanson et al 2015, Moreno-De-Luca et al 2015, Fetit et al 2020].

Based on current literature reports, ASD is diagnosed in approximately 20%-25% of individuals with the 16p11.2 recurrent deletion (i.e, with much greater frequency than in the general population, in which ASD is diagnosed in ~1:54 children) [Zufferey et al 2012, Chung et al 2021].

Neurologic Issues

Seizures are seen in about 25% of individuals with the 16p11.2 recurrent deletion [Zufferey et al 2012, Steinman et al 2016, Chung et al 2021]. Heterozygous pathogenic loss-of-function *PRRT2* (located at 16p11.2) variants (which cause paroxysmal kinesigenic dyskinesia; see following) also cause benign familial infantile seizures and infantile convulsions with choreoathetosis syndrome [Heron et al 2012], both of which have been reported in a number of individuals with the 16p11.2 recurrent deletion.

***PRRT2*-associated paroxysmal disorders** have been reported among individuals with the 16p11.2 recurrent deletion. Heterozygous loss-of-function pathogenic *PRRT2* variants are associated with autosomal dominant *PRRT2*-related disorder, which encompasses three allelic paroxysmal disorders of a disease spectrum: benign

familial infantile seizures (BFIS), paroxysmal kinesigenic dyskinesia (PKD), and PKD with infantile convulsions (PKD/IC), also known as infantile convulsions and choreoathetosis (ICCA). Among individuals with the 16p11.2 recurrent deletion, three individuals have been reported with BFIS and six individuals have been reported with PKD; however, it is notable that similar features have been reported in additional individuals with the 16p11.2 recurrent deletion in larger studies, though discrete classification among *PRRT2*-related phenotypes has not been pursued [Wang et al 2011, Lee et al 2012, Li et al 2012, Termsarasab et al 2014, Vlaskamp et al 2019, Garone et al 2020].

Neuroimaging findings

- The most common recurrent structural brain abnormalities are posterior fossa and/or craniocervical junction-related abnormalities (e.g., Chiari I malformation, cerebellar tonsillar ectopia, platybasia) [Zufferey et al 2012, D'Angelo et al 2016, Owen et al 2018]. Two persons with the 16p11.2 recurrent deletion were reported to have syringomyelia (accompanied by a Chiari I malformation in 1 person) [Schaaf et al 2011].
- Quantitative structural MRI analysis has shown a pervasive increase in volume throughout the brain, with white matter and thalami being the most dramatically affected [Qureshi et al 2014]. Thicker corpus callosum has also been noted [Owen et al 2018].

Other Medical Issues

Although consistent patterns of other medical problems are not observed, the following have been reported in individuals with the 16p11.2 recurrent deletion:

- Vertebral anomalies (often associated with scoliosis) were observed in 21% of 233 individuals with the deletion [Zufferey et al 2012].
- Hearing impairment (sensorineural and conductive hearing loss) is seen in up to 11% of individuals.
- Cardiac malformations have been reported in some individuals. Although most with a diagnosis of the 16p11.2 recurrent deletion have not had diagnostic cardiac imaging, limited clinical reports suggest that the incidence of cardiac malformations is slightly increased. Congenital heart disease was identified in 6% of 233 individuals with the 16p11.2 recurrent deletion [Zufferey et al 2012].
- The 16p11.2 recurrent deletion has been found to be more common in children with neuroblastoma compared to population controls [Egolf et al 2019]. While the 16p11.2 recurrent deletion is found in approximately 0.03% of the general population, it was identified by Egolf et al [2019] in 0.39% of children with neuroblastoma and represented a 13.9-fold increased risk of neuroblastoma. Neuroblastoma is typically a cancer of childhood with the majority of individuals diagnosed prior to age ten, and a median age of diagnosis of 19 months.
- Height is slightly below average for individuals who are not overweight and may be average for individuals who are overweight [Zufferey et al 2012].
- Macrocephaly is frequently observed (reported in 17% of affected individuals in the study of Steinman et al [2016]) and usually becomes apparent by age two years. Macrocephaly was more frequently observed in obese individuals with the 16p11.2 recurrent deletion (41.3%) than in non-obese individuals with the 16p11.2 recurrent deletion (12.5%) [Zufferey et al 2012]. Macrocephaly is usually not secondary to hydrocephalus.
- Craniosynostosis was observed in 2% of 233 individuals [Zufferey et al 2012].
- A characteristic pattern of dysmorphic features that would facilitate a clinical diagnosis is not observed in individuals with the 16p11.2 recurrent deletion, although abnormal palpebral fissures are noted in approximately 40% of individuals with the deletion [Stingl et al 2020].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed.

