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CSNK2B-Related Neurodevelopmental Disorder

Synonym: Poirier-Bienvenu Neurodevelopmental Syndrome (POBINDS)

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Summary

Clinical characteristics

CSNK2B-related neurodevelopmental disorder (*CSNK2B*-NDD), reported in more than 80 individuals to date, is characterized in most individuals by developmental delay (DD) / intellectual disability (ID) and seizures. Most young children have delays in speech and motor development. The majority of individuals older than age five years at the time of evaluation have ID ranging from borderline/mild to severe/profound. Seizures, present in most individuals, range in type and severity. While many individuals have pharmaco-responsive epilepsy, others have severe epilepsy with recurrent episodes of refractory status epilepticus. Less consistent findings include ataxia or impaired coordination, generalized hypotonia of infancy, neurobehavioral/psychiatric manifestations, and digital anomalies.

Diagnosis/testing

The diagnosis of *CSNK2B*-NDD is established in a proband with suggestive findings and a heterozygous *CSNK2B* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations: Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This includes multidisciplinary care by specialists in pediatrics, developmental pediatrics, neurology, physical medicine and rehabilitation, physical therapy, occupational therapy, speech therapy, social work, and medical genetics / genetic counseling.

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Surveillance: To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, routinely scheduled evaluations with multidisciplinary care providers are recommended.

Genetic counseling

CSNK2B-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Almost all probands reported to date whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo* pathogenic variant. Rarely, individuals diagnosed with *CSNK2B*-NDD have an affected parent. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if a parent of the proband is known to have the *CSNK2B* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Once the *CSNK2B* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *CSNK2B*-related neurodevelopmental disorder (*CSNK2B*-NDD) have been published.

Suggestive Findings

CSNK2B-NDD **should be considered** in probands with the following clinical findings and family history.

Clinical findings

- Mild-to-profound developmental delay (DD), intellectual disability (ID), or learning disability
- Epilepsy ranging from mild pharmaco-responsive epilepsy to severe intractable epilepsy with recurrent status epilepticus. Seizure types include the following:
  - Generalized tonic or tonic-clonic seizures
  - Absence seizures
  - Myoclonic seizures
  - Atonic or myoclonic-atonic seizures
  - Myoclonic-absence seizures
  - Focal-onset seizures

Less common and variable findings include the following:

- Ataxia or impaired coordination
- Generalized hypotonia of infancy
- Neurobehavioral/psychiatric manifestations
- Facial features
- Digital abnormalities
- Short stature

Family history. Because *CSNK2B*-NDD is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of *CSNK2B*-NDD **is established** in a proband with suggestive findings and a heterozygous *CSNK2B* pathogenic (or likely pathogenic) variant 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 likely pathogenic variants. (2) Identification of a heterozygous *CSNK2B* variant of uncertain significance does not 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 exome sequencing / genome sequencing [Manickam et al 2021, Smith et al 2023]. Other options include use of chromosomal microarray analysis (CMA) or a multigene panel. Note: Single-gene testing (sequence analysis of *CSNK2B*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability or epilepsy multigene panel** that includes *CSNK2B* 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*. Of note, given the rarity of *CSNK2B*-NDD, some panels for intellectual disability or epilepsy 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.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used. **Genome sequencing** is also possible. To date, the majority of reported *CSNK2B* pathogenic variants (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. Of note, some *CSNK2B* pathogenic splicing variants beyond the canonical splice site have been identified [Zhang et al 2022].

  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 *CSNK2B*-Related Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
CSNK2B	Sequence analysis [3]	~97.5% (78/80) [4]
	Gene-targeted deletion/duplication analysis [5]	~2.5% (2/80) [4]

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 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 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

CSNK2B-related neurodevelopmental disorder (*CSNK2B*-NDD) is characterized by seizures and variable degrees of developmental delay / intellectual disability. Less consistent findings include ataxia or impaired coordination, generalized hypotonia of infancy, neurobehavioral/psychiatric manifestations, digital abnormalities, and nonspecific facial features.

