U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Chan SHS, Nishino I. *CHKB*-Related Muscular Dystrophy. 2023 Mar 30. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

CHKB-Related Muscular Dystrophy

Synonym: Megaconial Congenital Muscular Dystrophy

Sophelia HS Chan, MD[1] and Ichizo Nishino, MD, PhD[2]

Created: March 30, 2023.

Summary

Clinical characteristics

CHKB-related muscular dystrophy (*CHKB*-MD), reported in 47 individuals to date, comprises congenital muscular dystrophy (CMD) (44 individuals) and adolescent-onset limb-girdle muscular dystrophy (LGMD) (3 individuals).

CMD: All affected children have developmental delay and speech delay; gross motor milestones are delayed with subsequent loss of ambulation over time. Most have intellectual disability of varying severity; some have no speech. Autism spectrum disorder or attention-deficit/hyperactivity disorder is common. Dilated cardiomyopathy, seen in 14 children, resulted in death from heart failure in five and cardiac transplantation in one. Seizures are seen in some individuals. Ichthyosis is common.

LGMD: Motor development is normal; all affected children start walking at the usual age. Two affected individuals presented with rhabdomyolysis. One had mild intellectual disability. Behavior abnormalities and dilated cardiomyopathy were not observed.

Diagnosis/testing

The diagnosis of *CHKB*-MD is established in a proband with suggestive findings and biallelic loss-of-function pathogenic variants in *CHKB* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no cure for *CHKB*-MD. Supportive care to improve quality of life, maximize function, and reduce complications typically involves multidisciplinary care by specialists in pediatric neurology, orthopedics, physical therapy, occupational therapy, developmental pediatrics, mental health, speech-language pathology, cardiology, dermatology, and clinical genetics.

Author Affiliations: 1 Division of Neurology, Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, LKS Faculty of Medicine, University of Hong Kong, Hong Kong SAR, China; Email: sophehs@hku.hk. 2 National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan; Email: nishino@ncnp.go.jp.

Surveillance: Evaluations to monitor existing findings and assess for the emergence of new findings/concerns are intended to promote development, mitigate comorbidities, and optimize function while maximizing quality of life.

Agents/circumstances to avoid: Avoid strenuous exercise and viral infections, which may exacerbate muscle weakness.

Genetic counseling

CHKB-MD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *CHKB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *CHKB* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

CHKB-Related Muscular Dystrophy: Phenotypic Spectrum [1, 2]
• Congenital muscular dystrophy (CMD) • Adolescent-onset limb-girdle muscular dystrophy (LGMD)

1. For other genetic causes of these phenotypes, see Differential Diagnosis.
2. No genotype-phenotype correlations for *CHKB*-related muscular dystrophy have been identified; individuals with the same biallelic *CHKB* pathogenic variants may present with CMD or adolescent-onset LGMD.

Diagnosis

No diagnostic criteria have been published for *CHKB*-related muscular dystrophy (*CHKB*-MD).

Suggestive Findings

CHKB-MD should be suspected in a proband with the following clinical, laboratory, and imaging findings and family history.

Clinical Findings

Congenital muscular dystrophy (CMD)

- Onset in infancy / early childhood of **significant muscle weakness**, especially affecting the proximal (limb-girdle muscles), that can include the following:
  - Hypotonia with head lag followed by inability to sit, stand, or walk
  - Delayed sitting and walking with waddling gait and positive Gower sign
  - Early loss of ambulation as weakness increases over time
  - Secondary scoliosis, hip subluxation, and joint contractures
- **Developmental delay / intellectual disability.** Ranges from mild to severe, with significant language impairment or no language development
- **Ichthyosis.** The skin is dry with fine white scaling that can be evident as early as birth, but is often recognized later, when the skin changes become more prominent in infancy, childhood, or adolescence. Skin involvement can be generalized or restricted to a small part of the body. The scalp, trunk, face, and forehead are most commonly involved.

Adolescent-onset limb-girdle muscular dystrophy (LGMD)

- **Mild limb-girdle muscle weakness** with waddling gait and positive Gower sign; secondary joint contractures
- Rarely presents as late-onset recurrent rhabdomyolysis triggered by strenuous exercise
- Intellectual disability (absent or mild)

***CHKB*-MD regardless of age of onset**

- **Behavioral issues.** Autistic features and/or behavioral problems such as attention-deficit/hyperactivity disorder; stereotypical hand movements
- **Cardiac involvement,** primarily dilated cardiomyopathy

Laboratory Findings

Serum creatine kinase (CK) levels. All individuals regardless of age of onset have elevated creatine kinase levels.

