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CLPB Deficiency

Synonyms: Caseinolytic Peptidase B Deficiency, CLPB Defect

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Summary

Clinical characteristics

CLPB (*c*aseino*l*ytic *p*eptidase *B*) deficiency is characterized by neurologic involvement and neutropenia, which can range from severe to mild. In severe CLPB deficiency, death usually occurs at a few months of age due to significant neonatal neurologic involvement (hyperekplexia or absence of voluntary movements, hypotonia or hypertonia, swallowing problems, respiratory insufficiency, and epilepsy) and severe neutropenia associated with life-threatening infections. Individuals with moderate CLPB deficiency present with neurologic abnormalities in infancy including hypotonia and feeding problems, and develop spasticity, a progressive movement disorder (ataxia, dystonia, and/or dyskinesia), epilepsy, and intellectual disability. Neutropenia is variable, but not life threatening. In those with mild CLPB deficiency there is no neurologic involvement, intellect is normal, neutropenia is mild and intermittent, and life expectancy is normal.

Diagnosis/testing

The diagnosis of CLPB deficiency is established in a proband by identification of biallelic pathogenic variants in *CLPB* or identification of one of several specific heterozygous *CLPB* pathogenic variants associated with autosomal dominant CLPB deficiency on molecular genetic testing.

Management

Treatment of manifestations: Treatment is supportive. A multidisciplinary team including a metabolic physician, pediatric neurologist, dietitian, and physical therapist is recommended. No specific dietary or metabolic treatment is available. Feeding therapy; gastrostomy tube placement for persistent feeding issues; treatment of seizures per neurologist; management of movement disorder per orthopedist, physical medicine and rehabilitation specialist, physical therapist, and occupational therapist; botulinum toxin injection in the salivary glands, extirpation of saliva glands, and/or rerouting of glandular ducts for excessive drooling; developmental support including early intervention (physical therapy, occupational therapy, and/or speech therapy) and special

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education services; granulocyte-colony stimulating factor to increase neutrophil counts to reduce the frequency of infections, especially in individuals with the mild or moderate phenotype; standard immunizations to prevent infections; treatment of cataracts per ophthalmologist; treatment of endocrine dysfunction per endocrinologist; treatment of renal disease per renal specialist; consider hematopoietic stem cell transplant in those without severe neurologic disease.

Surveillance: At each visit: assess for seizures, changes in tone, and movement disorders; assess growth, feeding, developmental progress, mobility, and family needs; measure white blood cell count with differential. Ophthalmology examination with frequency per ophthalmologist. Annually: TSH to assess thyroid function; assessment of gonadal function in females (beginning at age 10 years).

Agents/circumstances to avoid: Drugs potentially toxic to mitochondria, including chloramphenicol, aminoglycosides, linezolid, valproic acid, and nucleoside reverse transcriptase inhibitors.

Genetic counseling

CLPB deficiency associated with biallelic *CLPB* pathogenic variants is inherited in an autosomal recessive manner. CLPB deficiency associated with specific heterozygous *CLPB* pathogenic variants is inherited in an autosomal dominant manner.

- **Autosomal recessive CLPB deficiency.** If both parents are known to be heterozygous for a *CLPB* pathogenic variant associated with autosomal recessive CLPB deficiency, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *CLPB* pathogenic variants. Carrier testing for at-risk relatives requires prior identification of the *CLPB* pathogenic variants in the family.
- **Autosomal dominant CLPB deficiency.** All individuals reported to date with autosomal dominant CLPB deficiency have the disorder as the result of a *de novo CLPB* pathogenic variant. Each child of an individual with a heterozygous *CLPB* pathogenic variant has a 50% chance of inheriting the pathogenic variant.

Once the *CLPB* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for CLPB deficiency are possible.

Diagnosis

Suggestive Findings

CLPB (*c*aseino*l*ytic *p*eptidase *B*) deficiency **should be suspected** in individuals with the following clinical, laboratory, and imaging findings.