To date, more than 80 individuals have been identified with a *CSNK2B* pathogenic variant [Poirier et al 2017, Li et al 2019, Ernst et al 2021, Yang et al 2021, Asif et al 2022, Orsini et al 2022, Wilke et al 2022, Yang et al 2022, Zhang et al 2022, Trivisano et al 2023]. The following description is based on the well-documented phenotypic features of these individuals (see Table 2).

Table 2. *CSNK2B*-Related Neurodevelopmental Disorder: Select Features

Feature		% of Persons w/Feature
Neurodevelopmental delay or disability		89%
Intellectual disability / developmental delay		80%
Epilepsy/seizures		88%
Neurobehavioral/psychiatric manifestations		31%
Neurologic	Hypotonia	46%
	Ataxia / impaired coordination	12%
Endocrine / short stature		20%
Cardiovascular		12%

Poirier et al [2017], Li et al [2019], Ernst et al [2021], Yang et al [2021], Asif et al [2022], Orsini et al [2022], Wilke et al [2022], Yang et al [2022], Zhang et al [2022], Trivisano et al [2023]

Developmental delay (DD) and intellectual disability (ID). While most individuals have developmental delays and/or intellectual disability, there is marked variability in developmental outcomes.

The following discussion is based on information reported on 48 individuals in publications with at least two individuals with *CSNK2B*-NDD on whom neurodevelopmental outcomes and age of evaluation are included [Poirier et al 2017, Ernst et al 2021, Yang et al 2021, Yang et al 2022, Trivisano et al 2023]. Ages at the time of evaluation of these individuals ranged from younger than five years (16 individuals), 5-17 years (25 individuals), and 18 years and older (7 individuals).

Of these individuals, the majority (45/48) had developmental delays in at least one domain. Most (39/45) had both speech and motor delays. Of the three individuals reported not to have developmental delay, two were younger than age five years and one (age nine years at the time of evaluation) had a learning disability [Ernst et al 2021, Yang et al 2022].

- **Motor delay.** Of the 93% (42/45) who had motor delay, the average age of independent walking was 24 months. Sixteen of 21 individuals achieved independent walking by age three years. Five individuals walked after age three years (range: 4-7 years).

  Two males older than age five years were unable to ambulate independently by the time of evaluation; both had severe epilepsy with recurrent refractory status epilepticus associated with regression. The 12-year-old male lost the ability to walk independently at age nine years; the 26-year-old male had started to walk independently at age seven years but was unable to walk without assistance by the time of evaluation [Ernst et al 2021].

- **Speech delay.** Of the 40 of 46 individuals who had speech delays, five were nonverbal or minimally verbal at the time of evaluation. Three of the five were ages 5 to 17 years; two were adults.

Of those older than age five years at the time of evaluation, 23 of 29 had ID. Twelve had borderline or mild ID; five had moderate ID; five had severe or profound ID; and one individual's level of ID was not reported. Of the six who did not have intellectual disability, four had a learning disability.

Trivisano et al [2023] also described two families with multiple affected individuals with intrafamilial variability regarding developmental outcomes.

One study noted a possible difference in neurodevelopment outcomes between males and females, with males having a more severe intellectual disability (see Figure 1b in Ernst et al [2021]).

Epilepsy. Age of seizure onset ranged from during the neonatal period to age 10 years. Some individuals had febrile seizures only or an isolated unprovoked seizure and did not meet criteria for epilepsy. Ninety percent of individuals who had developed epilepsy by the time they were reported had their first seizure at age three years or younger [Ernst et al 2021, Yang et al 2022, Trivisano et al 2023].

Epilepsy types included generalized epilepsy, focal epilepsy, and combined generalized and focal epilepsy [Ernst et al 2021]. Seizure types included tonic-clonic, myoclonic, atonic, myoclonic-atonic, absence, atypical absence, myoclonic-absence, and tonic. While the most common seizure type was generalized tonic-clonic, seizures seen initially in infants were often focal or myoclonic [Ernst et al 2021].

