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SETBP1 Haploinsufficiency Disorder

Synonym: *SETBP1* Disorder

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Summary

Clinical characteristics

SETBP1 haploinsufficiency disorder (*SETBP1*-HD) is characterized by hypotonia and mild motor developmental delay; intellectual abilities ranging from normal to severe disability; speech and language disorder; behavioral problems (most commonly attention/concentration deficits and hyperactivity, impulsivity), and refractive errors and strabismus. Typically children with *SETBP1*-HD whose intellect is in the normal or borderline range (IQ 80-90) were diagnosed following genetic testing for behavioral problems and/or severe speech and language disorders (respectively: the inability to produce sounds in words correctly, and deficits in the understanding and/or expression of words and sentences). To date, 47 individuals with *SETBP1*-HD have been reported.

Diagnosis/testing

The diagnosis of *SETBP1*-HD is established in a proband with suggestive findings and a heterozygous pathogenic loss-of-function variant in *SETBP1* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is supportive, often including multidisciplinary specialists from pediatrics, neurology, physiatry, occupational and physical therapy, speech-language pathology, psychiatry, ophthalmology, and medical genetics. Early intervention programs and special education programs may be needed to address developmental disabilities.

Surveillance: Monitoring of: feeding and weight gain; developmental/educational progress and needs; speech and language progress and needs; psychiatric and behavioral interventions; ophthalmologic interventions.

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Genetic counseling

SETBP1-HD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Most probands reported to date whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo SETBP1* pathogenic variant. Rarely, individuals with *SETBP1*-HD may have the disorder as the result of a *SETBP1* pathogenic variant inherited from a parent with germline (or somatic and germline) mosaicism. Once the *SETBP1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

GeneReview Scope

Pathogenic variants in *SETBP1* are known to be associated with a spectrum of phenotypes ranging from *SETBP1* haploinsufficiency disorder and other phenotypes on the milder end to classic Schinzel-Giedion syndrome on the most severe end. This chapter specifically focuses on *SETBP1* haploinsufficiency disorder.

Spectrum of Phenotypes Associated with *SETBP1* Pathogenic Variants

Designation		Associated Pathogenic Variants	Comment
***SETBP1* haploinsufficiency disorder (topic of this *GeneReview*)**		Loss-of-function pathogenic variants (truncating variants / *SETBP1*-specific deletions)	Characterized by hypotonia & mild motor developmental delay; intellectual abilities ranging from normal to severe disability; speech & language disorder; behavioral problems; & refractive errors & strabismus
Schinzel-Giedion syndrome (SGS) phenotypic continuum	**Classic SGS**	Gain-of-function pathogenic variants in mutational hot spot (i.e., a 12-base-pair region in exon 4 encoding a canonical degron)	See Genetically Related Disorders.
	Atypical SGS	Gain-of-function pathogenic variants adjacent to – but not within –mutational hot spot	
***SETBP1*-related disorders (not SGS or *SETBP1* haploinsufficiency disorder)**		Missense pathogenic variants w/ unknown functional effects that are not adjacent to mutational hot spot	"SETBP1-related disorders" may be used to refer to phenotypes that are not consistent w/SGS or *SETBP1* haploinsufficiency disorder caused by *SETBP1* pathogenic variants that do not result in loss of function and are not within or near the SGS mutational hot spot. Note: "*SETBP1*-related disorders" has also been used to refer to all phenotypes associated w/ *SETBP1* pathogenic variants. See Genetically Related Disorders.

Diagnosis

No consensus clinical diagnostic criteria for *SETBP1* haploinsufficiency disorder have been published.

Suggestive Findings

SETBP1 haploinsufficiency disorder (*SETBP1*-HD) **should be considered** in individuals with the following clinical findings.

Clinical findings present in most individuals

- Motor developmental delay (in 97%)
- Developmental delay / mild-to-severe intellectual disability

- Learning difficulties
- Speech and language disorder (including childhood apraxia of speech)

Variable findings in infants or children

- Generalized hypotonia of infancy
- Feeding difficulties
- Seizures/epilepsy
- Behavior consistent with attention-deficit/hyperactivity disorder including impulsivity
- Other behaviors such as anxiety, aggression, sleep disturbances, self-injury and/or autism spectrum disorder
- Ophthalmologic findings: refractive errors (hypermetropia, myopia, astigmatism), strabismus)
- Digestive problems
- Subtle dysmorphic features in several individuals: ptosis, blepharophimosis, broad nasal bridge, hypertelorism, full nasal tip, and a high arched palate. See Figure 1 and Jansen et al [2021].