- Most commonly, levels are two to nine times the normal range.
- Less commonly, levels can be normal [Haliloglu et al 2015].
- During episodes of rhabdomyolysis, CK levels can be greater than 10,000 u/L [Brady et al 2016].

Imaging Findings

Brain MRI. Nonspecific changes in a few individuals included enlargement of cerebrospinal fluid spaces over cerebral convexities and lateral ventricles, thinning of the corpus callosum, delayed myelination, and cavum septum pellucidum [Mitsuhashi et al 2011b, Mitsuhashi & Nishino 2013, Haliloglu et al 2015, Bardhan et al 2021].

Brain MRS. Five of eight individuals had normal findings [Kutluk et al 2020, Bardhan et al 2021]. Abnormalities present in one individual each were significantly reduced choline-to-N-acetyl aspartate and choline-to-creatine ratios [Quinlivan et al 2013]; abnormal amino acid / lipid peaks [Haliloglu et al 2015]; and decreased choline-to-creatine peak [Haliloglu et al 2015].

Leg muscles [Quinlivan et al 2013, De Goede et al 2016, Chan et al 2020, Bardhan et al 2021]

- Thighs
  - Earliest involvement is in the posterior compartment [Bardhan et al 2021]; early involvement is also seen in the anterior compartment (quadriceps femoris) and the medial compartment (adductor magnus).
  - The adductor longus is relatively spared.
  - In advanced disease, extensive fatty replacement can occur.
- Calves. The extensor digitorum longus is relatively spared.

Muscle Histology

Although histologic findings on skeletal muscle biopsy are not necessary to consider when establishing the diagnosis of *CHKB*-MD, information is included here in the event that muscle biopsy was performed prior to molecular genetic testing (see Establishing the Diagnosis). All 38 of the 47 individuals reported with *CHKB*-MD who had a muscle biopsy showed mild dystrophic changes as well as the typical muscle histologic findings with megaconial features (i.e., peripheral accumulation of giant (enlarged) mitochondria in the muscle fibers with central depletion; see Nomenclature).

For information about muscle pathology and respiratory chain enzyme analysis, click here (pdf).

Family History

Family history is consistent with autosomal recessive inheritance (affected sibs and/or parental consanguinity). The absence of a known family history does not exclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *CHKB*-MD is established in a proband with suggestive findings and biallelic loss-of-function pathogenic (or likely pathogenic) variants in *CHKB* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. (2) Identification of biallelic *CHKB* variants of uncertain significance (or of one known *CHKB* pathogenic variant and one *CHKB* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) 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 (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing is an option when histologic findings on skeletal muscle biopsy reveal megaconial findings (see Suggestive Findings, Muscle Histology). Sequencing of *CHKB* detects small intragenic deletions/insertions and missense, nonsense, and splice site pathogenic variants. Typically, if only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications; however, to date no such variants have been identified as a cause of this disorder.

A myopathy/muscular dystrophy multigene panel that includes *CHKB* and other genes of interest (see Differential Diagnosis) 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. 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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. 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 *CHKB*-Related Muscular Dystrophy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CHKB	Sequencing analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported to date [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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. Nishino et al [1998], Mitsuhashi et al [2011b], Gutiérrez Ríos et al [2012], Mitsuhashi & Nishino [2013], Quinlivan et al [2013], Castro-Gago et al [2014], Cabrera-Serrano et al [2015], Haliloglu et al [2015], Oliveira et al [2015], Brady et al [2016], Castro-Gago et al [2016], De Fuenmayor-Fernández De La Hoz et al [2016], De Goede et al [2016], Vanlander et al [2016], Yis et al [2016], Marchet et al [2019], Chan et al [2020], Kutluk et al [2020], Bardhan et al [2021]
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 duplication.

Clinical Characteristics

Clinical Description

To date, 47 individuals have been identified with *CHKB*-related muscular dystrophy (*CHKB*-MD) [Gutiérrez Ríos et al 2012, Mitsuhashi & Nishino 2013, Quinlivan et al 2013, Castro-Gago et al 2014, Cabrera-Serrano et al 2015, Haliloglu et al 2015, Oliveira et al 2015, Brady et al 2016, Castro-Gago et al 2016, De Fuenmayor-Fernández De La Hoz et al 2016, De Goede et al 2016, Vanlander et al 2016, Yis et al 2016, Marchet et al 2019, Chan et al 2020, Kutluk et al 2020, Bardhan et al 2021].