The severity of epilepsy was highly variable [Ernst et al 2021]. At least one individual had only a single seizure at age 1.5 months by the time of evaluation at age 12 years, whereas many individuals had multiple seizures daily. Seizures tended to cluster in many individuals. While many individuals had pharmaco-responsive epilepsy, others had severe epilepsy with recurrent episodes of refractory status epilepticus [Li et al 2019, Ernst et al 2021, Trivisano et al 2023]. No anti-seizure medication (ASM) has been demonstrated to have specific efficacy in *CSNK2B*-NDD, and different ASMs have been reported to be effective in different individuals.

Although the course of epilepsy tended to improve with age, several individuals experienced increased seizure frequency between ages 7 and 12 years [Ernst et al 2021].

EEG is often characterized by generalized epileptiform discharges, including generalized spike-and-wave and polyspikes [Ernst et al 2021]. Epileptiform abnormalities most often were high amplitude generalized or lateralized polyspikes occurring during sleep [Ernst et al 2021].

Multifocal epileptiform abnormalities were also described [Trivisano et al 2023].

Less commonly, some individuals with epilepsy had EEG studies that did not report epileptiform abnormalities (e.g., Patient 5 in Trivisano et al [2023]).

Slowing of the EEG background was observed in about 50% of individuals [Ernst et al 2021, Trivisano et al 2023].

Neuroimaging. Brain MRI abnormalities are variable with no identifiable persistent patterns. Nonspecific findings reported in a few or single individuals include the following:

- Delayed myelination (3 individual) [Li et al 2019, Ernst et al 2021, Orsini et al 2022]
- Enlargement of subarachnoid spaces (2 individuals) [Yang et al 2021], which resolved in one individual on later imaging [Li et al 2019]
- Ventriculomegaly that resolved on later imaging (1 individual) [Yang et al 2022]
- Cortical gyral simplification [Orsini et al 2022]
- Periventricular gliosis (1 individual) [Ernst et al 2021]

- Pineal gland abnormalities [Trivisano et al 2023]
- Scattered signal abnormalities identified in gray and white matter [Yang et al 2021, Zhang et al 2022]

Hindbrain abnormalities reported in one or more individuals include T_2 hyperintensity and restricted diffusion in the pontine central tegmental tracts, pontine hypoplasia, cerebellar vermis hypoplasia with a large cisterna magna, and Chiari malformation [Ernst et al 2021].

Microcephaly, seen in one individual, was associated with severe intellectual disability [Orsini et al 2022].

Neurobehavioral/psychiatric manifestations. Behavioral manifestations (including tantrums, aggression, and hyperactivity) were reported in 26/83 individuals in well-described cohorts. Eleven individuals had autism spectrum disorder or autistic features; eight had attention-deficit/hyperactivity disorder (ADHD); and one had anxiety, depression, and obsessive-compulsive disorder [Asif et al 2022].

Other reported findings include the following:

- **Ataxia / poor coordination** (10/81 individuals) [Ernst et al 2021, Trivisano et al 2023]
- **Ectodermal anomalies** [Poirier et al 2017, Ernst et al 2021, Asif et al 2022, Orsini et al 2022, Wilke et al 2022, Zhang et al 2022, Trivisano et al 2023]
  - **Dental abnormalities** (14 individuals), including widely spaced teeth, small teeth, large central or superior incisors, hyperdontia, hypodontia, diastema, delayed tooth eruption, and prominence of the upper dental arch
  - **Skin findings** (several individuals), including soft/translucent skin, intermittent rashes, congenital scalp nevus sebaceous, vascular skin abnormality, partial hypopigmentation, and hypopigmented and hyperpigmented macules
  - **Hair findings** (3 individuals), including thin hair, one of whom had sparse temporal hair and coarse posterior hair
- **Endocrine/growth**
  - All five individuals reported by Yang et al [2022] had short stature. Of the two who underwent growth hormone (GH) stimulation testing, one had complete GH deficiency and one had partial GH deficiency.
  - One individual reported by Ernst et al [2021] had partial GH deficiency, short stature, and hypoglycemia of childhood, and another individual had delayed bone age / puberty.
  - One individual was noted to have growth delay [Orsini et al 2022], one was reported to have short stature [Asif et al 2022], and one was reported to have growth stagnation in infancy [Trivisano et al 2023].
- **Cardiovascular abnormalities.** Since each of the following cardiac abnormalities (reported in one individual) can be seen in the general population, it is unclear whether they are manifestations of *CSNK2B*-NDD or incidentally identified: congenital heart disease (unspecified) [Ernst et al 2021], patent foramen ovale [Ernst et al 2021], Ebstein anomaly and atrial septal defect [Asif et al 2022], fenestrated atrial septal defect [Asif et al 2022], Wolff-Parkinson-White syndrome [Asif et al 2022], episodes of supraventricular tachycardia at birth [Ernst et al 2021], mitral and tricuspid valve insufficiency [Orsini et al 2022], episode of unspecified cardiac arrhythmia at birth [Trivisano et al 2023], and aortic root dilatation (z score = 2.4].
- **Genital abnormalities.** Undescended testes were reported in two individuals; hypospadias and uterine agenesis was reported in one individual [Ernst et al 2021, Zhang et al 2022]. It is unclear if these are incidental findings or manifestations of *CSNK2B*-NDD.
- **Microcephaly and macrocephaly.** Multiple individuals have had either microcephaly (15%) [Ernst et al 2021, Asif et al 2022, Orsini et al 2022, Wilke et al 2022] or macrocephaly (7%) [Ernst et al 2021].
- **Digital abnormalities** include clinodactyly of fingers and toes; syndactyly of fingers and toes; polydactyly; tapered fingers; hypoplasia of fingers and toes; broad thumb; protonation of feet; nail hypoplasia; and both

