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NLM Citation: Roston A, Gibson W. *SETD1B*-Related Neurodevelopmental Disorder. 2022 Sep 29. 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/

SETD1B-Related Neurodevelopmental Disorder

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Created: September 29, 2022.

Summary

Clinical characteristics

SETD1B-related neurodevelopmental disorder (*SETD1B*-NDD) is characterized by developmental delay (mainly affecting speech and language), intellectual disability, seizures, autism spectrum disorder or autism-like behaviors, and additional behavioral concerns. Speech delay and/or language disorder has been reported in most affected individuals. Delay in gross motor skills and mild-to-moderate intellectual disability are common. Most affected individuals have seizures with variable onset and seizure type. Behavioral issues including hyperactivity, aggression, anxiety, and sleep disorders have been reported in approximately half of individuals. Less common features include ophthalmologic manifestations and feeding issues.

Diagnosis/testing

The diagnosis of *SETD1B*-NDD is established in a proband with developmental delay / intellectual disability and a heterozygous pathogenic variant in *SETD1B* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental support services and educational intervention; standard treatment with anti-seizure medication in those with seizures; early intervention as needed for feeding problems; standard orthopedic management and therapies for spasticity; routine management of ophthalmologic issues and hearing impairment; social work support and care coordination.

Surveillance: At each visit, assessment of growth, feeding, developmental progress, changes in seizures, behavioral issues, sleep issues, musculoskeletal issues, mobility, and need for social work support and care coordination.

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Genetic counseling

SETD1B-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Most individuals diagnosed with *SETD1B*-NDD have the disorder as the result of a *de novo* pathogenic variant. Vertical transmission of a *SETD1B* pathogenic variant from an affected mother to an affected child has been reported in one family. Each child of an individual with *SETD1B*-NDD has a 50% chance of inheriting the pathogenic variant. Once the *SETD1B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

SETD1B-related neurodevelopmental disorder (*SETD1B*-NDD) **should be considered** in individuals with the following clinical findings:

- Developmental delay (especially speech and language delay)
- Intellectual disability (ID)
- Seizures that are frequently refractory to treatment
- Autism spectrum disorder or autism-like behaviors
- Other behavioral concerns (hyperactivity, aggression, anxiety, sleep disorders)

Establishing the Diagnosis

The diagnosis of *SETD1B*-NDD **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *SETD1B* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP 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 [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *SETD1B* variant of uncertain significance does not establish or rule out a diagnosis.

Because the phenotype of *SETD1B*-NDD is indistinguishable from many other inherited disorders with ID and/or seizures, molecular genetic testing approaches can include use of **comprehensive genomic testing** (exome sequencing, genome sequencing) or a **multigene panel**.

Note: Single-gene testing (e.g., sequence analysis of *SETD1B*) is rarely useful and typically NOT recommended.

- **Comprehensive genomic testing** may be considered. **Exome sequencing** is most commonly used. To date, the majority of *SETD1B* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. **Genome sequencing** is also possible to detect variants outside the coding region.

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

- An **ID or epilepsy multigene panel** that includes *SETD1B* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition 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.

Resolution of variants of uncertain significance (VUS). Many disorders that perturb regulators of epigenetic processes result in a very specific DNA methylation pattern that is common to all affected individuals with pathogenic variants in that gene [Aref-Eshghi et al 2020]. Identification of an **episignature** characteristic of *SETD1B*-NDD can be used to resolve VUS in *SETD1B* [Krzyzewska et al 2019] (see Molecular Genetics). Laboratory geneticists should note that there may be more than one episignature associated with *SETD1B*-NDD, since loss-of-function and partial loss-of-function variants may produce episignatures that are different and distinguishable from episignatures produced by gain-of-function variants and variants with other modes of action.

Table 1. Molecular Genetic Testing Used in *SETD1B*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SETD1B	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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. Roston et al [2021], Weerts et al [2021], Weng et al [2022]
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.
6. To date, large multiexon *SETD1B* deletions/duplications have not been reported in individuals with *SETD1B*-related neurodevelopmental disorder.

Clinical Characteristics

Clinical Description

SETD1B-related neurodevelopmental disorder (*SETD1B*-NDD) is characterized by developmental delay (mainly affecting speech and language), intellectual disability, seizures, autism spectrum disorder or autism-like behaviors, and additional behavioral concerns including sleep disturbances. To date, 38 individuals have been identified with a pathogenic variant in *SETD1B* [Roston et al 2021, Weerts et al 2021, Álvarez-Mora et al 2022, Weng et al 2022]. The following description of the phenotypic features associated with *SETD1B*-NDD is based on these reports.

