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CTNNB1 Neurodevelopmental Disorder

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Summary

Clinical characteristics

CTNNB1 neurodevelopmental disorder (*CTNNB1*-NDD) is characterized in all individuals by mild-to-profound cognitive impairment and in up to 39% of reported individuals by exudative vitreoretinopathy, an ophthalmologic finding consistent with familial exudative vitreoretinopathy (FEVR). Other common findings include truncal hypotonia, peripheral spasticity, dystonia, behavior problems, microcephaly, and refractive errors and strabismus. Less common features include intrauterine growth restriction, feeding difficulties, and scoliosis.

Diagnosis/testing

The diagnosis of *CTNNB1*-NDD is established in a proband with suggestive findings and a heterozygous pathogenic variant in *CTNNB1* identified by molecular genetic testing

Management

Treatment of manifestations: There is no curative treatment. Supportive care by a multidisciplinary team often includes a neurologist, speech-language pathologist, physiatrist, occupational therapist, physical therapist, feeding team, pediatric ophthalmologist, audiologist, and developmental pediatrician.

Surveillance: Monitor neurologic findings for response to supportive interventions and emergence of new findings or concerns regarding developmental/educational progress, behavior issues, ophthalmologic findings and vision, and family support.

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Genetic counseling

CTNNB1-NDD is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Rarely, individuals diagnosed with *CTNNB1*-NDD inherited a *CTNNB1* pathogenic variant from a parent. Once the *CTNNB1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *CTNNB1* neurodevelopmental disorder (*CTNNB1*-NDD) have been published.

Suggestive Findings

CTNNB1-NDD **should be considered** in individuals with the following **clinical findings**:

- Mild-to-profound developmental delay or intellectual disability
- Exudative vitreoretinopathy with a range of findings observed in familial exudative vitreoretinopathy (FEVR) that include: asymptomatic peripheral retina avascularity, neovascularization, and fibrosis; a varying degree of visual impairment associated with macula and vessel dragging; and total blindness resulting from tractional and/or exudative retinal detachments [Panagiotou et al 2017, Coussa et al 2020, Rossetti et al 2021]
- Any of the following common features presenting in infancy or childhood:
  - Truncal hypotonia
  - Peripheral spasticity
  - Dystonia
  - Behavior problems including autism spectrum disorder, inattention, hyperactivity, aggression, self-mutilation, temper tantrums, anxiety, sleep disturbances, and restlessness
  - Microcephaly (≤2 SD below age- and sex-adjusted mean)
  - Other ophthalmologic findings including refractive errors (myopia, hypermetropia, astigmatism) and strabismus

Other less common features presenting in infancy or childhood:

- Intrauterine growth restriction
- Short stature
- Feeding difficulties
- Scoliosis
- Suggestive facial features (See Figure 1.)

Family history. Because *CTNNB1*-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 *CTNNB1* neurodevelopmental disorder (*CTNNB1*-NDD) **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *CTNNB1* 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

Figure 1. Facial features in individuals with *CTNNB1* neurodevelopmental disorder

Common findings are a bulbous nasal tip, thin upper lip, small alae nasi, and long and smooth philtrum. Less common findings are upslanting palpebral fissures and hypotelorism. Note thin, fair, or sparse hair, abnormal hair pattern, and fair skin complexion.

Patient 1. Chinese male. A: age 8 months; B: age 24 months; C: age 18 years, 3 months; D: age 20 years, 11 months

Patient 2. Chinese female. A: age 1 year, 1 month with her affected mother (age 32 years); B: age 5 years, 1 month

Patient 3. Chinese female. A: 1 year, 4 months; B: 4 years

Patient 4. White American female. 2 years, 11 months

Patient 5. Chinese male. 3 years, 7 months

Patient 6. Male. 4 years

Patient 7. Chinese female. A: 4 years, 4 months, B: 6 years, 10 months

Patient 8. German and Irish male. 5 years

Patient 9. White Western European female. 5 years, 2 months

Patient 10. Chinese male. 5 years, 3 months

Patient 11. White female. A: 9 years; B: 10 years; C: 11 years; D: 12 years; E: 13 years

Patient 12. Male. 9 years

Patient 13. Female. 14 years

Patient 14. European male. 16 years

Patient 15. White European male. 18 years

Patient 16. Thai female. 19 years

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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 *CTNNB1* 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 chromosomal microarray analysis (CMA). Other options include use of a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *CTNNB1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability (ID) multigene panel** that includes *CTNNB1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

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

  Genome sequencing is also possible.