long and short fingers [Ernst et al 2021, Asif et al 2022, Orsini et al 2022, Wilke et al 2022]. One individual with contractures of the first, fourth, and fifth fingers of one hand required surgery to release a trigger finger [Asif et al 2022].

- **Facial features.** In about half of individuals a facial gestalt can be seen, variably including a broad or narrow forehead; frontal bossing; wide-spaced and/or deep-set eyes; a wide and/or depressed nasal bridge; bulbous nose or broad nasal tip; underdeveloped ala nasi; smooth philtrum; thin vermilion of the upper lip; wide mouth; downturned corners of the mouth; prognathism; a pointed chin; and various ear abnormalities (e.g., overfolded helix, forward-facing ear lobes) [Asif et al 2022, Di Stazio et al 2023].

Intrafamilial variability. In one reported family, the proband had a history of neonatal hypoxia, hypotonia, moderate ID, epilepsy, and disruptive behavior disorder; the proband's father, who had the same *CSNK2B* pathogenic variant, had mild ID and febrile seizures that did not requirement treatment. In another family, the mother and proband had mild cognitive disability, whereas an affected sib with the same *CSNK2B* pathogenic variant had normal cognitive ability and ADHD [Trivisano et al 2023].

Prognosis. It is unknown whether life span in *CSNK2B*-NDD is abnormal. One individual is alive at age 36 years [Ernst et al 2021], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations have been established across all variant classes, given high phenotypic variability and the small total number of individuals reported to date, the small number of individuals with recurrent variants, and the inconsistent reporting of certain phenotypic features. Nonetheless, genotype-phenotype correlations have been proposed for missense variants affecting certain residues [Ernst et al 2021, Zhang et al 2022]:

- **Substitutions at p.Asp32 (p.Asp32Asn or p.Asp32His),** reported in individuals with intellectual disability and craniodigital anomalies [Asif et al 2022]
- **Missense variants in the zinc finger domain (amino acids 105-140),** associated with milder intellectual disability and more manageable seizures than *CSNK2B* missense variants in other domains [Zhang et al 2022]

Nomenclature

The term "intellectual disability-craniodigital syndrome (IDCS)" was proposed to refer to the phenotype observed in individuals with substitutions in *CSNK2B* at p.Asp32 [Asif et al 2022]. That these *CSNK2B* missense variants cause a distinct syndrome has been challenged, as individuals with other pathogenic *CSNK2B* variants have been reported with similar dysmorphisms and digital abnormalities [Di Stazio et al 2023] (see Genotype-Phenotype Correlations).

Prevalence

To date, more than 80 individuals have been identified with a *CSNK2B* pathogenic variant (see Clinical Description).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CSNK2B*.