Table 2. *SETD1B*-Related Neurodevelopmental Disorder: Frequency of Select Features

Feature	Proportion of Persons w/Feature [1]	Comment
Global developmental delay	36/38	
Speech delay / speech disorders	34/37	
Mild facial dysmorphism	35/38	Often nonspecific

Table 2. continued from previous page.

Feature	Proportion of Persons w/Feature [1]	Comment
Intellectual disability	25/38	
Seizures	30/38	
Autism spectrum disorder	26/37	Incl those w/autistic features
Other behavioral concerns	18/36	Hyperactivity, aggression, anxiety
Hypotonia	15/34	In infancy or childhood
Brain MRI abnormalities	8/34	MRI findings were nonspecific.
Sleep disturbances	6/36	
Speech regression	6/38	
Strabismus	4/38	
Feeding difficulties	3/32	

1. Denominator reflects the number of persons assessed for the feature.

Global developmental delay. Speech delay and/or language disorders have been reported in most affected individuals. The range of speech impairment varied from isolated delays to more severe impairments. Of individuals for whom age at first word was reported, 14 of 30 spoke their first word after age two years [Roston et al 2021, Weerts et al 2021]. Out of a cohort of 36 individuals with *SETD1B*-NDD, three individuals were nonverbal at ages 2.5, 3, and 3.5 years [Weerts et al 2021]. Only two individuals were reported not to have language delay, and they were very young (10 and 12 months) at the time of assessment [Weerts et al 2021].

Delay in gross motor skills is frequent. When reported specifically, age at first walking ranged from 12 months to 4.5 years. One individual was reported as having normal motor development at age seven years [Hiraide et al 2019]. Detailed reports of fine motor milestones in individuals with *SETD1B*-NDD have yet to be published.

Developmental regression was observed in six of 38 individuals with *SETD1B*-NDD, and regression did not always coincide with seizure onset. Regression primarily affected speech; detailed descriptions of motor regression have not been published [Roston et al 2021, Weerts et al 2021, Álvarez-Mora et al 2022, Weng et al 2022].

The two individuals with reported normal development were evaluated at ages one and two years, and additional information for these individuals is not available.

Intellectual disability (ID) appears to be typically mild to moderate: 13 individuals with mild ID and ten individuals with moderate ID were reported. One individual was reported to have severe ID [Weerts et al 2021] and another individual was reported to have profound ID [Hiraide et al 2018].

Note: Patients reported as "intellectually disabled" at age younger than three years are included in **global developmental delay**.

Seizures. Affected individuals typically presented with seizures by age five years, although seizure onset at older ages was reported in six individuals [Roston et al 2021, Weerts et al 2021]. Two individuals with *SETD1B*-NDD presented with seizures at age six months or younger [Weerts et al 2021].

Seizure types were heterogeneous, and often included multiple seizure types or evolving seizure patterns. Seizure types included absence (18 individuals), myoclonic (13 individuals), generalized tonic-clonic (12 individuals), focal (4 individuals), and atonic (2 individuals). Of note, at least four individuals demonstrated eyelid myoclonia [Roston et al 2021, Weerts et al 2021].

Seizures occurred daily in most individuals and were reported to worsen with age. Seizures were intractable in at least four individuals [Roston et al 2021, Weerts et al 2021]. However, some individuals reported improvement with anti-seizure medication. No consistently effective anti-seizure treatment was identified.

Feeding difficulties have been reported in a small proportion of individuals.

Other neurologic findings

- **Hypotonia** in infancy or early childhood was reported in 15 of 34 individuals [Roston et al 2021, Weerts et al 2021, Weng et al 2022].
- **Microcephaly**, with a head circumference of 2 SD below the mean, was identified in one adult with *SETD1B*-NDD [Weerts et al 2021].

Autism spectrum disorder and autistic features. The majority of reported individuals were either diagnosed with autism spectrum disorder (22/37) or had autistic features without a formal diagnosis (4 */37) [Roston et al 2021, Weerts et al 2021, Weng et al 2022].

* Includes patients reported as "autistic" at age younger than three years

Other behavioral concerns. Approximately half of reported individuals had other behavioral concerns including hyperactivity (10 individuals), aggression (9), anxiety (6), and sleep disturbance (6). A further three individuals demonstrated obsessive-compulsive behavior [Roston et al 2021, Weerts et al 2021, Weng et al 2022]. Behavioral issues have been more common in affected males.

Brain MRI abnormalities included nonspecific white matter hyperintensities, abnormalities of the corpus callosum, cystic encephalomalacia with ventriculomegaly, bilateral abnormal signals in multiple lobes, extensive abnormal gyral sulcation, delayed myelination and heterotopic grey matter, and periventricular leukomalacia. Of note, several individuals with abnormal brain MRI findings had an additional serious medical condition (e.g., periventricular leukomalacia in an individual with hypoplastic left heart) [Roston et al 2021, Weerts et al 2021, Weng et al 2022].