Prevalence

The most recent estimate is approximately 1:2,000 in the general population [Männik et al 2015, Chung et al 2021].

Genetically Related (Allelic) Disorders

16p11.2 Recurrent Duplication

Reciprocal ~593-kb duplication of 16p11.2 is the copy number variant most frequently associated with autism spectrum disorder (ASD), schizophrenia, and decreased BMI [D'Angelo et al 2016]. Other conditions associated with the duplication include attention-deficit/hyperactivity disorder (ADHD), anxiety, intellectual disability, and motor delays [Green Snyder et al 2016]. The prevalence is estimated to be approximately 0.05%–0.09% of the population [Männik et al 2015]. Adults with the 16p11.2 recurrent duplication often have fewer intellectual impairments or psychiatric disorders compared to their children who have the 16p11.2 recurrent duplication [Green Snyder et al 2016]. The duplication has also been reported in at least two individuals with childhood-onset schizophrenia [Walsh et al 2008].

The phenotype of the 16p11.2 recurrent duplication shows more variability than the phenotype of the 16p11.2 recurrent deletion; however, most individuals with the 16p11.2 recurrent duplication are identified by CMA performed in the evaluation of developmental delay, intellectual disability, or ASD, conferring an ascertainment bias that makes the phenotype associated with the 16p11.2 recurrent duplication difficult to establish.

- In a study of 270 individuals with the 16p11.2 recurrent duplication, the mean full-scale IQ (FSIQ) was 78.8 with 30% meeting criteria for a diagnosis of intellectual disability. FSIQ measures were significantly lower than in relatives who did not have the 16p11.2 recurrent duplication [D'Angelo et al 2016]. Individuals with the 16p11.2 recurrent duplication with lower FSIQ often display other impairments in motor, language, and social skills [Green Snyder et al 2016].
- ASD has been found to be slightly more common in those with the 16p11.2 recurrent duplication (20%) than in those with the 16p11.2 recurrent deletion (16%), and individuals with the 16p11.2 recurrent duplication with ASD have lower cognition than those with the 16p11.2 recurrent deletion with ASD [D'Angelo et al 2016].
- Seizures are observed in approximately 20% of individuals with the 16p11.2 recurrent duplication [D'Angelo et al 2016, Green Snyder et al 2016].
- Head circumference tends to be smaller in individuals with the 16p11.2 recurrent duplication than in their relatives without the duplication [D'Angelo et al 2016].
- In addition, the 16p11.2 recurrent duplication is associated with underweight and a lower body mass index (BMI). The reciprocal impact of both the 16p11.2 recurrent deletion and duplication indicate that severe obesity (deletion) and being underweight (duplication) could have mirror etiologies, possibly through contrasting effects on energy balance [Jacquemont et al 2011, D'Angelo et al 2016].

Whereas 16p11.2 recurrent deletions are often *de novo*, a larger proportion of recurrent duplications are inherited. Parents with a 16p11.2 recurrent duplication may not have a history of developmental delay, ID, or ASD but may have more subtle neurobehavioral manifestations.

16p11.2-p12.2 Deletion

At least two individuals with much larger deletions that include the 16p11.2 recurrent deletion region have been described [Ballif et al 2007, Battaglia et al 2009]. In both individuals, the deletion was larger than 8 Mb, causing a more severe phenotype.

Differential Diagnosis

The differential diagnosis of the 16p11.2 recurrent deletion is broad due to the clinical variability and the presence of relatively common abnormal phenotypes that occur in affected individuals including developmental delay and autism spectrum disorder. All chromosome anomalies and genes known to be associated with intellectual disability (see OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series) should be included in the differential diagnosis of the 16p11.2 recurrent deletion.