Contiguous gene deletions involving *CSNK2B*

- A contiguous gene deletion in the 6p21.33 region involving *CSNK2B* and 36 additional genes was reported in a child with macrocephaly, facial dysmorphisms, and mild intellectual disability [Ohashi et al 2021]. This child also had a history of one febrile seizure in the setting of a viral infection. He started walking at age 24 months and speaking at age 38 months. Brain MRI at age four years showed incomplete hippocampal infolding (hippocampal malrotation is a radiologic finding of uncertain significance often reported in individuals with epilepsy but without clear causal relationship). Though nonspecific, mild intellectual disability and varying speech and motor delays have been seen in individuals with *CSNK2B*-NDD. Isolated febrile seizures have also been seen in individuals with *CSNK2B*-NDD [Ernst et al 2021].
- A *de novo* 4.8-Mb deletion involving *CSNK2B* was reported in the DECIPHER database; no clinical information was available.
- A *de novo* 1.2-Mb deletion involving *CSNK2B* was reported in the DECIPHER database; clinical findings included delayed speech and language, growth delay, short stature, motor delay, and seizures.

Differential Diagnosis

The phenotypic features associated with *CSNK2B*-related neurodevelopmental disorder (*CSNK2B*-NDD) are not sufficient to diagnose this condition clinically. All disorders with intellectual disability and/or epilepsy without other distinctive findings should be considered in the differential diagnosis. See OMIM Phenotypic Series for genes associated with the following:

- Autosomal dominant intellectual developmental disorders
- Early-onset epilepsy

Management

No clinical practice guidelines for *CSNK2B*-related neurodevelopmental disorder (*CSNK2B*-NDD) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder and similar disorders.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CSNK2B*-NDD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. *CSNK2B*-Related Neurodevelopmental Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI • EEG incl sleep study to characterize any recurrent abnormal episodes & evaluate for subtle or subclinical seizures
Ataxia / Poor coordination	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)
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurobehavioral/ psychiatric manifestations	Mental health eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Cardiovascular	Referral to cardiologist	Echocardiogram & EKG to assess for any cardiovascular abnormalities
Genital anomalies	Urology eval	If clinical findings warrant
Endocrine	Referral to endocrinologist	To inform & diagnose growth delays
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *CSNK2B*-NDD to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine 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; *CSNK2B*-NDD = *CSNK2B*-related neurodevelopmental disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *CSNK2B*-NDD. Supportive treatment to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. *CSNK2B*-Related Neurodevelopmental Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral manifestations	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• No ASM has been demonstrated to have specific efficacy in *CSNK2B*-NDD. • Different ASMs have been reported to be effective in different persons. • Education of parents/caregivers [1]
Ataxia / Poor coordination	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Cardiovascular	Standardized treatment for any cardiovascular issues identified	
Genital anomaly	Per treating urologist	
Endocrine	Per treating endocrinologist	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

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

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, 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.
  - 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).

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

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

Neurobehavioral/Psychiatric 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, behavioral pediatric neurologist, or developmental pediatrician.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. *CSNK2B*-Related Neurodevelopmental Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	At each visit
Development	Monitor developmental progress & educational needs.	
Feeding	• Measure growth parameters. • Evaluate nutritional status & safety of oral intake.	
Neurobehavioral/ psychiatric manifestations	Assess for anxiety, ADHD, ASD, aggression, & self-injury.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Cardiovascular	For those known to have cardiovascular abnormalities	Per treating cardiologist
Genital anomalies	Evaluate for genitourinary anomalies.	Per treating urologist
Endocrine	Assess linear growth.	Per treating endocrinologist
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).	At each visit
Transition to adult care	Develop realistic plans for adult life (See American Epilepsy Society Transitions from Pediatric Epilepsy to Adult Epilepsy Care plan for independence and independence unlikely.)	Starting by age ~10 yrs

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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

Genetic Counseling

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

Mode of Inheritance

CSNK2B-related neurodevelopmental disorder (*CSNK2B*-NDD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Almost all probands reported to date with *CSNK2B*-NDD whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo CSNK2B* pathogenic variant.
- Rarely, individuals diagnosed with *CSNK2B*-NDD have an affected parent. Transmission of a *CSNK2B* pathogenic variant from an affected parent to an affected child has been reported in two families to date [Trivisano et al 2023].
- Molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- 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 CSNK2B* pathogenic variant.