Family history. Because *SETBP1* haploinsufficiency disorder is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, a proband may have an affected sib or a parent with mild findings suggestive of *SETBP1* haploinsufficiency disorder.

Establishing the Diagnosis

The diagnosis of *SETBP1* haploinsufficiency disorder **is established** in a proband with suggestive findings and a heterozygous **pathogenic** (or likely pathogenic) loss-of-function variant in *SETBP1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *SETBP1* variant of uncertain significance does not itself establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with chromosomal microarray analysis (CMA). Other options include use of a multigene panel or comprehensive genomic testing. Note: Single-gene testing (sequence analysis of *SETBP1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability (ID) multigene panel** that includes *SETBP1* and other genes of interest (see Differential Diagnosis) limits 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*. Of note, given the rarity of *SETBP1* haploinsufficiency disorder, some panels for intellectual disability may not include this gene. (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.

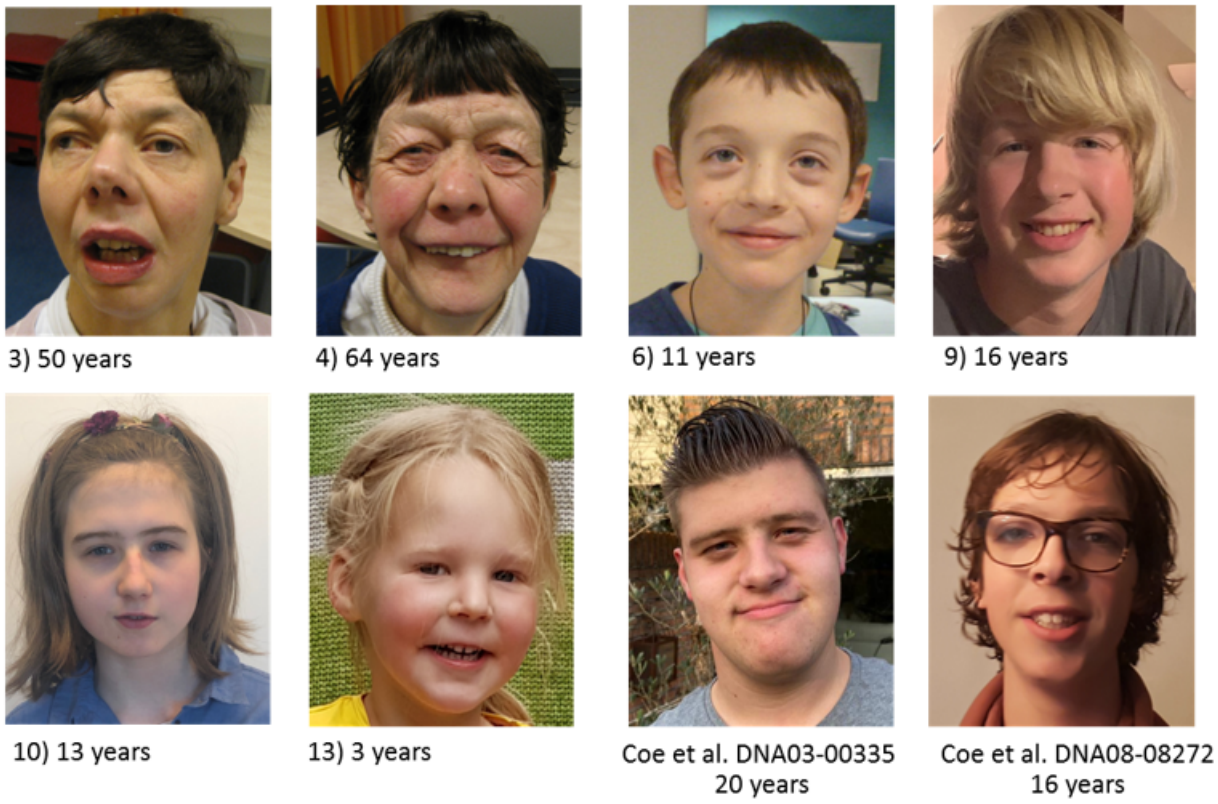

Figure 1. Clinical photographs of individuals with *SETBP1* haploinsufficiency disorder. The numbers refer to the patient numbers in Jansen et al [2021]. Individuals 3 and 4 are sisters.

