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DYRK1A Syndrome

Bregje WM van Bon, MD, PhD,[1] Bradley P Coe, PhD,[2] Bert BA de Vries, MD, PhD,[1] and Evan E Eichler, PhD[2]

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Summary

Clinical characteristics

DYRK1A syndrome is characterized by intellectual disability including impaired speech development, autism spectrum disorder including anxious and/or stereotypic behavior problems, and microcephaly. Affected individuals often have a clinically recognizable phenotype including a typical facial gestalt, feeding problems, seizures, hypertonia, gait disturbances, and foot anomalies. The majority of affected individuals function in the moderate-to-severe range of intellectual disability; however, individuals with mild intellectual disability have also been reported. Other medical concerns relate to febrile seizures in infancy; the development of epilepsy with seizures of the atonic, absence, and generalized myoclonic types; short stature; and gastrointestinal problems. Ophthalmologic, urogenital, cardiac, and/or dental anomalies have been reported.

Diagnosis/testing

The diagnosis of *DYRK1A* syndrome is established in a proband with suggestive findings and a heterozygous pathogenic variant in *DYRK1A* identified by molecular genetic testing.

Management

Treatment of manifestations: Educational and therapy programs to address the specific needs identified; routine treatment of epilepsy under the care of a neurologist; standard treatment for orthopedic, dental, cardiac, urogenital, ophthalmologic, constipation, and other medical issues.

Surveillance: Regular monitoring and guidance for educational and behavior problems, growth parameters and nutritional status, and safety of oral intake; regular lifelong follow up as determined by specialists for issues present affecting heart, eyes, and teeth.

Author Affiliations: 1 Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands; Email: bregje.vanbon@radboudumc.nl; Email: bert.devries@radboudumc.nl. 2 Department of Genome Sciences, University of Washington School of Medicine, Seattle, Washington; Email: bcoe@u.washington.edu; Email: eee@gs.washington.edu.

Genetic counseling

DYRK1A syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. If the *DYRK1A* pathogenic variant identified in the proband is not identified in either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism. Once the *DYRK1A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

DYRK1A syndrome **should be considered** in individuals with mild-to-severe psychomotor developmental delay (DD) or intellectual disability (ID) AND any of the following additional features presenting in infancy or childhood:

- Intrauterine growth retardation
- Microcephaly
- Typical facial gestalt:
    - During infancy and childhood facial features include prominent ears, deep-set eyes, mild upslanted palpebral fissures, a short nose with a broad nasal tip, and retrognathia with a broad chin.
    - In adulthood, the nasal bridge may become high and the alae nasi underdeveloped, giving the nose a more prominent appearance [van Bon et al 2016].
- Neonatal feeding difficulties that may persist
- Epilepsy (febrile seizures, atonic seizures, absence seizures, and generalized myoclonic seizures)
- Hypertonia
- Abnormal gait
- Behavioral problems such as autism spectrum disorder, anxiety, and/or sleep disturbances
- Foot anomalies: mild cutaneous syndactyly of toes 2-4; hallux valgus; and short fifth toe
- Vision abnormalities (strabismus, myopia, hypermetropia, retinal anomalies, optic atrophy, coloboma)
- Urogenital anomalies (undescended testes, hypoplastic scrotum, micropenis, inguinal hernia, renal abnormalities)

Establishing the Diagnosis

The diagnosis of *DYRK1A* syndrome **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *DYRK1A* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *DYRK1A* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability typically begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is typically either a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *DYRK1A*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *DYRK1A*) that cannot be detected by sequence analysis.

- **An intellectual disability (ID) multigene panel** that includes *DYRK1A* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID, whereas some multigene panels may not.

  Genome sequencing is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *DYRK1A* Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DYRK1A	Sequence analysis [3]	87% [4]
	Gene-targeted deletion/duplication analysis [5]	13% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Oegema et al [2010] and Valetto et al [2012]) may not be detected by these methods.