Clinical Findings

The disease spectrum of CLPB deficiency ranges from severe to mild.

All phenotypes. Congenital or infantile cataracts can be present in individuals with severe to mild phenotypes.

Severe (prenatal / infantile) phenotype

- Polyhydramnios, fetal contractures, intrauterine growth restriction
- Microcephaly
- Hyperekplexia, absence of voluntary movements, respiratory insufficiency, and swallowing problems

Moderate (infantile / early childhood) phenotype

- Hypotonia or hypertonia
- Seizures
- Spasticity
- Ataxia, tremor and dystonia, dyskinesia
- Intellectual disability

Mild phenotype

- No neurologic involvement
- Normal intellect

Laboratory Findings

Neutropenia beginning at birth can be chronic or intermittent (especially during infections) with absolute neutrophil count ranging from severe (<0.5 per mm^3) to mild (<1.5 per mm^3)

Elevated urinary excretion of 3-methylglutaconic acid (3-MGA) (typically 2x-10x the reference range) has been observed in the majority of affected individuals to date. Note: Individuals with isolated neutropenia may have normal urine 3-MGA levels.

Imaging Findings

Initial brain MRI is often unremarkable; however, during infancy, progressive cerebral and cerebellar atrophy are seen on follow-up MRI in the majority of affected individuals [Wortmann et al 2015] (full text).

Establishing the Diagnosis

The diagnosis of CLPB deficiency **is established** in a proband with one or more suggestive findings and/or ONE of the following identified on molecular genetic testing (see Table 1):

- Biallelic *CLPB* pathogenic (or likely pathogenic) variants
- A heterozygous *CLPB* pathogenic (or likely pathogenic) variant associated with autosomal dominant CLPB deficiency (See Genotype-Phenotype Correlations.)

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

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel, single-gene testing) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a mild phenotype indistinguishable from many other inherited disorders with intellectual disability and neurologic findings or neutropenia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of CLPB deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *CLPB* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected; to date such variants have not been identified as a cause of this disorder.

  Note: Targeted analysis for c.803C>T, a known founder variant, can be performed first in individuals of Inuit ancestry (see Table 7).

- **A multigene panel** that includes *CLPB* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by intellectual disability and neurologic findings and/or neutropenia **comprehensive genomic testing,** which does not require the clinician to determine which gene is likely involved, is the best option. **Exome sequencing** is most commonly used; **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 CLPB Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CLPB	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Capo-Chichi et al [2015], Kanabus et al [2015], Saunders et al [2015], Wortmann et al [2015], Kiykim et al [2016], Pronicka et al [2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

Clinical Characteristics

Clinical Description

The clinical phenotype of CLPB deficiency ranges from severe to mild as determined by neurologic involvement and neutropenia. Children with neonatal onset or early-infantile onset have severe involvement and may die from complications of their disease, whereas those with late-infantile and early-childhood onset have a milder clinical presentation [Pronicka et al 2017].

To date a total of 32 individuals from 16 families with biallelic *CLPB* pathogenic variants have been reported in the literature (n=14 [Wortmann et al 2015], n=5 [Pronicka et al 2017], n=5 [Saunders et al 2015], n=4 [Capo-Chichi et al 2015], n=2 [Kanabus et al 2015], and n=1 [Kiykim et al 2016]). Most have been identified as neonates; all were symptomatic by early childhood.

Autosomal dominant CLPB deficiency has been reported in 16 probands (from 16 families) with severe to mild phenotypes [Wortmann et al 2021, Warren et al 2022].