Management

No clinical practice guidelines for the 16p11.2 recurrent deletion have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with the 16p11.2 recurrent deletion, 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 the 16p11.2 Recurrent Deletion

System/Concern	Evaluation	Comment
Constitutional	In those age >2 yrs: measure growth parameters & calculate BMI.	To assess for obesity
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For those age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Neurologic	Neurologic eval incl assessment for movement disorders & dystonia, & for signs/symptoms of brain stem dysfunction [1]	• To incl brain MRI w/particular assessment for posterior fossa &/or craniocervical junction-related abnormalities [2] • Consider EEG if seizures are a concern.
Musculoskeletal	AP & lateral spinal radiographs	To assess for vertebral anomalies/scoliosis
	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Endocrinologic	Consider obtaining fasting blood glucose & hemoglobin A1c.	To screen for diabetes in those who are overweight
Hearing	Audiology eval	To assess for hearing loss

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Cardiovascular	Auscultation for heart murmur	Consider echocardiography in those w/signs/symptoms suggestive of a congenital heart defect.
	Blood pressure	To screen for hypertension in those who are overweight
Genetic counseling	By genetics professionals [3]	To inform affected persons & their families re nature, MOI, & implications of the 16p11.2 recurrent deletion in order to facilitate medical & personal decision making
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; BMI = body mass index; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Such as chronic headache (especially occipital), neck pain, oropharyngeal dysfunction, sleep apnea, gait disturbance, and scoliosis
2. Including Chiari I malformation, cerebellar tonsillar ectopia, and platybasia
3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with the 16p11.2 Recurrent Deletion

Manifestation/Concern	Treatment	Considerations/Other
Obesity	Initiation of weight management & nutrition counseling: • Control food intake w/normal portion sizes & limitation of intake between meals. • Maintain active lifestyle.	• Esp important in young children before excessive weight gain begins • ↑ calories specifically ingested in absence of hunger suggest that close supervision of portion size & meal times can be beneficial.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Psychiatric/Behavioral	Standard treatment per psychologist &/or psychiatrist	See Social/Behavioral Concerns.
Epilepsy	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]
Paroxysmal kinesigenic dyskinesia	Consideration of low doses of carbamazepine or phenytoin	
Dystonia	Standard treatment per neurologist	May incl use of antiparkinsonian drugs
Chiari I malformation / Syringomyelia	Standard treatment per neurosurgeon	
Scoliosis	Standard treatment per orthopedist	
Type II diabetes	Standard treatment per endocrinologist	May incl use of an oral hypoglycemic medication in addition to healthy diet & exercise
Hearing	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Congenital heart defect	Standard treatment per cardiologist	
Hypertension		
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.

ASM = anti-seizure medication; 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.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, and speech therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- For muscle tone abnormalities including dystonia, consider involving appropriate specialists to aid in management of antiparkinsonian medications.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder (ADHD), when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with the 16p11.2 Recurrent Deletion

System/Concern	Evaluation	Frequency
Constitutional	In those age >2 yrs: measure growth parameters & calculate BMI.	At each visit
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone, mvmt disorders, & signs/symptoms of spinal cord dysfunction.[1]	
Musculoskeletal	Physical exam for scoliosis	At each visit in childhood until skeletal maturity
Endocrinologic	Consider annual fasting blood glucose & hemoglobin A1c.	Annually or as clinically indicated in overweight or obese children & adults
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
Hearing	Audiology eval	Annually during first 3 yrs of life or as clinically indicated
Cardiovascular	Blood pressure	At each visit in childhood & adulthood for those who are overweight or obese
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy

1. Such as chronic headache (especially occipital), neck pain, oropharyngeal dysfunction, sleep apnea, gait disturbance, and scoliosis

Agents/Circumstances to Avoid

Some medications used to treat behavioral problems (e.g., clozapine, olanzapine) may lead to excessive weight gain. When possible, use medications that are not associated with weight gain.

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

The 16p11.2 recurrent deletion is *de novo* in most probands. Less commonly, the deletion is transmitted from a parent to a child in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The 16p11.2 recurrent deletion is *de novo* in approximately 93% of reported probands whose parents have undergone genomic testing.
- Approximately 7% of probands inherited the 16p11.2 recurrent deletion from a parent. Parents with a 16p11.2 recurrent deletion typically do not have a history of ID or ASD but may have more subtle neurodevelopmental and behavioral manifestations.
- Genomic testing that will detect the 16p11.2 recurrent deletion present in the proband is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment. The 16p11.2 recurrent deletion has been detected in mildly affected and unaffected parents.
- If the 16p11.2 recurrent deletion identified in the proband is not identified in either confirmed biological parent, the following possibilities should be considered:
    - The proband has a *de novo* deletion.
    - The proband inherited a deletion from a parent with germline (or somatic and germline) mosaicism [Kumar et al 2008, Weiss et al 2008, Steinman et al 2016].

      Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a genetic alteration that is present in the germ cells only.
- The 16p11.2 recurrent deletion has not been reported to have a parent-of-origin bias.