Forty-four had congenital muscular dystrophy and three had adolescent-onset limb-girdle muscular dystrophy. The following description of the phenotypic features associated with *CHKB*-MD is based on these reports (see Table 2).

Table 2. *CHKB*-Related Muscular Dystrophy: Frequency of Select Features

Features	Phenotype	
	Congenital muscular dystrophy (n=44)	Limb-girdle muscular dystrophy (n=3)
Muscular dystrophy	• 11/44 were able to sit but not walk. • Of the 34 whose walking age was known, 8 walked at usual age & 26 were delayed. • 3 eventually lost ambulation.	• All started walking at usual age. • 2 had presented w/adolescent- or adult-onset rhabdomyolysis.
DD/ID	• All 44 had DD/ID. • 2 had borderline intellect; 42 had mild, moderate, or severe ID.	1 had mild ID.
Speech delay	Of the 43 whose level of speech was known, 40 had speech delay; 3 had no speech.	1 had selective mutism [1]

Table 2. continued from previous page.

Features	Phenotype	
	Congenital muscular dystrophy (n=44)	Limb-girdle muscular dystrophy (n=3)
ASD/ADHD	17 had ASD; 3 had ADHD.	Not observed
Ichthyosis	16 persons	
Dilated cardiomyopathy	• 14 had dilated cardiomyopathy, 5 of whom died of severe heart failure between ages 25 mos & 23 yrs. • 1 had a heart transplant at age 10 yrs & made a good recovery.	
Seizures	8 persons	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DD = developmental delay; ID = intellectual disability

1. A severe anxiety disorder manifesting as inability to speak in certain social situations

Congenital Muscular Dystrophy (CMD)

Muscle involvement. Floppiness after birth is common, and all children have delayed motor development. Some individuals could sit alone but could not stand or walk. Most of those who acquired ambulation started walking after age 18 months.

Children at the milder end of the spectrum of CMD started walking at the usual age, around age one year, and presented with limb-girdle muscular dystrophy before age three years. The weakness can become more apparent during puberty, causing difficulty with stairs or episodes of weakness during viral infection or intercurrent illness. Typically, Gower sign is present, with difficulty rising from the floor. Assistance is required getting from sitting to standing.

Lower-limb proximal weakness causes a broad-based waddling gait. The proximal and generalized muscle weakness often progresses over time, with some individuals losing independent ambulation. Facial weakness is rare [Chan et al 2020, Bardhan et al 2021].

Contractures, mostly at the knees and ankles due to the significant lower-limb weakness, are common [Haliloglu et al 2015, De Goede et al 2016, Yis et al 2016, Chan et al 2020, Bardhan et al 2021]. In contrast, secondary scoliosis and hip subluxation are rare [Chan et al 2020].

Muscle strength can fluctuate during febrile intercurrent illness or vaccination.

- One individual lost ambulation at age 21 years following acute life-threatening pancreatitis complicated by acute respiratory distress syndrome [Quinlivan et al 2013].
- Two individuals experienced temporary episodes of increased falling after an infection (upper respiratory tract infection in one and chickenpox in the other) [Quinlivan et al 2013]. One of these individuals also had had a transient loss of movement of one leg following routine vaccination during infancy [Quinlivan et al 2013].
- Another individual experienced increased weakness (including complete loss of motor skills) after viral or febrile intercurrent illnesses but fully recovered over several weeks [Cabrera-Serrano et al 2015].

Some individuals with truncal and limb muscle weakness develop scoliosis [Chan et al 2020, Bardhan et al 2021] and joint contractures.

Intellectual disability, a prominent clinical feature of CMD, ranges from mild to profound. Borderline intelligence, though uncommon, has been reported in two individuals [Castro-Gago et al 2014, Chan et al 2020]. Many individuals also have speech delay; some cannot communicate in words or have limited speech for communication.

Autism spectrum disorder (ASD). Many individuals with congenital muscular dystrophy also have ASD with significant language impairment. They often have social communication difficulties with brief eye contact, echolalia, empathy issues, repetitive motor mannerisms, and aggressive behavior. Some individuals with ASD also have stereotypical hand movements resembling a Rett syndrome-like presentation [Haliloglu et al 2015, Bardhan et al 2021].

Attention-deficit/hyperactivity disorder (ADHD). Some individuals with congenital muscular dystrophy were also reported to have aggressive behavior, attention deficits, and hyperactivity with impulsive behavior [Castro-Gago et al 2014, Haliloglu et al 2015, Kutluk et al 2020].