Table 2. CLPB Deficiency: Frequency of Select Features

Feature	Proportion of Persons w/Feature		Comment
	AR CLPB deficiency	AD CLPB deficiency [1]	
Prenatal manifestations	17/32	Unknown	Polyhydramnios, fetal contractures, IUGR
Altered muscle tone	28/32	5/16	
Movement disorder	20/32	0/16	
Seizures	18/32	7/16	
Brain atrophy	14/32	4/16	
DD/ID	22/26 [2]	7/16	
Neutropenia	26/32	15/16	
Cataracts	17/32	2/16	
Elevated urinary 3-MGA	32/32	6/16	

3-MGA = 3-methylglutaconic acid; AD = autosomal dominant; AR = autosomal or recessive; DD = developmental delay; ID = intellectual disability; IUGR = intrauterine growth restriction

1. Autosomal dominant CLPB deficiency is caused by specific heterozygous *CLPB* pathogenic variants (see Genotype-Phenotype Correlations).

2. Early demise of individuals with autosomal recessive CLPB deficiency may prevent identification of developmental delay / intellectual disability.

Severe Phenotype

Neurologic. Affected infants come to attention at birth with significant neurologic involvement that can include hyperekplexia or absence of voluntary movements, hypotonia or hypertonia, swallowing problems, respiratory insufficiency, microcephaly, and epileptic seizures (with a burst suppression pattern on EEG). All affected infants require neonatal intensive care.

These infants show no motor or intellectual development, and generally die in the first months of life.

Retrospectively, many mothers of infants with the severe phenotype reported issues during the pregnancy, including decreased or increased fetal movements and intrauterine growth restriction [Pronicka et al 2017].

Neutropenia. All infants with the severe phenotype had chronic, severe congenital neutropenia (absolute neutrophil count [ANC] <500 per mm^3) associated with life-threatening infections. Several affected infants progressed to a myelodysplastic syndrome / leukemia-like condition within the first months of life.

Cataracts. While many, but not all, individuals with CLPB deficiency have bilateral congenital or infantile cataracts, their presence is not associated with the severity of the neurologic involvement or neutropenia.

Moderate Phenotype

Neurologic. The neonatal course is often complicated by adaptive problems in the broadest sense as well as neurologic abnormalities that are comparable to but less severe than those observed in the severe phenotype (e.g., hypotonia and feeding problems).

Subsequent neurologic involvement varies. In many with neonatal onset, generalized hypotonia progresses during childhood to spasticity (mainly of the legs). Many have an infantile-onset progressive movement disorder that can include ataxia, dystonia, or dyskinesia of varying severity. Several individuals have epileptic seizures that can be difficult to treat. All but two have intellectual disability that ranges from mild learning disability to very limited development of all cognitive and motor functions.

Neutropenia with variable ANC is common. Some affected individuals are only neutropenic during infections, and some have recurrent (although not life-threatening) infections, including in the neonatal period.

Growth. Linear growth is unremarkable; feeding problems are common and often lead to poor weight gain.

Other. Many individuals had biochemical evidence of endocrine abnormalities (e.g., hypothyroidism, premature ovarian failure / hypergonadotropic hypogonadism).

Mild Phenotype

Mildly affected individuals show only some clinical signs and symptoms without progression and survive without significant disease burden into adulthood.

Neurologic. There is no neurologic involvement; intellect is normal.

Neutropenia is mild and intermittent without increased risk of infection.

Other findings. Nephrocalcinosis and renal cysts without associated medical complications have been described in two individuals with the mild phenotype [Kanabus et al 2015].

Genotype-Phenotype Correlations

Individuals with the most severe phenotypes often have pathogenic variants predicted to lead to the complete absence of functional protein.

Autosomal dominant CLPB deficiency has been reported in six individuals with the following pathogenic variants: c.1211A>C (p.Lys404Thr), c.1280C>T (p.Pro427Leu), c.1678G>A (p.Gly560Arg), and c.1681C>T (p.Arg561Trp); phenotype varied from severe to mild. These variants disturb refoldase and to a lesser extent ATPase activity of CLPB in a dominant-negative manner. Urinary excretion of 3-methylglutaconic acid (3-MGA) was elevated in all six individuals assessed [Wortmann et al 2021].