Two individuals were first reported by Coe et al [2014]. An update of their clinical features was given by Jansen et al [2021].

Reprinted from Jansen et al [2021]

- **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 *SETBP1* Haploinsufficiency Disorder

Gene [1]	Method	Proportion Pathogenic Variants [2] Identified by Method
SETBP1	Sequence analysis [3]	88% [4]
	Gene-targeted deletion/duplication analysis [5]	12%[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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; 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 Jansen et al [2021], Morgan et al [2021], and 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.

Clinical Characteristics

Clinical Description

The most common clinical manifestations of *SETBP1* haploinsufficiency disorder (*SETBP1*-HD) are mild motor developmental delay and hypotonia, speech and language disorder, intellectual disability, attention-deficit/hyperactivity disorder (ADHD), and refractive errors and strabismus.

To date, 47 individuals with *SETBP1*-HD have been reported [Leonardi et al 2020, Jansen et al 2021, Morgan et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports (Table 2).

Table 2. *SETBP1* Haploinsufficiency Disorder: Frequency of Select Features

Feature		Frequency of Feature
Delayed motor milestones		>90%
Speech and language disorder		>95%
Intellectual disability	Mild	≤30%
	Moderate	~30%
	Severe	~20%
Normal or borderline IQ		20%
Behavior problems	ADHD-like	75%
	Other	13%-25%
Feeding difficulties		60%
Ophthalmologic involvement		50%
Excessive drooling		35%
Ankyloglossia		25%
Digestive problems		>20%
Cryptorchidism		20% of males

Table 2. continued from previous page.

Feature	Frequency of Feature
Febrile seizures	20%

Based on Leonardi et al [2020], Jansen et al [2021], and Morgan et al [2021]
ADHD = attention-deficit/hyperactivity disorder

Delayed Motor Milestones

Gross motor abilities are generally better than fine motor abilities [Jansen et al 2021, Morgan et al 2021]. Ninety-four per cent had generalized motor delay or disorder [Morgan et al 2021]. Hypotonia may be noted in infancy and is commonly observed during childhood.

Sitting, crawling, and walking are delayed. Average age of sitting unsupported is six to 15 months, crawling nine to 19 months, and walking 13 to 36 months.

Fine motor development is delayed in about 70% of affected children. In particular, some children have difficulty with handwriting, which can further affect development of written language and/or exacerbate literacy difficulties [Morgan et al 2021].

Speech and Language Disorder

The terms speech disorder and language disorder are often used interchangeably. Although they often co-occur, each can occur independently, providing evidence that they are separate entities.

Speech involves producing sounds in words with the correct breath support, voicing, resonance, articulation, prosody, and accuracy. Language involves meaning, i.e., the understanding and expression of words (vocabulary) and sentences (grammar).

Speech disorders and language disorders can each be further classified clinically.

Speech disorders. The five most common speech disorder diagnoses are included in Table 3. Children with *SETBP1*-HD present with speech delay (first words by 18 months in 50%) due to a severe childhood apraxia of speech (seen in 80%) [Morgan et al 2021]. With speech therapy (see Management), childhood apraxia of speech resolves, and dysarthria becomes more evident.

Children with *SETBP1*-HD also have phonologic disorder which places them at risk for longer-term literacy difficulties (i.e., disorders of spelling and reading).

Due to the childhood apraxia of speech, some children remain minimally verbal for years and augment their speech and language with sign language, gestures, or augmentative and assistive communication devices [Morgan et al 2021]. (See Management.)

Table 3. Speech Disorders: Definitions

Speech Disorder		Definition
Articulation	**Functional disorder**	Inability to accurately produce ≥1 sounds (e.g., lisp on /s/) in the absence of explainable cause (e.g., no hearing impairment, no orofacial structural deficits) [Morgan & Günther 2017]
	Structural disorder	Inability to accurately produce ≥1 sounds due to orofacial structural impairment (e.g., cleft lip or palate, malocclusion of mandible & maxilla, missing teeth) [Morgan & Günther 2017]

Table 3. continued from previous page.