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

Table 1. Molecular Genetic Testing Used in *CTNNB1* Neurodevelopmental Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
CTNNB1	Sequence analysis [4]	All variants reported to date [5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

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. Information on individuals with genotypes involving a contiguous gene deletion of *CTNNB1* and adjacent genes are not included in this table (see Genetically Related Disorders).
4. 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.
5. de Ligt et al [2012], Dubruc et al [2014], Tucci et al [2014], Kuechler et al [2015], Dixon et al [2016], Winczewska-Wiktor et al [2016], Kharbanda et al [2017], Li et al [2017], Panagiotou et al [2017], Pipo-Deveza et al [2018], Karolak et al [2019], Sun et al [2019], Wang et al [2019], Coussa et al [2020], Ke & Chen [2020], Rossetti et al [2021], Ho et al [2022]
6. 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.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

CTNNB1 neurodevelopmental disorder (*CTNNB1*-NDD) is characterized in all individuals by mild-to-profound cognitive impairment and in some individuals by exudative vitreoretinopathy. Exudative vitreoretinopathy, observed in up to 39% of reported individuals, is often diagnosed in early childhood and may present in infancy in those with significantly compromised vision [Sun et al 2019, Coussa et al 2020]. Other common findings include truncal hypotonia, peripheral spasticity, dystonia, behavior problems, microcephaly, and refractive errors and/or strabismus. Less common features include intrauterine growth restriction, feeding difficulties, and scoliosis.

To date, at least 57 individuals have been identified with a pathogenic variant in *CTNNB1* [Tucci et al 2014, Kuechler et al 2015, Dixon et al 2016, Winczewska-Wiktor et al 2016, Kharbanda et al 2017, Li et al 2017, Panagiotou et al 2017, Pipo-Deveza et al 2018, Karolak et al 2019, Sun et al 2019, Wang et al 2019, Coussa et al 2020, Jin et al 2020, Ke & Chen 2020, Rossetti et al 2021, Ho et al 2022]. The following description of the phenotypic features associated with *CTNNB1*-NDD is based on reports that included sufficient phenotypic information. (Note: Information on three individuals heterozygous for a pathogenic variant in a gene in addition to *CTNNB1* [Karolak et al 2019, Ho et al 2022] are not included in Table 2 or in the following discussion.)

Table 2. Select Features of *CTNNB1* Neurodevelopmental Disorder

Feature	# of Persons w/Feature / # Assessed	Comment
Neurodevelopmental		
DD/ID	57/57 (100%)	
Speech delay	38/39 (97.4%)	
Motor delay	36/36 (100%)	

Table 2. continued from previous page.

Feature		# of Persons w/Feature / # Assessed	Comment
Behavior problems	Autistic features	19/41 (46.3%)	Incl persons w/poor eye contact & stereotypies
	ADHD	7/41 (17.1%)	
	Aggression / self-mutilation	18/37 (48.6%)	
	Sleep disturbances	9/26 (34.6%)	
Truncal hypotonia		39/47 (83%)	
Peripheral spasticity		43/48 (89.6%)	
Dystonia		8/37 (21.6%)	
Ataxia		10/28 (35.7%)	
Microcephaly		42/52 (80.8%)	
Ophthalmologic [1]			
Exudative vitreoretinopathy		9/23 (39.1%)	Characterized by peripheral retinal avascularity, neovascularization w/ secondary fibrosis, vessel pruning, retinal folds assoc w/exudates & traction complicated by temporal dragging of macula & vessels, retinal holes, & retinal detachment
Strabismus		31/56 (55.4%)	
Refractive errors [2]		15/56 (26.8%)	Incl myopia, hypermetropia, & astigmatism
Other			
IUGR		10/44 (22.7%)	
Short stature		8/39 (20.5%)	
Feeding difficulties		14/35 (40%)	
Scoliosis		6/30 (20%)	

ADHD = attention-deficit/hyperactivity disorder; DD = developmental delay; ID = intellectual disability; IUGR = intrauterine growth restriction

Based on Tucci et al [2014], Kuechler et al [2015], Dixon et al [2016], Winczewska-Wiktor et al [2016], Kharbanda et al [2017], Li et al [2017], Panagiotou et al [2017], Pipo-Deveza et al [2018], Karolak et al [2019], Sun et al [2019], Wang et al [2019], Coussa et al [2020], Jin et al [2020], Ke & Chen [2020], Rossetti et al [2021], Ho et al [2022]

1. Dixon et al [2016], Li et al [2017], Panagiotou et al [2017], Coussa et al [2020], Rossetti et al [2021]

2. Myopia was detected in three of 56 reported individuals (5.4%) and hypermetropia in 14 of 56 reported individuals (25%).