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

- If one of the parents has the 16p11.2 recurrent deletion identified in the proband, the risk to each sib of inheriting the deletion is 50%. It is not possible to predict the phenotype in sibs who inherit a 16p11.2 recurrent deletion; family members with the deletion may be mildly affected or have features similar to those of the proband.
- If the 16p11.2 recurrent deletion identified in the proband cannot be detected in parental leukocyte, the recurrence risk to sibs is approximately 1% because of the possibility of parental germline mosaicism for the deletion [Kumar et al 2008, Weiss et al 2008].

Offspring of a proband. Each child of an individual with the 16p11.2 recurrent deletion has a 50% chance of inheriting the deletion; it is not possible to predict the phenotype in offspring who inherit the deletion.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the 16p11.2 recurrent deletion, the parent's family members may also have the deletion.

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 the 16p11.2 recurrent deletion.

Prenatal Testing and Preimplantation Genetic Testing

Once a 16p11.2 recurrent deletion has been identified in a family member, prenatal and preimplantation genetic testing are possible.

Although the prenatal finding of a 16p11.2 recurrent deletion cannot be used to reliably predict the phenotype, the majority of individuals with the 16p11.2 recurrent deletion have language delay and cognitive disability.

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.

- **Chromosome Disorder Outreach Inc.**
  Phone: 561-395-4252
  Email: info@chromodisorder.org
  chromodisorder.org
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  rarechromo.org
- **Simons Searchlight Registry**
  Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.
  Phone: 855-329-5638
  Fax: 570-214-7327
  Email: coordinator@simonssearchlight.org
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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. 16p11.2 Recurrent Deletion: Genes and Databases

Critical Region	Gene	Chromosome Locus	Protein	ClinVar

Table A. continued from previous page.

AUTS14	*Not applicable*	16p11.2	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 16p11.2 Recurrent Deletion (View All in OMIM)

611913	CHROMOSOME 16p11.2 DELETION SYNDROME, 593-KB

Molecular Pathogenesis

The 16p11.2 recurrent deletion is mediated by nonallelic homologous recombination (NAHR) between flanking 147-kb low-copy repeat sequences with 99.5% sequence identity [Ghebranious et al 2007, Sebat et al 2007, Kumar et al 2008, Marshall et al 2008, Weiss et al 2008]. The reciprocal duplication is also mediated by NAHR at the same site.

Mechanism of disease causation. Loss of function of some or all of the genes within the deleted region (See **Notable genes typically included in this region**.)

Laboratory technical considerations. The 16p11.2 recurrent deletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.

Notable genes typically included in this region. The 16p11.2 recurrent deletion involves the loss of one chromosome segment containing 25 annotated genes or transcripts [Kumar et al 2008, Marshall et al 2008, Weiss et al 2008]. The recurrent deletion is flanked by segmental duplications that contain four additional genes.

How deletion of these genes results in the clinical manifestations associated with the 16p11.2 recurrent deletion is largely unknown, but ongoing investigations have identified the roles of some key genes and their associated functional pathways as responsible for the phenotypic features.

While most of the genes at 16p11.2 exhibited dosage-dependent expression pattern [Migliavacca et al 2015], the pathogenic functions of each gene or their combinations require further examination.

- ***PRRT2.*** Heterozygous loss-of-function *PRRT2* pathogenic variants are associated with autosomal dominant *PRRT2*-related disorder, which encompasses three allelic paroxysmal disorders: paroxysmal kinesigenic dyskinesia (38.7%); benign familial infantile epilepsy (41.7%); and infantile convulsions with choreoathetosis syndrome (14.3%) [Heron et al 2012, Schubert et al 2012, van Vliet et al 2012, Ebrahimi-Fakhari et al 2015]. These phenotypes have been reported in a small number of individuals with the 16p11.2 recurrent deletion.
- ***KCTD13.*** A smaller (~118-kb) deletion within 16p11.2 that segregated with ASD and other neurodevelopmental abnormalities has been identified [Crepel et al 2011]. One of the five genes at this interval, *KCTD13*, was identified as a major driver for the neuroanatomic phenotypes of the 16p11.2 recurrent deletion [Golzio et al 2012]. This gene is associated with ciliary function, which is thought to be significantly disrupted in individuals with the 16p11.2 recurrent deletion or duplication [Migliavacca et al 2015].
- ***TBX6.*** It has been determined that vertebral abnormalities and scoliosis observed in some individuals with the 16p11.2 recurrent deletion result from a combination of a *TBX6* null allele (i.e., the recurrent deletion) and hypomorphic allele [Wu et al 2015].

Chapter Notes

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