Nonspecific facial features. Many individuals with *SETD1B*-NDD were reported to have unusual craniofacial features, but without a clear recognizable pattern. Ear anomalies were common (e.g., overfolded helices, differences of ear lobe morphology, ear pits, ear tags). Several individuals had a high anterior hairline, frontal bossing, or anterior hairline recession [Roston et al 2021, Weerts et al 2021, Weng et al 2022]. Thickened facial features (e.g., full cheeks, thick lips, broad or bulbous nasal tip, wide nasal root) were frequently reported; it is unknown if coarse facial features were secondary to anti-convulsant therapy.

Ophthalmologic features. Strabismus has been reported infrequently; astigmatism, amblyopia, and myopia have also been reported [Weerts et al 2021].

Other. Each reported in one individual:

- Dysplastic kidneys requiring transplant, an anteriorly placed anus, clubfeet, tethered cord, and contractures [Weerts et al 2021]
- Cryptorchidism requiring surgery [Weerts et al 2021]
- Hearing impairment [Weerts et al 2021]
- Hypoplastic left heart [Weerts et al 2021]
- Patent ductus arteriosus [Roston et al 2021]

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

The penetrance of *SETD1B*-NDD is predicted to be high. To date, no individuals have been confirmed to have inherited a pathogenic variant from an unaffected parent, and one individual inherited a pathogenic variant from an affected parent [Roston et al 2021, Weerts et al 2021].

Prevalence

SETD1B-NDD is rare, with only 38 individuals with a pathogenic (or likely pathogenic) *SETD1B* variant reported to date. Males appear to be disproportionately represented in the literature; 24 of 38 reported individuals are male (male-to-female ratio: ~1.7:1) [Roston et al 2021, Weerts et al 2021, Álvarez-Mora et al 2022, Weng et al 2022].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline intragenic *SETD1B* pathogenic variants.

Contiguous gene deletions involving *SETD1B*. At least seven individuals with large deletions encompassing *SETD1B* and adjacent genes have been described. Limited clinical information is available for many of these individuals. However, individuals with contiguous deletions including *SETD1B* share some phenotypic features with individuals with *SETD1B*-NDD, including intractable seizures and mild-to-profound intellectual disability. Dermatologic abnormalities were reported in several individuals with contiguous deletions (e.g., café au lait macules, eczema, hyper- and hypopigmentation) [Baple et al 2010, Qiao et al 2013, Palumbo et al 2015, Labonne et al 2016, Den et al 2019]. One individual inherited the microdeletion from an apparently healthy father [Chouery et al 2013].

Differential Diagnosis

Because the phenotypic features associated with *SETD1B*-related neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

No clinical practice guidelines for *SETD1B*-related neurodevelopmental disorder (*SETD1B*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SETD1B*-NDD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *SETD1B*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Neurologic	• Neurologic eval • EEG	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval if feeding difficulties present in neonatal period	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in those w/ dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular mvmt, best corrected visual acuity, refractive errors, strabismus, & more complex findings that may require subspecialty referral
Hearing	Audiologic eval	Assess for hearing loss.
Sleep	Sleep study	In obese persons & in persons w/daytime somnolence to assess for obstructive sleep apnea
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *SETD1B*-NDD 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; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; *SETD1B*-NDD = *SETD1B*-related neurodevelopmental disorder
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *SETD1B*-Related Neurodevelopmental Disorder

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Education of parents/caregivers [1] • Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Seizures are frequently refractory to multiple ASMs & may require frequent follow up. • To date, there are no published trials or data re implementation of ketogenic diet & effects on seizure control.

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Feeding difficulties	• 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
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Ophthalmologic involvement	Treatment of refractive errors &/or strabismus	
	Low vision services	• Children: through early intervention programs &/or school district • Adults: referral to low vision clinic &/or community vision services
Hearing	Hearing aids may be helpful; per otolaryngologist.	Community hearing services through early intervention or school district
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 home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD/ID = developmental delay /intellectual disability; 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. Individuals with *SETD1B*-NDD may demonstrate developmental regression, even in the absence of seizures, and a normal initial evaluation should not preclude continued monitoring and support during early childhood.

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 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 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

Table 5. Recommended Surveillance for Individuals with *SETD1B*-Related Neurodevelopmental Disorder

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Development	Monitor developmental progress & educational needs.	• At each visit • Persons w/*SETD1B*-NDD may demonstrate developmental regression, even in absence of seizures, & normal initial eval should not preclude continued monitoring & support during early childhood.
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & mvmt disorders.	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Sleep	Assess for sleep disturbance.	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

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.