Neurodevelopmental Features

Developmental delay (DD) and intellectual disability (ID). All reported individuals had mild-to-severe developmental delay / intellectual disability, with reported IQ scores ranging from 28 to 72, although results of formal IQ testing were not always available [Tucci et al 2014, Kuechler et al 2015, Wang et al 2019]. While the number of affected adults reported is limited, some adults with *CTNNB1*-NDD were able to care for themselves as well as raise children with support from other family members [Panagiotou et al 2017, Wang et al 2019, Ho et al 2022].

Regression in ability to ambulate and cognitive function was reported in some affected individuals, which may be explained by progressive peripheral spasticity and/or visual impairment [Tucci et al 2014, Kuechler et al 2015, Winczewska-Wiktor et al 2016, Kharbanda et al 2017].

Motor delay is common and may be partly attributed to central hypotonia and/or peripheral spasticity.

- Age of walking with assistance ranged from 21 months to 12 years.
- Some affected individuals continued to require assistance for walking as adults and some regressed to become wheelchair bound [Tucci et al 2014].

Speech delay is common. First words are often delayed, but some individuals speak in sentences. One affected individual remained nonverbal as an adult [Tucci et al 2014]. Some individuals had more advanced verbal comprehension when compared to expressive language skills as evidenced by their use of sign language [Tucci et al 2014, Kuechler et al 2015]. Some affected individuals had speech apraxia and dysarthria [Kuechler et al 2015, Kharbanda et al 2017, Pipo-Deveza et al 2018].

- Age of first words in individuals with developmental delay ranged from 12 months to 14 years.
- Age of ability to speak in sentences was between six and 14 years in those who were able.

Behavior problems included inattention, hyperactivity, self-mutilation, and aggression toward others. Some affected individuals are described to be happy, friendly, and sociable, although restlessness, excessive crying, and temper tantrums have also been reported. Autistic features such as poor eye contact, frequent stereotypic movements, and restricted interests were described in some affected individuals. Sleep disturbances are common.

Truncal hypotonia, reported in the majority of individuals with *CTNNB1*-NDD, may be the first sign prompting medical attention.

Peripheral spasticity often progresses with age, although some affected infants may have hypertonia at birth [Kuechler et al 2015]. While some may develop a subtle increase in tone only evident upon detailed examination, others may have spasticity warranting specific management (see Management).

The lower limbs are often affected, whereas the upper limbs have milder involvement. Spinal MRI is often unremarkable, although tethered cord, syringomyelia, and lipomyelomeningocele have been reported [Kuechler et al 2015, Dixon et al 2016, Rossetti et al 2021].

Movement disorders. Dystonia, the most common reported movement disorder, can be focal or generalized [Wang et al 2019, Ho et al 2022]. Diurnal fluctuation, reported in one individual, improved with administration of levodopa [Pipo-Deveza et al 2018]. Bradykinesia, oral facial dyspraxia, apraxia of upward gaze, and choreoathetoid movements have been described on occasion [Winczewska-Wiktor et al 2016, Kharbanda et al 2017, Rossetti et al 2021].

Ataxia. Gait is occasionally described to be wide-based and ataxic, despite the lower-limb spasticity [Kuechler et al 2015, Winczewska-Wiktor et al 2016, Kharbanda et al 2017, Wang et al 2019].

Neuroimaging. While brain imaging is normal in the majority of affected individuals, structural brain anomalies include corpus callosum hypoplasia, hydrocephalus, abnormal gyration of temporal lobe, absent right fornix, hypoplastic brain stem, delayed bilateral frontal lobe myelination, arachnoid cyst, and frontal pachygyria [Kuechler et al 2015, Winczewska-Wiktor et al 2016, Jin et al 2020].

Ophthalmologic Features

Exudative vitreoretinopathy, the most distinctive ophthalmologic finding, is consistent with familial exudative vitreoretinopathy (FEVR), which is caused by incomplete retinal angiogenesis resulting in retinal ischemia. This peripheral retinal avascularity leads to increased neovascularization, which can cause fibrosis and resultant traction and retinal detachment [Dixon et al 2016].