Speech Disorder		Definition
Phonologic	**Delay**	Delay in understanding/use of sounds; use of speech error patterns that will have resolved in >90% of age-related peers based on normative data (e.g., a 6-yr-old substituting /b/ for /f/ in fish) [Dodd et al 2018]
	Disorder	Inability to understand or correctly use sounds to convey meaning. Use of atypical (i.e., seen in <10% of population at any age) speech errors; e.g., sound preference substitution, where a favorite sound is used in place of the correct phoneme (e.g., /d/ for /k/ in cup, /d/ for /n/ in knife, and /d/ for /sh/ in shoe [Dodd et al 2018]. Phonologic disorder places a child at greater risk for literacy disorder [Foy & Mann 2012].
Motor speech disorders	**Childhood apraxia of speech (CAS)**	Inability to produce sounds & syllables consistently in correct order w/clarity & correct prosody [Morgan & Günther 2017]; 3 core diagnostic CAS features (ASHA 2007): • Inconsistent error production on consonants & vowels across repeated production of syllables or words • Lengthened & impaired coarticulatory transitions between sounds & syllables • Inappropriate prosody
	Dysarthria	Impairment of neuromuscular control & tone (e.g., spasticity, ataxia, fluctuating tone, uncoordinated & involuntary movements) → deficits across ≥1 subdomains of speech (i.e., phonation, articulation, prosody, & resonance) [Braden et al 2021]
	Stuttering	Impairment of speech fluency characterized by repetitions (of sounds, syllables, words, &/or phrases), prolongation of sounds, & hesitations &/or blocks (i.e., when a child tries to speak but no sound comes out) [Reilly et al 2015]

Language disorders. Children with *SETBP1*-HD have a mild-to-moderate expressive and receptive language disorder (Table 4). In about 30% of affected individuals, receptive language may be better than expressive language [Morgan et al 2021].

Children are typically sociable with a strong desire to communicate, yet social language is poorer than for typically developing peers.

Table 4. Language Disorders: Definitions

Language Disorder	Definition
Receptive language disorder	A deficit in understanding language relative to peers. ≥1 sub-domains of language may be affected (e.g., semantics, sentence structure).
Expressive language disorder	A deficit in producing language relative to peers. ≥1 sub-domains of language may be affected (e.g., semantics, sentence structure).

Intellectual Disability (ID)

The spectrum of intellectual disability (noted in 80% of individuals) ranges from mild to severe.

Children with *SETBP1*-HD whose intellect is in the normal or borderline range (IQ 80-90) typically were diagnosed following genetic testing for severe speech and language disorder and/or behavioral problems.

Behavioral Problems

Most commonly reported are attention/concentration deficits and hyperactivity, and impulsivity, leading in many instances to a diagnosis of ADHD. Other behavioral problems include anxiety, autism spectrum disorder (ASD), sleep disturbances, self-injury, and other aggressive behaviors. Some children have autism or autistic

features and social communication disorders. While many children with *SETBP1*-HD are not diagnosed with ASD, many have restricted interests and sensory sensitivities that overlap with an ASD phenotype.

Additional Findings

Ophthalmologic involvement includes refractive errors, most commonly hypermetropia, and less commonly astigmatism and myopia. Strabismus is also seen.

Feeding difficulties. Poor sucking and slow feeding related to hypotonia can be evident in the neonatal period and infancy. Some children require nasogastric tube feeding. Beyond infancy and into the preschool years, some children experience problems chewing lumpy or solid foods.

Excessive drooling. Some young children have difficulty managing saliva, resulting in excessive drooling that may in turn lead to skin irritation.

Ankyloglossia (i.e., a short frenulum) is more common than in the healthy population (prevalence is 3%-5%). While a short frenulum is not related to delays in speech development, it can affect articulation and pronunciation. A short frenulum may contribute to feeding difficulties.

Cryptorchidism is noted in about 20% of males, although to date *SETP1*-HD has not been associated with other urogenital abnormalities.

Digestive problems include diarrhea, constipation, food allergies, reflux, and GERD.

Seizures/epilepsy. The majority of seizures (reported in ~20% of individuals) were infantile febrile seizures.

Epilepsy was reported in three individuals, all of whom had generalized seizures [Coe et al 2014, Leonardi et al 2020]. In two of three, onset was in infancy; in the third onset was at age 22 years. After epileptic seizures ceased in one child at age six years, anti-seizure medication was successfully discontinued.