Ichthyosis. Many individuals with ichthyosis have dry skin and white scaling that can lead to pruritus and excoriation marks [Quinlivan et al 2013, Yis et al 2016, Bardhan et al 2021]. The ichthyosis can be diffused and generalized, affecting the trunk, face, and scalp, with relative sparing of the limbs, hands, and feet [Quinlivan et al 2013, Haliloglu et al 2015].

Dilated cardiomyopathy, identified in 14 individuals with CMD between early childhood and adulthood, is characterized by decreased left ventricular function [Mitsuhashi & Nishino 2013, Quinlivan et al 2013, Haliloglu et al 2015, Oliveira et al 2015, Vanlander et al 2016, Marchet et al 2019, Kutluk et al 2020].

One boy with dilated cardiomyopathy and severe heart failure was successfully rescued initially by a left ventricular assist device (LVAD), followed by heart transplantation at age 10 years. One year after transplantation, he was stable with normal biventricular function [Vanlander et al 2016].

The five individuals who died of complications of their cardiomyopathy included:

- A boy, diagnosed with dilated cardiomyopathy at age 21 months, who died at age 26 months from heart failure [Haliloglu et al 2015];
- A boy who died at age eight years following acute deterioration after gastrostomy surgery from previously undiagnosed dilated cardiomyopathy [Quinlivan et al 2013];
- A girl who died at age 10 years [Marchet et al 2019];
- Two individuals who died at ages 13 years and 23 years, respectively [Mitsuhashi & Nishino 2013].

Seizures. Eight individuals developed seizures with episodes of generalized convulsions [Mitsuhashi & Nishino 2013, Haliloglu et al 2015, Marchet et al 2019] or repeated unresponsive staring episodes with head turning and eye deviation [Gutiérrez Ríos et al 2012].

Other

- **Cardiac anomalies.** Three individuals were reported with patent ductus arteriosus, atrial septal defect, or mitral valve prolapse; however, it is unclear if these cardiac anomalies are related to *CHKB* variants [Mitsuhashi & Nishino 2013, Haliloglu et al 2015].
- **Sensorineural hearing loss.** One girl had mild left sensorineural hearing loss diagnosed before age five years [Chan et al 2020].
- **Other skin lesions.** Two sibs with ichthyosis also had nummular eczema [Yis et al 2016], one individual had atopic dermatitis [Haliloglu et al 2015], and another individual had psoriasis [Castro-Gago et al 2016]. It is unclear if these are related to *CHKB*-MD.
- **Feeding issues** requiring gastrostomy tube were reported in one child [Quinlivan et al 2013].

  One individual had recurrent abdominal pain and failure to gain weight [Quinlivan et al 2013], and another had acute pancreatitis [Quinlivan et al 2013]. As no other individuals with *CHKB*-MD have been reported to have these findings, it is not clear whether these are specifically associated with *CHKB*-MD.

Adolescent-Onset Limb-Girdle Muscular Dystrophy (LGMD)

The three individuals with this phenotype had normal motor development at a younger age and only presented in adolescence with mild walking difficulty due to limb-girdle muscle weakness [Brady et al 2016, De Fuenmayor-Fernández De La Hoz et al 2016].

Though uncommon, two sibs presented with late-onset rhabdomyolysis without prior significant weakness [Brady et al 2016].

- Following a febrile upper respiratory tract infection at age 16 years, the older sister presented with generalized myalgia and significantly increased limb weakness that required use of a wheelchair; she eventually recovered and was able to resume walking without assistance. Subsequently she had mild non-progressive limb-girdle muscle weakness; however, when she exercised, she had myalgia. She also had multiple episodes of rhabdomyolysis with myoglobinuria requiring hospitalization followed by extended recovery periods. The episodic worsening of her symptoms was often associated with acute illness.
- The younger brother, who also had had no prior significant clinical weakness, had postexercise myalgia starting at age 12 years [Genge et al 1995]. At the last report at age 36 years, he had had mild non-progressive limb-girdle muscle weakness, acceptable exercise tolerance, and one episode of rhabdomyolysis.

Cognitive ability is either unaffected [Brady et al 2016] or characterized by mild intellectual disability [De Fuenmayor-Fernández De La Hoz et al 2016].

Language performance can be normal [Brady et al 2016] or can manifest as selective mutism, a severe anxiety disorder in which the individual was unable to speak in certain social situations [De Fuenmayor-Fernández De La Hoz et al 2016].

Cardiomyopathy has not been observed.