Manifestations of FEVR can range from an incidental finding of localized peripheral retinal avascularity that does not affect vision, to total blindness resulting from tractional and exudative retinal detachments. Although the majority of individuals reported with *CTNNB1*-related FEVR have neovascularization, subretinal exudation, retinal folds, and retinal detachments, ascertainment bias should be taken into account [Coussa et al 2020].

Significant visual impairment was reported in 17.5% (10/57) of affected individuals; 7% (4/57) of affected individuals were legally blind [Li et al 2017, Panagiotou et al 2017, Wang et al 2019, Ke & Chen 2020, Rossetti et al 2021].

Other ophthalmologic findings commonly observed in individuals with neurodevelopmental disorders (who do not have exudative vitreoretinopathy) include strabismus and refractive errors (astigmatism, myopia, and hypermetropia).

Other Features

Growth. The majority of affected individuals were born at term; intrauterine growth restriction is common. Inadequate weight gain and postnatal short stature (height ≥2 SD below the mean) may be present without apparent feeding difficulties.

Microcephaly (head circumference ≥2 SD below the mean) is often acquired but may be present at birth. Microcephaly may progress as affected individuals age [Kuechler et al 2015]. One individual with microcephaly had craniosynostosis [Ho et al 2022].

Feeding difficulties / gastrointestinal problems. Feeding problems are common; gastrointestinal problems can include gastroesophageal reflux disease, swallowing difficulties, and oromotor dyspraxia. If not managed properly, feeding difficulties may result in aspiration and inadequate weight gain (see Management).

Musculoskeletal anomalies are in general uncommon except for scoliosis. Other findings such as pes cavus, syndactyly, flat feet, clubfoot, and polydactyly have been reported [Kuechler et al 2015, Ke & Chen 2020].

Prognosis. Based on current data, life span is not limited in individuals with *CTNNB1*-NDD, as several adults have been reported. The majority of these adults (age range 37-50 years) were identified by follow-up parental studies at the time of diagnosis of an affected child. Data on possible progression of behavior abnormalities or neurologic findings are limited.

Genotype-Phenotype Correlations

To date, no genotype-phenotype correlations have been identified [Rossetti et al 2021].

Panagiotou et al [2017] suggest that *CTNNB1* variants associated with clinically significant FEVR are truncating variants that lead to escape of nonsense-mediated decay, whereas *CTNNB1* variants associated with mild, clinically insignificant FEVR alter the uncharacterized beta-catenin carboxy-terminal domain.

Prevalence

As of October 2021, 57 individuals with *CTNNB1*-NDD have been reported. While not known, the incidence is estimated to be 2.6-3.2 in 100,000 births [López-Rivera et al 2020].

Genetically Related (Allelic) Disorders

Nonsyndromic familial exudative vitreoretinopathy (FEVR). Heterozygous germline pathogenic variants in *CTNNB1* were reported in two families with nonsyndromic FEVR [Panagiotou et al 2017]. Intrafamilial variability was observed in these affected individuals, whose eye manifestations ranged from asymptomatic to legally blind. While the majority of the heterozygous family members showed features consistent with the

diagnosis of FEVR, one adult had only unilateral focal retinal degeneration without evidence of retinal avascularity, and another child (age 9 on latest examination) in the same family was asymptomatic. To date, there is no known genotype-phenotype correlation between *CTNNB1* variants that cause neurodevelopmental disorders and nonsyndromic FEVR.

Contiguous gene deletions. Deletions encompassing *CTNNB1* and part of the contiguous gene *ULK4* have been reported in two individuals with clinical manifestations consistent with *CTNNB1* neurodevelopmental disorder (*CTNNB1*-NDD) [Dubruc et al 2014, Kuechler et al 2015]. No findings other than those described in *CTNNB1*-NDD were reported in these individuals; however, the involvement of *ULK4* may possibly have contributed to their phenotypes despite evidence to date that *ULK4* has no known human disease association.

Sporadic tumors (including endometrial endometrioid adenocarcinoma, lung adenocarcinoma, colon adenocarcinoma, prostate adenocarcinoma, and hepatocellular carcinoma) occurring as single tumors in the absence of any other findings of *CTNNB1*-NDD frequently contain a somatic pathogenic variant in *CTNNB1* that is **not** present in the germline (www.mycancergenome.org). In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

The cognitive and motor features of *CTNNB1* neurodevelopmental disorder (*CTNNB1*-NDD) overlap with cerebral palsy, movement disorders (e.g., hereditary spastic paraplegia), and intellectual disability disorders (see OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series) and are not sufficient to diagnose this condition.