- The proband inherited a *CSNK2B* pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a *CSNK2B* pathogenic variant that is present in the germ (gonadal) 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 a parent of the proband is known to have the *CSNK2B* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Of note, significant intrafamilial clinical variability has been observed in the two families reported to date with recurrence [Trivisano et al 2023] (see Clinical Description, **Intrafamilial variability**).
- If the *CSNK2B* 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 possibility of parental gonadal mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with *CSNK2B*-NDD has a 50% chance of inheriting the *CSNK2B* 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 *CSNK2B* 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 and parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CSNK2B* 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 and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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.

- **CSNK2B Neurodevelopmental Syndrome Foundation**

  It is the mission of the CSNK2B Foundation to bring awareness and education to CSNK2B Neurodevelopmental Syndrome and to enrich the lives of those affected by accelerating research, treatments and by chasing a cure for CSNK2B.

  Email: info@csnk2b.org

  csnk2b.org

- **American Epilepsy Society**
  aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  canadianepilepsyalliance.org
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Epilepsy and Seizures
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  rarechromo.org
- **Simons Searchlight Registry**
  Simons Searchlight aims to further the understanding of rare genetic neurodevelopmental disorders.
  Phone: 855-329-5638
  Fax: 570-214-7327
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  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. CSNK2B-Related Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
CSNK2B	6p21.33	Casein kinase II subunit beta	CSNK2B	CSNK2B

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 CSNK2B-Related Neurodevelopmental Disorder (View All in OMIM)

115441	CASEIN KINASE II, BETA; CSNK2B
618732	POIRIER-BIENVENU NEURODEVELOPMENTAL SYNDROME; POBINDS

Molecular Pathogenesis

CSNK2B encodes casein kinase II subunit beta (CK2β), a regulatory subunit of casein kinase II (CK2), a serine/threonine kinase implicated in many diverse cellular functions. The holoenzyme is a heterotetramer comprised of two catalytic alpha subunits (combinations of α and α') flanking a beta subunit, the latter specifically encoded by *CSNK2B* [Niefind et al 2001]. Casein kinase is ubiquitously expressed with high levels of expression in the brain [Guerra et al 1999]. The alpha subunit is encoded by *CSNK2A1*, which has also been associated with neurodevelopmental disease [Okur et al 2016] (see Okur-Chung Neurodevelopmental Syndrome).

Mechanism of disease causation. The mechanism of disease causation in *CSNK2B*-related neurodevelopmental disorder is not fully understood. Because a subset of *CSNK2B* pathogenic variants is expected to result in reduced beta subunit expression, haploinsufficiency appears to be one important disease mechanism [Di Stazio et al 2023]. Indirect support for reduced CK2β expression as a cause of nervous system dysfunction comes from experimental evidence showing altered dendritic arborization and synaptic physiology because of *CSNK2B* knockdown in neural stem cells [Yang et al 2018]. Although reduced holoenzyme formation and activity is the presumed relevant consequence of *CSNK2B* haploinsufficiency, holoenzyme-independent mechanisms are also possible.

It is unclear whether some *CSNK2B* missense pathogenic variants might be hypomorphic alleles or have a dominant-negative effect in reducing activity of the heterotetramer in a more profound way (as proposed by Asif et al [2022]).

Table 6. *CSNK2B* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001320.7 NP_001311.3	c.94G>A	Asp32Asn	Substitutions at p.Asp32 have been reported in persons w/ID & craniodigital anomalies [Asif et al 2022]. The suggestion that these missense variants cause a distinct syndrome has been challenged, as persons w/other *CSNK2B* pathogenic variants have similar phenotypes [Di Stazio et al 2023].
	c.94G>C	p.Asp32His	

ID = intellectual disability
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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The CTRND at Columbia University is actively involved in ongoing clinical and translational research on *CSNK2B*-related neurodevelopmental disorder. Contact Dr Sands (tts27@cumc.columbia.edu) with clinical questions or research interests.

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