Clinical Characteristics

Clinical Description

DYRK1A syndrome is characterized by intellectual disability including impaired speech development, autism spectrum disorder with anxious and/or stereotypic behavior problems, and microcephaly. Affected individuals often have a clinically recognizable phenotype including a typical facial gestalt, feeding problems, seizures, hypertonia, gait disturbances, and foot anomalies [van Bon et al 2016].

To date, 68 individuals have been reported with a pathogenic variant in *DYRK1A* [Møller et al 2008, van Bon et al 2011, Courcet et al 2012, O'Roak et al 2012, Redin et al 2014, Bronicki et al 2015, Ji et al 2015, Ruaud et al 2015, Luco et al 2016, van Bon et al 2016, Earl et al 2017, Evers et al 2017, Murray et al 2017, Blackburn et al

2019, Qiao et al 2019, Lee et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of *DYRK1A* Syndrome

Feature	Frequency of Persons w/Feature [1]	Comment
DD/ID	100%	
Hypertonia	12/33	
Gait disturbance	24/45	
Speech impairment	100%	All have speech delay; however, some do speak at a later age.
Feeding problems	93%	
Epilepsy	65%	Some have only febrile seizures in infancy.
ASD	46%	↑ to 69% when broadening criteria to incl ASD-related behaviors w/o formal diagnosis
Anxiety	27%	
Hyperactivity	10/35	
Sleep disturbance	6/15	Not often reported on in studies
Microcephaly	95%	
Weight (<−2 SD)	49%	
Short stature	44%	
Eye abnormalities	79%	
Characteristic facial features	90%	
Cardiac defects	9/48	
Gastrointestinal problems	30%	
Urogenital anomalies	40%	
Musculoskeletal features	10%	
Dental anomalies	6/36	

ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability
1. Some studies have had limited phenotypic descriptions; thus, information is not available on all features. When the number of individuals evaluated with a particular feature is <50, a fraction (rather than a %) is used, with the denominator indicating the total number evaluated for the feature.

Developmental delay (DD) and intellectual disability (ID). Generalized hypertonia may already be noted during the first months of life. Motor development is often impaired by gait disturbances and hypertonia.

- Although some individuals achieve independent walking at the upper age limit of normal, the majority achieve walking after age two to three years.
- The majority are described as having a broad-based/ataxic gait [Ji et al 2015, van Bon et al 2016]. A more detailed report describes a lilting gait with forward lean to the upper body, arms bent and held tight against the body, and hands splayed [Earl et al 2017].

All individuals show delayed development of speech. Some individuals learn to speak; others show a lack of speech or the use of one- to two-word utterances only. In general, expressive language is more severely affected than receptive language.

The majority of affected individuals function in the moderate-to-severe range of intellectual disability; however, individuals with mild intellectual disability have also been reported.

Other neurodevelopmental features

- **Abnormal tone.** Generalized hypertonia may already be noted during the first months of life.
- **Feeding problems** due to difficulties with suck and swallowing and gastrointestinal reflux occur in the majority of infants. Feeding problems may persist during childhood and adulthood, warranting tube feeding in some affected individuals [van Bon et al 2016].

Epilepsy. Febrile seizures during infancy are common. About 50% of affected individuals develop epilepsy including seizures of the atonic, absence, and generalized myoclonic types [Courcet et al 2012, Bronicki et al 2015, Ji et al 2015, van Bon et al 2016].

Behavior problems. Autism spectrum disorders, stereotypies, anxious behavior, hyperactivity, and sleep disturbances (difficulty falling asleep, awakening at night) have been observed [van Bon et al 2016, Earl et al 2017]. In almost half of affected individuals an official ASD diagnosis has been reported. However, this percentage increases to almost 70% when broadening the criteria to include ASD-related behaviors without a formal diagnosis [Earl et al 2017].