The ophthalmologic features of *CTNNB1*-NDD overlap with other types of pediatric retinal diseases including retinopathy of prematurity (ROP), Coats disease, Norrie disease, and persistent fetal vasculature. Differention between these disorders is essential during retinal evaluation. Differential diagnoses for exudative vitreoretinopathy are shown in Table 3.

Table 3. Pediatric Retinal Diseases in the Differential Diagnosis of *CTNNB1* Neurodevelopmental Disorder and Exudative Vitreoretinopathy

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*CTNNB1*-NDD	Distinguishing from *CTNNB1*-NDD
FZD4 *LRP5* *NDP* *TSPAN12* *ZNF408*	Exudative vitreoretinopathy (OMIM PS133780)	AD AR XL [1]	Exudative vitreoretinopathy	Other systemic involvement uncommon
NDP	Norrie disease (See *NDP*-Related Retinopathies.)	XL	DD & various eye complications incl retinal detachment	Presence of retrolental pseudoglioma & incomplete foveal development
KIF11	Microcephaly ± chorioretinopathy, lymphedema, or intellectual disability (OMIM 152950)	AD	Microcephaly & DD; various eye involvement incl exudative vitreoretinopathy	Lymphedema

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/*CTNNB1*-NDD	Distinguishing from *CTNNB1*-NDD
PLK4 *TUBGCP4* *TUBGCP6*	Microcephaly & chorioretinopathy (OMIM PS251270)	AR	Microcephaly & DD; various eye involvement incl exudative vitreoretinopathy	Cerebral & cerebellar atrophy; pachygyria

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; XL = X-linked
1. NDP-related exudative vitreoretinopathy is inherited in an X-linked manner. *FZD4*-, *TSPAN12*-, and *ZNF408*-related exudative vitreoretinopathy are inherited in an autosomal dominant manner. *LRP5*-related exudative vitreoretinopathy is inherited in an autosomal dominant or autosomal recessive manner.

Management

No clinical practice guidelines for *CTNNB1* neurodevelopmental disorder (*CTNNB1*-NDD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CTNNB1*-NDD, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *CTNNB1* Neurodevelopmental Disorder

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• Assess for spasticity & dystonia. • Consider MRI of spine if evidence of lower limb spasticity to assess for possibility of underlying tethered cord.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • 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
Speech delay	Eval by speech-language pathologist	Assess need for alternative communication.
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk, swallowing difficulties, reflux & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Ophthalmologic	Routine exam	To assess for refractive error, strabismus
	Retinal exam	• To assess for the range of retinal manifestations of exudative vitreoretinopathy at time of 1st diagnosis (incl early infancy) [1] • May require fluorescein angiography
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of *CTNNB1*-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; *CTNNB1*-NDD = *CTNNB1* neurodevelopmental disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Panagiotou et al [2017], Coussa et al [2020]
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care by a multidisciplinary team often includes a neurologist, speech-language pathologist, physiatrist, occupational therapist, physical therapist, feeding team, ophthalmologist, audiologist, and developmental pediatrician.

Table 5. Treatment of Manifestations in Individuals with *CTNNB1* Neurodevelopmental Disorder

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	• Regular PT w/stretching • Botulinum toxin & intrathecal baclofen injection may be considered. [1] • Consider need for positioning & mobility devices, disability parking placard.
Movement disorders	Standard treatment per neurologist	Treatment w/levodopa may be considered.

Table 5. continued from previous page.

Manifestation/Concern		Treatment	Considerations/Other
Ophthal-mologic	**Exudative vitreoretinopathy**	Per treating retina specialist	• For retinal findings only evident on wide-field FA: discuss w/treating retina specialist for consideration of prophylactic laser due to ↑ risk of retinal detachment. • For significant retinal findings: argon laser photocoagulation, scleral buckling &/or pars plana vitrectomy to attempt to halt progressive changes & ↓ complications [2]
	Low vision	Low vision services	Community services through early intervention &/or school district
	Refractive errors & strabismus	Per treating ophthalmologist	
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.

FA = fluorescein angiogram; OT = occupational therapy; PT = physical therapy
1. Kuechler et al [2015]
2. Coussa et al [2020]

Developmental Delay / Intellectual Disability Management Issues

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

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

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

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.