Six different heterozygous *CLPB* pathogenic variants, c.1163C>A (p.Thr388Lys), c.1488T>A (p.Asn496Lys), c.1669G>A (p.Glu557Lys), c.1681C>G (p.Arg561Gly), c.1682G>A (p.Arg561Gln), and c.1858C>T (p.Arg620Cys), were identified in ten unrelated individuals with congenital neutropenia with or without neurologic features and/or cataracts. Urinary excretion of 3-MGA was not elevated in the five individuals in

whom it was assessed. All six pathogenic variants were near the C-terminal ATP-binding domain and were predicted to interact with the ATP-binding pocket [Warren et al 2022].

Prevalence

CLPB deficiency is rare. A total of 32 individuals with autosomal recessive CLPB deficiency have been reported to date (n=14 [Wortmann et al 2015], n=5 [Pronicka et al 2017], n=5 [Saunders et al 2015], n=4 [Capo-Chichi et al 2015], n=2 [Kanabus et al 2015], n=1 [Kiykim et al 2016]), and 16 individuals with autosomal dominant CLPB deficiency have been reported (n=10 [Warren et al 2022], n=6 [Wortmann et al 2021]). The affected individuals reported are of European, North American, and Asian ancestry.

In the largely Inuit population of Greenland the carrier frequency of the c.803C>T variant (associated with autosomal recessive CLPB deficiency) was determined to be 3.3% - comparable to carrier frequencies of other founder variants in Greenland [Saunders et al 2015].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Table 3. Disorders to Consider in the Differential Diagnosis of CLPB Deficiency

Discriminating Feature	Gene(s)	Disorder	MOI	Additional Hallmarks [1] of Disorder
3-MGA-uria [2]	*AGK*	AGK defect (Sengers syndrome) (See DNA mtDNA Maintenance Defects Overview.)	AR	Characteristic combination of bilateral cataracts, hypertrophic cardiomyopathy, & no to mild ID. Can be lethal in neonatal period but survivors to adulthood w/mild involvement are known.
	AUH	AUH defect (3-methylglutaconyl-CoA hydratase deficiency) (OMIM 250950)	AR	Adult-onset progressive spasticity & dementia w/characteristic slowly developing radiologic picture of extensive leukoencephalopathy [3]. Uniquely distinguished by ↑ urinary excretion of 3-HIVA.
	DNAJC19	DNAJC19 defect (DCMA syndrome) (OMIM 610198)	AR	Characteristic combination of childhood-onset dilated cardiomyopathy, non-progressive cerebellar ataxia, testicular dysgenesis, growth failure
	OPA3	OPA3 defect (See Costeff Syndrome.)	AR	In infants: optic atrophy & movement disorder (ataxia or extrapyramidal disorder)
	SERAC1	MEGD(H)EL syndrome (See SERAC1 Deficiency.)	AR	Neonatal hypoglycemia & liver failure [4]. In 2nd yr of life: progressive SNHL & neurologic manifestations (truncal hypotonia, spasticity of limbs, dystonia, severe ID/DD, Leigh syndrome-like findings on MRI).

Table 3. continued from previous page.