Pregnancy Management

In general, women with epilepsy or a seizure disorder of any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication (ASM) during pregnancy reduces this risk. However, exposure to ASM may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from ASM exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of ASM to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM during

pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

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

SETD1B-related neurodevelopmental disorder (*SETD1B*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with *SETD1B*-NDD have the disorder as the result of a *de novo SETD1B* pathogenic variant.
- Vertical transmission of a *SETD1B* pathogenic variant from an affected mother to an affected child has been reported in one family [Weerts et al 2021].
- 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.
    - 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.

      * A parent with somatic and germline mosaicism for an *SETD1B* pathogenic variant may be mildly/minimally affected.
- The family history of some individuals diagnosed with *SETD1B*-NDD may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to have the *SETD1B* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *SETD1B* pathogenic variant identified 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 the parents have not been tested for the *SETD1B* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *SETD1B*-NDD because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *SETD1B*-NDD has a 50% chance of inheriting the *SETD1B* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *SETD1B* pathogenic variant, the parent's family members may be at risk.

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 affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SETD1B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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.

- **American Epilepsy Society**

  www.aesnet.org

- **Canadian Epilepsy Alliance**

  Canada

  Phone: 1-866-EPILEPSY (1-866-374-5377)

  www.canadianepilepsyalliance.org

- **Epilepsy Canada**

Canada

Phone: 877-734-0873

Email: epilepsy@epilepsy.ca

www.epilepsy.ca

- **Epilepsy Foundation**

  Phone: 301-459-3700

  Fax: 301-577-2684

  www.epilepsy.com

- **National Institute of Neurological Disorders and Stroke (NINDS)**

  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)

  Epilepsy Information Page

- **Simons Searchlight Registry**

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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. SETD1B-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
SETD1B	12q24.31	Histone-lysine N-methyltransferase SETD1B	SETD1B	SETD1B

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 SETD1B-Related Neurodevelopmental Disorder (View All in OMIM)

611055	SET DOMAIN-CONTAINING PROTEIN 1B; SETD1B
619000	INTELLECTUAL DEVELOPMENTAL DISORDER WITH SEIZURES AND LANGUAGE DELAY; IDDSELD

Molecular Pathogenesis

Histone methyltransferases (HMTs) are a group of proteins that modify chromatin, thus regulating gene expression, through the addition of methyl groups to histones. A specific class of HMTs is the H3K4 family (histone-3-methyl-4), which methylate the fourth lysine residue on the tail of histone 3. This epigenetic modification allows for the packaging of DNA into heterochromatin. *SETD1B* encodes the protein SET domain-containing protein 1B (SETD1B), a lysine-specific methyltransferase involved in histone methylation [Yang & Ernst 2017]. In combination with four additional subunits, SETD1B forms the catalytic component of one of these HMT enzymes and assists in epigenetic regulation of gene expression [Nagase et al 1999, Lee et al 2007].

Therefore, SETD1B is believed to be an epigenetic modifier of chromatin structure, affecting expression of multiple downstream genes [Nagase et al 1999].

Studies have shown a strong effect of SETD1B function on DNA methylation. Specifically, it has been suggested that loss of SETD1B function may lead to the insufficient production of H3K4me3 and DNA hypermethylation in specific loci. This specific epigenetic methylation signature associated with *SETD1B* loss-of-function variants was used to reclassify two *SETD1B* variants of uncertain significance as pathogenic [Krzyzewska et al 2019].

Mechanism of disease causation. It is believed that *SETD1B*-related neurodevelopmental disorder (*SETD1B*-NDD) is most likely caused by loss-of-function or partial loss-of-function *SETD1B* variants; however, further functional studies are required to confirm this mechanism [Roston et al 2021, Weerts et al 2021].

Cancer and Benign Tumors

Somatic variants affecting H3K4 methyltransferases, including SETD1B, have been identified in various tumors. Functional studies have suggested a role for both gain-of-function and loss-of-function variants in hematologic malignancies [Schmidt et al 2014, Yang & Ernst 2017]. Somatic *SETD1B* variants have been identified in endometrial cancer and may have a role in predicting the degree of myometrial invasion [García-Sanz et al 2017]. To date, malignancy has been described in only one individual with *SETD1B*-NDD; a well-differentiated tubular adenocarcinoma of the sigmoid colon was diagnosed in an individual at age 30 years [Hiraide et al 2018]. No affected individuals have to date been reported to develop malignancies in childhood [Roston et al 2021, Weerts et al 2021, Álvarez-Mora et al 2022, Weng et al 2022].

Chapter Notes

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Acknowledgments

The authors would like to thank the many individuals with *SETD1B*-related neurodevelopmental disorder who generously gave their permission to be included in this research.

Revision History

- 29 September 2022 (sw) Review posted live
- 10 June 2022 (wg) Original submission

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