Skeletal abnormalities observed in 14 individuals include bilateral hip dysplasia, abnormal vertebrae at birth, hyperkyphosis, hyperlordosis, increased lumbar lordosis, and (in 10 of the 14 individuals) slight abnormalities of the extremities including bilateral fifth finger clinodactyly, slight 2-3 syndactyly, brachydactyly, and *pes cavus* [Jansen et al 2021].

Subtle dysmorphic features in several individuals include ptosis, blepharophimosis, broad nasal bridge, hypertelorism, full nasal tip, and a high arched palate. See Figure 1 and Jansen et al [2021].

Other

The following were normal:

- Growth parameters in general (e.g., weight, height, head circumference)
- MRI findings in 19 of 22 individuals (for whom data were available). Of the remaining three, two had delayed myelination and one had a thin corpus callosum and a rotated hippocampal tail [Leonardi et al 2020, Jansen et al 2021].

The possible relationship of the following findings to *SETBP1*-HD is unknown, given the high frequency of these findings in the general population:

- Recurrent ear infections (~25% of infants)
- Dry skin and/or eczema (20% of individuals)
- Different types of hearing impairment (3 individuals)

Prognosis

Based on current data, life span is not shortened in *SETBP1*-HD, as several adults have been reported. To date, data are limited on possible progression of behavioral abnormalities and/or neurologic findings.

Genotype-Phenotype Correlations

SETBP1 loss-of-function variants have no genotype-phenotype correlations.

Prevalence

To date, 47 individuals with *SETBP1*-HD have been reported in the medical literature. (While additional information about *SETBP1* variants observed in affected individuals has been reported in genetic databases and/or the literature, this information is not included in this chapter due to absent or limited clinical information.)

The prevalence of *SETBP1*-HD is unknown.

Genetically Related (Allelic) Disorders

Schinzel-Giedion syndrome (SGS), an ultra-rare multisystem disorder caused by gain-of-function pathogenic variants in a *SETBP1* mutational hot spot, is characterized by global neurodevelopmental impairment leading to moderate-to-profound intellectual disability, epilepsy (often refractory to treatment), hypotonia, spasticity, dysautonomia, hearing loss, and cerebral visual impairment. Atypical SGS, reported in five individuals to date, is caused by pathogenic *SETBP1* variants in proximity to – but not within – the mutational hot spot. The broad spectrum of clinical features of variable severity partially overlaps with classic SGS.

***SETBP1*-related disorders.** The term "*SETBP1*-related disorders" may be used to refer to variable neurodevelopmental phenotypes (i.e., phenotypes that are not consistent with classic SGS, atypical SGS, or *SETBP1* haploinsufficiency disorder) associated with pathogenic missense *SETBP1* variants of unknown functional effect that are not within or adjacent to the mutational hot spot (see medRxiv).

Sporadic tumors (including myelodysplastic/myeloproliferative neoplasms, atypical chronic myeloid leukemia, chronic myelomonocytic leukemia, and juvenile myelomonocytic leukemia as well as in secondary acute myeloid leukemia) may contain a somatic gain-of-function variant in *SETBP1* that is not present in the germline [Makishima 2017]. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Because the phenotypic features associated with *SETBP1* haploinsufficiency disorder overlap with many genetic conditions, all disorders with intellectual disability and severe speech disorder 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 *SETBP1* haploinsufficiency disorder (*SETBP1*-HD) have been published. Management recommendations below are based on information in the current literature and the Authors' clinical experience.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SETBP1* haploinsufficiency disorder, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *SETBP1* Haploinsufficiency Disorder

System/Concern		Evaluation	Comment
For all persons	**Constitutional**	Height, weight	
	DD in general (language, social, motor, &/or cognitive)	Developmental assessment (by school system, neurologist, &/or developmental medicine)	Assess developmental skills (incl cognitive, language, social, motor, & adaptive) & need for developmental services.
	Speech & language disorder	Speech-language pathology eval	• Evaluate speech production & receptive/expressive language in all children regardless of age. • To evaluate for specific speech diagnoses & make recommendations re appropriate treatments when warranted • To perform audiometry to exclude hearing loss (although this is not an associated feature)
	Psychiatric/ behavioral concerns	Neurologic, psychiatry, &/or developmental medicine eval	To screen for behavioral concerns incl ADHD, impulsivity, anxiety, sleep disturbances, &/or those suggestive of ASD
	Ophthalmologic involvement	Ophthalmologic eval	To assess for refractive errors, strabismus
	Genetic counseling	Genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of *SETBP1* haploinsufficiency disorder in order to facilitate medical & personal decision making
	Family support & resources		Assess use of community or online resources such as Parent to Parent. Assess need for: • Social work involvement for parental support; • Home nursing referral; • Early intervention referral; • Case management support referral.
Based on concern	**Seizures / Neurologic exam findings**	Neurologic eval	• Evaluate events suggestive of seizures; consider EEG if seizures are a concern. • Evaluate for abnormalities of tone (e.g., hypotonia). • Perform neurologic exam to evaluate for focal &/or other abnormalities that may warrant brain MRI.