Discriminating Feature	Gene(s)	Disorder	MOI	Additional Hallmarks [1] of Disorder
	TAFAZZIN (formerly *TAZ*)	TAZ defect (See Barth syndrome.)	XL	In affected males: growth delay in infancy, cardiomyopathy (left ventricular noncompaction), neutropenia, myopathy, typical facial features, hypocholesterolemia, & cognitive phenotype
	TMEM70	TMEM70 defect (OMIM 614052)	AR	No specific syndromic presentation to date. Typically in neonates: hyperammonemia, lactic acidosis, muscular hypotonia, hypertrophic cardiomyopathy, psychomotor retardation. In those surviving neonatal period: DD.
	Unknown	Not otherwise specified 3-MGA-uria (former 3-MGCA 4)		Normal 3-methylglutaconyl-CoA hydratase enzyme activity & no defect in *TAFAZZIN*, *OPA3*, *SERAC1*, *TMEM70*, *DNAJC5*, *AUH*, or *AGK*
Congenital neutropenia & cyclic neutropenia	*ELANE*	*ELANE*-related neutropenia	AD	Isolated neutropenia; no involvement of CNS or other organs
	G6PC3	G6PC3 deficiency	AR	Presence of cardiovascular &/or urogenital abnormalities
	GATA1	*GATA1*-related X-linked cytopenia	XL	Typical presentation in affected males: bleeding disorder & anemia; neutropenia occurs later
	DNAJC21 *EFL1* *SBDS* *SRP54*	Shwachman-Diamond syndrome	AR AD [5]	Intestinal malabsorption due to exocrine pancreatic dysfunction
	WAS	X-linked severe congenital neutropenia (See *WAS*-Related Disorders.)	XL	Isolated neutropenia; no involvement of CNS or other organs

Table 3. continued from previous page.

Discriminating Feature	Gene(s)	Disorder	MOI	Additional Hallmarks [1] of Disorder
Hyperekplexia	*ARHGEF9*	Early-infantile epileptic encephalopathy 8 (OMIM 300607)	XL	
	GLRA1 *GLRB* *SLC6A5*	Hereditary hyperekplexia	AD AR [6]	Generalized stiffness immediately after birth normalizes in 1st yrs of life. Unexpected (esp auditory) stimuli cause excessive startle reflex (eye blinking, flexor spasm of the trunk), followed by short period of generalized stiffness in which voluntary movements are impossible. Neutropenia/severe infections, respiratory insufficiency, & swallowing problems are not seen in neonates; affected persons improve over time.
	GPHN	Molybdenum cofactor deficiency, complementation group C (See Molybdenum Cofactor Deficiency.)	AR	

3-HIVA = 3-hydroxyisovaleric acid; 3-MGA = 3-methylglutaconic acid; AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; mtDNA = mitochondrial DNA; SNHL = sensorineural hearing loss; XL = X-linked

1. In addition to discriminative feature shown in column 1

2. Increased urinary excretion of 3-MGA, known as 3-methylglutaconic aciduria (3-MGA-uria), is a relatively common finding in children investigated for suspected inborn errors of metabolism [Wortmann et al 2013]. Click here (pdf) for information on classification of inborn errors of metabolism in which 3-methylglutaconic aciduria is a discriminative feature.

3. Wortmann et al [2010]

4. Sarig et al [2013]

5. Shwachman-Diamond syndrome (SDS) caused by pathogenic variants in *DNAJC21*, *EFL1*, or *SBDS* is inherited in an autosomal recessive manner. SDS caused by pathogenic variants in *SRP54* is inherited in an autosomal dominant manner.

6. Hereditary hyperekplexia caused by pathogenic variants in *GLRA1* or *GLRB* is inherited in an autosomal recessive or (less commonly) an autosomal dominant manner. Hereditary hyperekplexia caused by pathogenic variants in *SLC6A5* is usually inherited in an AR manner (AD inheritance reported in 1 family).

Management

No clinical practice guidelines for CLPB deficiency have been published.

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with CLPB Deficiency

System/Concern	Evaluation	Comment
Neurologic	• Complete physical & neurologic exam • Brain MRI	
	• Complete eval of feeding & diet to determine need for tube feeding or gastrostomy • Eval of excessive drooling to determine if ↑ risk of aspiration &/or dehydration	For those w/significant neurologic problems

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education • Consider IQ testing in persons diagnosed at an older age.
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)
Immune function	ANC to determine need for G-CSF treatment.	
Eyes	Complete ophthalmologic exam to evaluate for cataracts	
Endocrine function	TSH to assess thyroid function	
	Eval of ovarian function per endocrinologist &/or gynecologist	In females beginning at age 10 yrs
Renal	Renal ultrasound exam to assess for nephrocalcinosis &/or cysts	In all persons at diagnosis incl infants
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of CLPB deficiency 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.	For those diagnosed in infancy or childhood

ADL = activities of daily living; ANC = absolute neutrophil count; G-CSF = granulocyte-colony stimulating factor; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; TSH = thyroid-stimulating hormone
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment is supportive. Care is best provided by a multidisciplinary team including a metabolic pediatrician, pediatric neurologist, dietitian, and physical therapist when possible. No specific dietary or other metabolic treatment is available.