Growth

- **Microcephaly, intrauterine growth restriction, and/or oligohydramnios** may be noted prenatally. Head circumference at birth is between −1 and −4 SD and abnormally slow head growth causes the deviation to further increase over time to −2 to −5 SD in the majority (95%) of individuals. Low birth weight (<−2 SD) has also frequently been reported.
- **Low weight and a slender build** later in life are also common [Courcet et al 2012, Deciphering Developmental Disorders Study Group 2015, Ruaud et al 2015, van Bon et al 2016]. Only four individuals have been reported with a weight above the 50th percentile [Bronicki et al 2015, Luco et al 2016, van Bon et al 2016].
- **Short stature** (<−2 SD) has been reported in about 44% of individuals. Onset may occur prior to birth or later in childhood. A height above the 50th percentile has been reported in two individuals [Bronicki et al 2015, Ji et al 2015, van Bon et al 2016, Evers et al 2017].

Sensory impairment. Eye abnormalities are common and typically include strabismus, astigmatism, and hypermetropia. However, iris coloboma, optic nerve dysfunction, corneal clouding, early cataract, and retinal detachment have also been reported [Bronicki et al 2015, Ji et al 2015, van Bon et al 2016, Earl et al 2017].

Neuroimaging. Brain imaging may show findings indicative of global cerebral underdevelopment or hypomyelination. It may detect enlarged ventricles, myelination delay, cortical brain atrophy, hypoplasia of the corpus callosum, a small brain stem, and/or a hypoplastic pituitary stalk [Bronicki et al 2015, Ji et al 2015, van Bon et al 2016, Evers et al 2017].

Other associated features

- **Facial features.** During infancy and childhood facial features include prominent ears, deep-set eyes, mild upslanted palpebral fissures, a short nose with a broad nasal tip, and retrognathia with a broad chin. In adulthood, the nasal bridge may become high and the alae nasi underdeveloped, giving the nose a more prominent appearance [van Bon et al 2016].
- **Cardiac defects** include atrial septum defect, ventricular septum defect, hypoplastic left heart, aortic valve and pulmonary valve abnormalities, aortic stenosis, and patent ductus arteriosus.
- **Gastrointestinal problems** mainly include gastrointestinal reflux and (sometimes severe) constipation.

- **Urogenital anomalies** may include undescended testes, hypoplastic scrotum, shawl scrotum, micropenis, hypospadias, inguinal hernia, frequent urinary infections, vesicoureteral reflux, and unilateral renal agenesis.
- **Musculoskeletal features.** In about 10% of affected individuals scoliosis, kyphosis, and/or pectus excavatum has been reported. Several individuals show a typical foot anomaly: a combination of mild cutaneous syndactyly of toes 2-4, hallux valgus, and a short fifth toe has been noted in several individuals [van Bon et al 2016].
- **Dental anomalies** including widely spaced teeth, extreme calculus (hardened dental plaque), delayed primary dentition, neonatal teeth, and supernumerary teeth have also been reported.

Prognosis. Based on current data, life span is not limited by this condition as several adult individuals have been reported. Data on possible progression of behavior abnormalities or neurologic findings are still limited.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Penetrance is likely to be 100% in individuals with a *de novo* pathogenic variant. Haploinsufficiency of *DYRK1A* has not been observed in control populations. Expressivity is similar in males and females [van Bon et al 2016].

Prevalence

Studies have demonstrated that *DYRK1A* syndrome accounts for 0.1%-0.5% of individuals with intellectual disability and/or autism [Courcet et al 2012, O'Roak et al 2012, Deciphering Developmental Disorders Study Group 2015, van Bon et al 2016].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DYRK1A*.

Individuals with chromosome 21q22.13 deletions that include *DYRK1A* may have features similar to *DYRK1A* syndrome, including mild-to-severe developmental delay, impaired speech, ataxia-like gait disturbances, short stature, low weight, seizures, and distinctive facial features. To date, no clear difference in phenotype has been reported [Valetto et al 2012]. These deletions are very rare. Larger deletions that also include other chromosomal bands may show more severe phenotypes (see DECIPHER).

Differential Diagnosis

Intellectual disability and microcephaly, the most frequent findings in the *DYRK1A* syndrome, have an extensive differential diagnosis.