Table 5. continued from previous page.

System/Concern		Evaluation	Comment
	Motor delay	PT, OT, &/or physical medicine & rehab eval	Assess: • Gross motor & fine motor skills; • Mobility, activities of daily living, & need for adaptive devices; • Need for ongoing PT (to improve gross motor skills) &/or ongoing OT (to improve fine motor skills, sensory processing).
	Feeding difficulties	Nutrition / feeding team eval (OT, SLP)	To evaluate risk of aspiration, & nutritional status
	Digestive problems	Gastrointestinal or nutritionist eval	To determine cause of diarrhea, constipation, &/or reflux
	Musculoskeletal	Orthopedics / physical medicine & rehab / PT eval	Evaluate for join hyperextensibility, *pes cavus*, back curvature, hypotonia.
	Excessive drooling		Excessive drooling & difficulty w/transition to chewable solids esp in the early yrs
	Ankyloglossia	Routine pediatric exam	Ankyloglossia may contribute to feeding difficulties, but not to the speech disorder in children w/*SETBP1*-HD.
	Cryptorchidism	Routine pediatric exam	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DD = developmental delay; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; SLP = speech-language pathology
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment is supportive, often including multidisciplinary specialists from pediatrics, neurology, physiatry, occupational and physical therapy, speech-language pathology, psychiatry, ophthalmology, and medical genetics.

Table 6. Treatment of Manifestations in Individuals with *SETBP1* Haploinsufficiency Disorder

Manifestation/Concern	Treatment	Considerations/Other
Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Motor delay		
Hypotonia	PT & OT to improve strength	
Speech & language disorder	• Speech & language therapy tailored to child's individual profile & developmental age • Consider early reading & spelling support as age appropriate.	Augmentative or alternative communication devices in the early years are proven to optimize communication development.
Behavioral disorders	Standardized treatment by neurologist, developmental medicine, &/or psychiatrist familiar w/neurodevelopmental behavior problems	May need to develop an educational behavioral intervention plan (BIP)
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]
Sensory processing issues	Sensory integration therapy w/OT	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Infant feeding issues	Feeding therapy; to help coordination of oral movements for feeding or sensory-related feeding issues. Food & fluids can be modified for safety	• Low threshold for clinical feeding eval • VFSS recommended if aspiration is suspected
Refractive error &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	
Excessive drooling		Some persons may be treated w/medication (e.g., glycopyrrolate) [2]
Ankyloglossia	Frenectomy	↓ tongue movement may limit feeding. However, frenulotomy will not improve phonologic, apraxic, or dysarthric speech disorder(s).
Cryptorchidism	Orchidopexy	
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. • Connect to parent advocacy group.	Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy/therapist; PT = physical therapy; VFSS = videofluoroscopic swallowing study

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

2. See NICE guidelines on oral glycopyrronium bromide.

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-language, 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 and results from referral to Child Find programs. 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.
    - Vocational opportunities and programming including vocational rehabilitation should be considered early with a focus on achievement of meaningful employment
- 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

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

Oral motor dysfunction. Feeding therapy (typically from a speech-language pathologist or occupational therapist) is recommended to help improve coordination of oral movement skills for feeding or sensory-related feeding issues using relevant approaches including postural modification and altering the consistency of food and fluid [Morgan et al 2012]. Mothers may need support from a breastfeeding or lactation consultant in the early weeks or months of life.

Gross motor dysfunction. Physical therapy may be recommended for difficulty with crawling, walking, running, and building strength resulting from hypotonia.

Speech and language disorder. Consider evaluation for nonverbal support or alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals with severe speech and 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.