To date, no deaths have been reported this group of individuals.

Genotype-Phenotype Correlations

No genotypic-phenotypic correlations for *CHKB*-MD have been identified.

Differing phenotypes in individuals of the same ethnicity who were homozygous for the same CHKB variant include the following:

- **c.598delC (p.Gln200ArgfsTer11).** The phenotypes of two unrelated girls of Chinese heritage homozygous for this variant spanned the clinical spectrum [Chan et al 2020]. Patient 1 had limb-girdle weakness, moderate intellectual disability, and autism spectrum disorder, and died suddenly of an unknown cause at age 10 years [Authors, personal communication]. Patient 2 had marked muscle weakness (with early loss of ambulation and early-onset scoliosis and hip subluxation) and borderline intelligence (IQ: 60-79), with normal cardiac function at age nine years.
- **c.677+1G>A.** Three unrelated individuals of Turkish heritage homozygous for this variant had different presentations. One was unable to walk and had moderate intellectual disability, whereas the other two had delayed walking. Of the two individuals who had delayed walking, one eventually lost ambulation at age 17 years and had severe intellectual disability, and the other had a static motor course and mild intellectual disability [Haliloglu et al 2015].
- **c.810T>A (p.Tyr270Ter).** The phenotypes of two boys of Spanish heritage from different families homozygous for this variant spanned the clinical spectrum. One had generalized weakness (i.e., inability to sit without support) and marked intellectual disability [Castro-Gago et al 2016], and the other had mild limb-girdle weakness and borderline intelligence [Castro-Gago et al 2014].

- **c.1031+1G>A.** Three unrelated individuals of Turkish heritage homozygous for this variant had different presentations. Two boys were unable to walk at ages two years and three years, respectively, whereas one girl able to walk at age 15 months [Haliloglu et al 2015].

Nomenclature

CHKB-related muscular dystrophy is also referred to as megaconial congenital muscular dystrophy because on histologic examination the mitochondria in the skeletal muscles of affected individuals are greatly enlarged (looking like "dabs" rather than points) and appear to be in the periphery of most fibers, leaving the central area empty. (The term "megaconial" means "giant mitochondria.")

Prevalence

The prevalence of *CHKB*-MD is not known. On the Orphanet website (www.orpha.net), the estimated prevalence is less than 1:1,000,000. To date, 47 affected individuals have been reported (see Clinical Description).

In 73 individuals from India with congenital muscular dystrophy, pathogenic variants in *CHKB* were identified in four families; thus, *CHKB*-MD accounted for 5.5% of this CMD cohort [Bardhan et al 2021].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Disorders of interest in the differential diagnosis of *CHKB*-related muscular dystrophy (*CHKB*-MD) are summarized in:

- Table 3. Muscular Dystrophies Associated with Neurobehavioral Disorders;
- Table 4. Limb-Girdle Muscular Dystrophies Associated with Cardiomyopathy;
- Table 5. Metabolic Disorders Associated with Recurrent Rhabdomyolysis.

Of note, none of the disorders listed in Tables 3, 4, and 5 are associated with peripheral accumulation of giant (enlarged) mitochondria in muscle fibers.

Table 3. Differential Diagnosis of *CHKB*-Related Muscular Dystrophy: Muscular Dystrophies Associated with Neurobehavioral Disorders

Gene	Disorder	MOI	Features of Differential Diagnosis	
			Similar to *CHKB*-MD	Distinguishing from *CHKB*-MD
B3GALNT2 [1] *GMPPB* [2] *POMGNT1* [3]	Alpha-dystroglycanopathy (muscle-eye-brain disease; Walker-Warburg syndrome)	AR	• Muscle weakness due to muscular dystrophy • ASD, cognitive impairment, & epilepsy are common.	• Structural eye & brain malformations • Moderately ↑ CK • Muscle biopsy shows loss of alpha-dystroglycan protein.

Table 3. continued from previous page.

Gene	Disorder	MOI	Features of Differential Diagnosis	
			Similar to *CHKB*-MD	Distinguishing from *CHKB*-MD
DMD	Duchenne muscular dystrophy [4] (See Dystrophinopathies.)	XL	• Muscle weakness due to muscular dystrophy • Language delay, DD, ASD, & ADHD are common. • Epilepsy can occur. • Dilated cardiomyopathy is common (although onset occurs in adolescence or early adulthood).	• Skeletal muscle weakness progresses more rapidly. • Much higher CK levels • Muscle biopsy shows loss of dystrophin protein.
DMPK	Myotonic dystrophy type 1 (congenital & classic DM1)	AD	• Significant hypotonia w/ weakness • ASD & cognitive impairment are common.	Weakness improved w/age in congenital DM1.