Table 5. Treatment of Manifestations in Individuals with CLPB Deficiency

Manifestation/Concern	Treatment	Considerations/Other
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 if clinical signs or symptoms of dysphagia
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Movement disorders	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices & disability parking placard.
Excessive drooling	Botulinum toxin injection in salivary glands, extirpation of saliva glands, &/or rerouting of glandular ducts [2]	
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Neutropenia	Subcutaneous G-CSF	To ↑ neutrophil counts & ↓ frequency of infections, esp in those w/mild or moderate phenotype [2]
	Standard immunizations per pediatric/adult guidelines to prevent infection	
	Consider HSCT in those presenting w/severe congenital neutropenia & w/o severe neurologic disease.	
Cataracts	Treatment per ophthalmologist	
Endocrine dysfunction	Treatment per endocrinologist	
Renal	Treatment per renal specialist	
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; G-CSF = granulocyte-colony stimulating factor; HSCT = hematopoietic stem cell transplant; 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.

1. SB Wortmann, personal communication

Developmental Delay / Intellectual Disability Management Issues

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

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

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

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

- IEP services:

- An IEP provides specially designed instruction and related services to children who qualify.
- IEP services will be reviewed annually to determine whether any changes are needed.
- Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
- Vision consultants should be a part of the child's IEP team to support access to academic material.
- PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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

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

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-

generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Surveillance

Table 6. Recommended Surveillance for Individuals with CLPB Deficiency

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & mvmt disorders.	At each visit
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Development	Monitor developmental progress & educational needs.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Neutropenia	White blood cell count w/differential	
Eyes	Ophthalmologic exam	Per ophthalmologist in those w/ cataracts
Endocrine	TSH to assess thyroid function	Annually
	Follow-up labs/assessment of gonadal function per endocrinologist &/or gynecologist	In females annually beginning at age 10 yrs
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy; TSH = thyroid-stimulating hormone

Agents/Circumstances to Avoid

Drugs potentially toxic to mitochondria (including chloramphenicol, aminoglycosides, linezolid, valproic acid, and nucleoside reverse transcriptase inhibitors) should be avoided.

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

CLPB deficiency associated with biallelic *CLPB* pathogenic variants is inherited in an autosomal recessive manner. CLPB deficiency associated with specific heterozygous *CLPB* pathogenic variants (see Genotype-Phenotype Correlations) is inherited in an autosomal dominant manner. To date, *CLPB* pathogenic variants reported in individuals with autosomal dominant CLPB deficiency have not been identified in individuals with autosomal recessive CLPB deficiency or in healthy carriers (e.g., parents and sibs of individuals with autosomal recessive CLPB deficiency).

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with biallelic *CLPB* pathogenic variants are presumed to be heterozygous for a *CLPB* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *CLPB* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) of pathogenic variants known to be associated with autosomal recessive CLPB deficiency are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *CLPB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of inheriting neither of the familial *CLPB* pathogenic variants.
- The clinical manifestations of CLPB deficiency are variable and may differ between sibs who inherit identical biallelic *CLPB* pathogenic variants.
- Heterozygotes (carriers) of pathogenic variants known to be associated with autosomal recessive CLPB deficiency are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Unless an affected individual's reproductive partner also has autosomal recessive CLPB deficiency or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *CLPB*.
- The c.803C>T founder variant has a carrier frequency of 3.3% in the Inuit population of Greenland (see Prevalence).