- **Intellectual disability.** See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

- **Primary microcephaly (PM)** is a group of rare, phenotypically and etiologically heterogeneous disorders of brain growth characterized by (1) a head circumference close to or below −2 SD at birth and below −3 SD by age one year; (2) absence of extracephalic anomalies; and (3) mild-to-severe intellectual disability. Additional clinical or neuroimaging features can be associated. Most PMs are inherited in an autosomal recessive manner. To date, pathogenic variants in more than 100 genes are responsible for PM (see *ASPM* Primary Microcephaly; for review, see Jayaraman et al [2018]).

In *DYRK1A* syndrome, microcephaly often develops before birth or in the first months after birth and intrauterine growth restriction is variable. The occurrence of additional findings should distinguish this syndrome from other disorders in which primary microcephaly occurs.

Diagnoses that may be considered in individuals with multiple findings suggestive of *DYRK1A* syndrome include those summarized in Table 3.

Table 3. Disorders with Multiple Findings Suggestive of *DYRK1A* Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Features of Differential Disorder	
			Overlapping w/*DYRK1A* syndrome	Distinguishing from *DYRK1A* syndrome
Deficient expression or function of maternally inherited *UBE3A* allele	Angelman syndrome	See footnote 1.	Microcephaly, [2] seizures, & absence of speech	Specific EEG pattern; [2] facial gestalt & behavior
MECP2	*MECP2* disorders	XL	Speech impairment, epilepsy, microcephaly, growth retardation, stereotypic behavior, & feeding difficulties	Developmental regression is observed in classic Rett syndrome.
TCF4 [3]	Pitt-Hopkins syndrome	AD	ID, lack of speech, seizures, & microcephaly (may develop postnatally)	Episodic hyperventilation &/or breath-holding; different facial features
ZEB2 [4]	Mowat-Wilson syndrome	AD	Moderate-to-severe ID, severe speech impairment, growth retardation w/microcephaly, & seizures	More likely to be assoc w/ variety of malformations incl Hirschsprung disease & genitourinary anomalies (features not typical of *DYRK1A* syndrome)

AD = autosomal dominant; AR = autosomal recessive; ASD = autism spectrum disorder; ID = intellectual disability; MOI = mode of inheritance

1. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function: typically less than 1% risk for probands with a deletion or uniparental disomy, and as high as 50% for probands with an imprinting defect or a pathogenic variant of *UBE3A*. See Angelman Syndrome.

2. Microcephaly in *DYRK1A* syndrome appears more severe than in Angelman syndrome [Courcet et al 2012].

3. Pitt-Hopkins syndrome is caused by haploinsufficiency of *TCF4* resulting from either a pathogenic variant in *TCF4* or a deletion of the chromosome region in which *TCF4* is located (18q21.2). See Pitt-Hopkins Syndrome.

4. Mowat-Wilson syndrome is associated with: a heterozygous pathogenic variant involving *ZEB2* (in ~84% of affected individuals), a heterozygous deletion of 2q22.3 involving *ZEB2* (~15% of affected individuals), or a chromosome rearrangement that disrupts *ZEB2* (~1% of individuals). See Mowat-Wilson Syndrome.

Management

No clinical practice guidelines for *DYRK1A* syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of the disease and needs in an individual diagnosed with *DYRK1A* syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *DYRK1A* Syndrome

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Neuromuscular	Orthopedics / physical medicine & rehab / PT eval	To incl assessment of: • Ambulation • Hypertonia & spine curvature • Mobility, ADL, & need for adaptive devices
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status & gastroesophageal reflux • Consider eval for gastric tube placement in those w/dysphagia &/or aspiration risk. • Eval for constipation &/or overflow diarrhea
Neurologic	Neurologic eval	• Consider brain MRI. • Consider EEG if seizures are a concern.
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Sleep history	Sleep eval	Incl polysomnography/EEG when indicated
Eyes	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular movement, strabismus, hypermetropia, & retina exam
Cardiovascular	Cardiologic eval to incl echocardiogram	For valve, aorta, & septal defects
Urogenital anomalies	Urogenital eval to incl renal ultrasound	For structural renal defects & undescended testes/hypospadias
Dental anomalies	Dental exam	For wide spaced teeth, supernumerary teeth, & ↑ calculus
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *DYRK1A* syndrome to facilitate medical & personal decision making
Family support & resources	DYRK1A.org	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; PT = physical therapy