In terms of verbal development, difficulties with motor planning (apraxia) are severe in the early years of life and intensive evidence-based motor speech therapies should be applied [Morgan et al 2018]. Early phonologic awareness tasks should be implemented to support speech and later literacy development. Therapies addressing

both receptive and expressive semantics and grammar are also recommended. The optimal intervention will be tailored to the child's specific profile as it changes during 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 neurologist, developmental specialist, or psychiatrist.

Surveillance

Table 7. Recommended Surveillance for Individuals with *SETBP1* Haploinsufficiency Disorder

System/Concern	Evaluation	Frequency
Overall neurodevelopment	Monitor developmental progress & educational needs.	As recommended by neurologist or developmental pediatrician overseeing neurodevelopment
Speech & language disorder	• Assessment of ongoing therapy initiated w/early interventional services • Referral to AAC specialist over time if warranted • Eval for speech disorder subtype over time if warranted	As recommended by speech-language pathologist
Motor delay	OT/PT assessment of mobility, self-help skills, as well as ongoing therapy	As recommended by OT/PT
Skeletal	Monitor skeletal or neuromuscular problems.	As recommended by treating pediatrician or neurologist
Psychiatric/ behavioral concerns	Behavioral assessment for signs of ADHD, ASD, anxiety, aggressive behavior, &/or sleep disturbances	As recommended by treating neurologist, developmental pediatrician, or psychiatrist
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	As recommended by feeding team
Neurologic	Evaluate those w/seizures as clinically indicated.	As recommended by treating neurologist
	Assess for new manifestations such as seizures, changes in tone, movement disorders.	As recommended by treating neurologist
Ophthalmologic involvement	By treating ophthalmologist	As recommended by ophthalmologist
Digestive problems	By treating gastroenterologist	As recommended by gastroenterologist
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	As needed

AAC = augmentative and alternative communication; ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapist; PT = physical therapist

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

SETBP1 haploinsufficiency disorder (*SETBP1*-HD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *SETBP1* haploinsufficiency disorder whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo SETBP1* 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 and parental identity testing has confirmed biological maternity and paternity, 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 is unlikely to detect 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:

- If the *SETBP1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is presumed to be low but is slightly greater than that of the general population because of the possibility of parental mosaicism; presumed parental mosaicism has been reported in one family with sib recurrence [Jansen et al 2021].
- If a parent of the proband is known to have the *SETBP1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.

Offspring of a proband. Each child of an individual with *SETBP1* haploinsufficiency disorder has a 50% chance of inheriting the *SETBP1* pathogenic variant.

Other family members. Given that most probands with *SETBP1* haploinsufficiency disorder reported to date have the disorder as a result of a *de novo SETBP1* 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 and to young adults who are mildly affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SETBP1* 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.

- **SETBP1 Society**
  P.O. Box 301584
  Austin TX 78703
  Phone: 512-522-8072
  Email: info@setbp1.org
  www.setbp1.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **Apraxia Kids**
  Phone: 412-785-7072
  Email: info@apraxia-kids.org
  apraxia-kids.org
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net

- **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
  www.simonssearchlight.org

Molecular Genetics

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

Table A. SETBP1 Haploinsufficiency Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SETBP1	18q12.3	SET-binding protein	SETBP1 database	SETBP1	SETBP1

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 SETBP1 Haploinsufficiency Disorder (View All in OMIM)

611060	SET-BINDING PROTEIN 1; SETBP1
616078	INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL DOMINANT 29; MRD29

Molecular Pathogenesis

SETBP1 encodes SET-binding protein (SEB), which regulates transcription processes by binding to different promotor regions. Although SEB is highly expressed during brain development, its precise functions and molecular mechanisms in the brain and neuronal pathways are still largely unknown.

Mechanism of disease causation. Haploinsufficiency of the SET-binding protein

Cancer and Benign Tumors

Somatic gain-of-function *SETBP1* pathogenic variants have been identified in several types of myelodysplastic/myeloproliferative neoplasms, including atypical chronic myeloid leukemia, chronic myelomonocytic leukemia, and juvenile myelomonocytic leukemia, as well as in secondary acute myeloid leukemia [Makishima 2017]. To date, these activating variants are limited to the cells in these neoplasms.

The *SETBP1* pathogenic variants that cause *SETBP1* haploinsufficiency disorder are germline loss-of-function variants present in every cell in the body of the affected individual. These loss-of-function variants are not associated with an increase in tumorigenesis.

Chapter Notes

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