    - Vision consultants should be a part of the child's IEP team to support access to academic material.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of Levodopa, 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 6. Recommended Surveillance for Individuals with *CTNNB1* Neurodevelopmental Disorder

System/Concern		Evaluation	Frequency
Feeding		• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Neurologic		Monitor those w/spasticity &/or mvmt disorder as clinically indicated.	
		Assess for new manifestations (e.g., changes in tone, mvmt disorders).	
Development		Monitor developmental progress & educational needs.	
Psychiatric/Behavioral		Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal		Physical medicine, OT/PT assessment of mobility, self-help skills	
Ophthalmologic	**Exudative vitreoretinopathy**	For progression of retinal findings	Per treating retina specialist
	Low vision	For changes in vision	Per low vision clinic
	Refractive errors & strabismus	For changes in refractive error & strabismus	Per treating ophthalmologist
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

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

CTNNB1 neurodevelopmental disorder (*CTNNB1*-NDD) 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 *CTNNB1*-NDD whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo CTNNB1* pathogenic variant.
- Rarely, individuals diagnosed with *CTNNB1*-NDD inherited a *CTNNB1* pathogenic variant from a parent. In two families with maternal transmission of *CTNNB1*-NDD, the mothers had developmental delay, visual problems, peripheral spasticity, and microcephaly; however, these features were less severe than those in their affected daughters [Wang et al 2019, Ho et al 2022].
- 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. Germline mosaicism was reported in one family with two affected offspring and normal parental studies [Kuechler et al 2015]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

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

- If a parent of the proband is known to have the *CTNNB1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *CTNNB1* 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 germline mosaicism [Kuechler et al 2015].

Offspring of a proband. Each child of an individual with *CTNNB1*-NDD has a 50% chance of inheriting the *CTNNB1* pathogenic variant.

Other family members. Given that most probands with *CTNNB1*-NDD reported to date have the disorder as a result of a *de novo CTNNB1* pathogenic variant, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CTNNB1* 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.

- **Advancing CTNNB1 Cures and Treatments (ACCT)**
  Email: info@curectnnb1.org
  www.curectnnb1.org
- **CTNNB1 Foundation**
  Phone: 386 31 731 269
  Email: spela@ctnnb1-foundation.org
  www.ctnnb1-foundation.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **MedlinePlus**
  Intellectual Disability
- **Unique: Understanding Rare Chromosome and Gene Disorders**
  United Kingdom
  Phone: +44 (0) 1883 723356
  Email: info@rarechromo.org
  rarechromo.org
- **Simons Searchlight Registry**
  Phone: 855-329-5638
  Email: coordinator@simonssearchlight.org
  CTNNB1

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. CTNNB1 Neurodevelopmental Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CTNNB1	3p22.1	Catenin beta-1	CTNNB1 database	CTNNB1	CTNNB1

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 CTNNB1 Neurodevelopmental Disorder (View All in OMIM)

116806	CATENIN, BETA-1; CTNNB1
615075	NEURODEVELOPMENTAL DISORDER WITH SPASTIC DIPLEGIA AND VISUAL DEFECTS; NEDSDV

Molecular Pathogenesis

CTNNB1 encodes beta-catenin, a coactivator in the Wnt signaling pathway and a key component in cadherin adhesion complex essential in cell-cell adhesion. In vivo studies in knockout mice suggest that beta-catenin/cadherin interactions regulate synaptic plasticity and neuronal network connectivity and that disruption could lead to brain malformations and a neurodevelopmental disorder [Tucci et al 2014]. The Wnt signaling pathway is also crucial for mammalian vascular development of the eye. Dysregulation in norrin-beta-catenin signaling caused by pathogenic variants in the genes encoding coreceptors for Wnt ligands such as *LRP5* and *FZD4*, and the ligand *NDP* leads to the angiogenesis defects associated with familial exudative vitreoretinopathy [Nikopoulos et al 2010].

Mechanism of disease causation. Loss of function (i.e., haploinsufficiency)

Cancer and Benign Tumors

CTNNB1 somatic variants that result in continuous activation of beta-catenin signaling and an accumulation of nuclear beta-catenin occur in diverse cancer types, including endometrial endometrioid adenocarcinoma, lung adenocarcinoma, colon adenocarcinoma, prostate adenocarcinoma, and hepatocellular carcinoma [Zhan et al 2017, Holt et al 2021]. These somatic *CTNNB1* variants commonly occur in hot spots in exon 3 that encode serine-threonine phosphorylation sites for glycogen synthase kinase 3-beta, which plays a role in beta-catenin degradation.

To date there is no evidence that individuals with the loss-of-function *CTNNB1* germline variants causing *CTNNB1* neurodevelopmental disorder are at increased risk for cancer [Ho et al 2022].

Chapter Notes

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