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

Treatment of Manifestations

Standard treatment is recommended for orthopedic, dental, cardiac, urogenital, ophthalmologic, constipation, and other medical issues.

Table 5. Treatment of Manifestations in Individuals with *DYRK1A* Syndrome

Manifestation/Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hypertonia / Gait disturbances	Early intervention w/PT	• A mobility device (e.g., wheeled walker) may be useful for children w/serious gait disturbances. • Consider disability parking placard for parents.
Feeding problems / Poor weight gain	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
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]
Sleep disturbance	Therapeutic mgmt	Type of mgmt depends on cause of sleep problem (e.g., adapt seizure medication, behavioral therapy, correct sleep hygiene, melatonin).
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; DD = developmental delay; ID = intellectual disability; 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, speech, and feeding 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 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 and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

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, when necessary.

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

Surveillance

Regular lifelong follow up as determined by specialists for issues present affecting heart, eyes, and teeth is recommended.

Table 6. Recommended Surveillance for Individuals with *DYRK1A* Syndrome

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Hypertonia	Monitor for development of scoliosis & development of stiff gait.	
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Psychiatric/ Behavioral	Monitor for behavior problems.	
Vision	Follow up by ophthalmologist	When vision is normal, periodic follow up every 3-5 yrs
Gastrointestinal	Monitor for constipation or overflow diarrhea.	At each visit

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

DYRK1A syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with *DYRK1A* syndrome whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo DYRK1A* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant 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.

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

- To date, all individuals with *DYRK1A* syndrome whose parents have undergone molecular genetic testing have had a *de novo* pathogenic variant, suggesting a low risk to sibs.
- If the *DYRK1A* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If a parent of the proband is known to have the *DYRK1A* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.

Offspring of a proband. To date, individuals with *DYRK1A* syndrome are not known to reproduce. The risk to offspring of an affected individual of inheriting the variant is 50%.

Other family members. Given that, to date, all reported probands with *DYRK1A* syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo DYRK1A* pathogenic variant, the risk to other family members is presumed to be low.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low, as the proband most likely has a *de novo DYRK1A* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

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.

- **DYRK1A Syndrome International Association (DSIA)**
  www.dyrk1a.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net

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. DYRK1A Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
DYRK1A	21q22.13	Dual specificity tyrosine-phosphorylation-regulated kinase 1A	DYRK1A	DYRK1A

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 DYRK1A Syndrome (View All in OMIM)

600855	DUAL-SPECIFICITY TYROSINE PHOSPHORYLATION-REGULATED KINASE 1A; DYRK1A
614104	INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL DOMINANT 7; MRD7

Molecular Pathogenesis

DYRK1A encodes the dual-specificity tyrosine phosphorylation-regulated kinase 1A, a highly conserved protein that plays an essential role in the development of the central nervous system. The protein is a regulator of brain growth and function, including neurogenesis, neuronal proliferation and differentiation, synaptic transmission, and neurodegeneration.

DYRK1A syndrome is caused by haploinsufficiency of the *DYRK1A* protein product. Heterozygous *DYRK1A* loss-of-function pathogenic variants include disruptive balanced translocation, deletion, and truncating sequence variants.

Several missense pathogenic variants have also been identified; most are located in the kinase domain, clustering in the proximity of the ATP binding pocket and the catalytic center. These pathogenic variants affect the catalytic domain, leading to abolishment of kinase activity [Widowati et al 2018].

Mechanism of disease causation. Haploinsufficiency resulting from inactivation of one *DYRK1A* allele

Chapter Notes

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