Other family members. Each sib of a heterozygous parent is at a 50% risk of being heterozygous for a *CLPB* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *CLPB* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- All individuals reported to date with autosomal dominant CLPB deficiency have the disorder as the result of a *de novo CLPB* 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 *CLPB* 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 may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with autosomal dominant CLPB deficiency may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- The clinical manifestations of CLPB deficiency are variable and may differ between sibs who inherit a *CLPB* pathogenic variant associated with autosomal dominant CLPB deficiency.
- If the *CLPB* pathogenic variant detected in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *CLPB* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be slightly greater than that of the general population because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a heterozygous *CLPB* pathogenic variant has a 50% chance of inheriting the *CLPB* pathogenic variant.

Other family members. Given that all probands with autosomal dominant CLPB deficiency reported to date have the disorder as a result of a *de novo CLPB* pathogenic variant, the risk to other family members is presumed to be low; however, if a parent has the *CLPB* 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 with CLPB deficiency or are carriers (or are at risk of being carriers) of autosomal recessive CLPB deficiency.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *CLPB* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CLPB deficiency are possible. Note: Because intrafamilial variability is observed in CLPB deficiency, the prenatal finding of one pathogenic variant (in families with autosomal dominant CLPB deficiency) or two pathogenic variants (in families with autosomal recessive CLPB deficiency) cannot be used to predict clinical manifestations or disease course.

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.

- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.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. CLPB Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
CLPB	11q13.4	Mitochondrial disaggregase	CLPB	CLPB

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 CLPB Deficiency (View All in OMIM)

616254	CASEINOLYTIC PEPTIDASE B; CLPB
616271	3-METHYLGLUTACONIC ACIDURIA, TYPE VIIB; MGCA7B

Molecular Pathogenesis

CLPB, a mitochondrial protein of poorly known function in human, is a member of the large AAA (ATPases associated with diverse cellular activities) protein superfamily. Members of this superfamily are involved in various processes, such as DNA replication and repair and protein disaggregation and refolding, and operate as part of dynein motors, as chelatases or proteases [Snider et al 2008]. CLPB has been shown to be involved in protein refolding [Mróz et al 2020].

Mechanism of disease causation. Loss of function

***CLPB*-specific laboratory technical considerations.** The canonic splice isoform of *CLPB*, NM_030813.5, consists of 17 exons. Three other isoforms (NM_001258392.2, NM_001258393.2, NM_001258394.2) result in a shorter open reading frame. NM_001258394.2 has more exons than NM_030813.5 resulting in a longer transcript; however, the resulting protein is shorter and has a different N terminus because an additional exon in NM_030813.5 (between exons 2 and 3) contains an alternate start codon. Until proven otherwise, molecular genetic testing should include all exons of all isoforms.

Table 7. Notable *CLPB* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_030813.6 NP_110440.1	c.803C>T	p.Thr268Met	Founder variant in Inuit of Greenland [Saunders et al 2015]
	c.1163C>A	p.Thr388Lys	See Genotype-Phenotype Correlations.
	c.1211A>C	p.Lys404Thr	
	c.1280C>T	p.Pro427Leu	
	c.1488T>A	p.Asn496Lys	
	c.1669G>A	p.Glu557Lys	
	c.1678G>A	p.Gly560Arg	
	c.1681C>G	p.Arg561Gly	
	c.1681C>T	p.Arg561Trp	
	c.1682G>A	p.Arg561Gln	
	c.1858C>T	p.Arg620Cys	

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

Author Notes

Dr SB Wortmann and Prof RA Wevers are interested in patients with elevated urinary excretion of 3-methylglutaconic acid. Combining the clinical, biochemical, and neuroradiologic findings of these patients, they are able to define homogeneous subgroups. Next-generation sequencing is then used to identify the underlying genetic disorders in these subgroups, followed by biochemical investigations to characterize the function of the affected protein.

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