AD = autosomal dominant; ADHD = attention-deficit/hyperactivity disorder; AR = autosomal recessive; ASD = autism spectrum disorder; CK = creatine kinase; CMD = congenital muscular dystrophy; DD = developmental delay; DM1 = myotonic dystrophy type 1; MOI = mode of inheritance; XL = X-linked

1. D'haenens et al [2022]
2. Astrea et al [2018]
3. OMIM 606822
4. Fujino et al [2018], Pascual-Morena et al [2022]

Table 4. Differential Diagnosis of *CHKB*-Related Muscular Dystrophy: Limb-Girdle Muscular Dystrophies Associated with Cardiomyopathy

Gene	Disease	MOI	Features of Differential Diagnosis	
			Similar to *CHKB*-MD [1]	Distinguishing from *CHKB*-MD
DMD	Becker muscular dystrophy (See Dystrophinopathies.)	XL	Dilated cardiomyopathy (usually w/onset in adolescence or early adulthood) is common.	• Moderately ↑ CK • Cognition is generally spared. • Muscle biopsy shows loss of dystrophin protein.
DPM3	*DPM3*-related alpha-dystroglycanopathy (OMIM 612937)	AR	Dilated cardiomyopathy (usually in late teens or adulthood) is common.	• Moderately ↑ CK. • Abnormal N-glycosylation of serum proteins [2] • Muscle biopsy shows loss of alpha-dystroglycan protein.
FKRP	*FKRP*-related alpha-dystroglycanopathy [3]	AR	Dilated cardiomyopathy (usually adult onset) is common.	• Moderately ↑ CK • Muscle biopsy shows absent alpha-dystroglycan protein.
LAMA2	Late-onset *LAMA2* muscular dystrophy	AR	Epilepsy & dilated cardiomyopathy may occur.	• Moderately ↑ CK • White matter changes on brain MRI • Muscle biopsy shows loss of merosin protein.
LMNA	*LMNA*-related dystrophy (See Emery-Dreifuss Muscular Dystrophy.)	AD	Dilated cardiomyopathy is common.	Moderately ↑ CK

Table 4. continued from previous page.

Gene	Disease	MOI	Features of Differential Diagnosis	
			Similar to *CHKB*-MD [1]	Distinguishing from *CHKB*-MD
TTN	*TTN*-related LGMD [4]	AR	Dilated cardiomyopathy	Mildly to moderately ↑ CK

AD = autosomal dominant; AR = autosomal recessive; LGMD = limb-girdle muscular dystrophy; MOI = mode of inheritance; XL = X-linked
1. In addition to limb-girdle muscle weakness
2. See www-sciencedirect-com.eproxy.lib.hku.hk/topics/medicine-and-dentistry/blood-proteins.
3. Libell et al [2020]
4. Misaka et al [2019]

Table 5. Differential Diagnosis of *CHKB*-Related Muscular Dystrophy: Metabolic Disorders Associated with Recurrent Rhabdomyolysis

Gene	Disease	MOI	Features of Differential Diagnosis	
			Similar to *CHKB*-MD [1]	Distinguishing from *CHKB*-MD
AVADVL	Later-onset episodic myopathy w/ intermittent rhabdomyolysis (See Very Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency.)	AR	Myalgia & weakness	Prolonged rhabdomyolysis triggered by exercise, fasting, cold exposure, or fever
CPT2 [2]	Carnitine palmitoyltransferase II deficiency, myopathic form	AR	Myalgia	• No cardiac involvement • No sign of myopathy between attacks • Prolonged rhabdomyolysis triggered by exercise, fasting, cold exposure, or stress
PYGM [2]	Glycogen storage disease type V (McArdle disease)	AR	Myalgia & weakness	• No cardiac involvement • Exercise-induced rhabdomyolysis

AR = autosomal recessive; MOI = mode of inheritance
1. In addition to recurrent rhabdomyolysis
2. Gooch et al [2021]

Management

No clinical guidelines for *CHKB*-related muscular dystrophy (*CHKB*-MD) have been published.

Management should follow the Standard of Care Guidelines for congenital muscular dystrophy [Wang et al 2010].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CHKB*-MD, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with *CHKB*-Related Muscular Dystrophy

System/Concern		Evaluation	Comments
Neurologic complication	**Muscle weakness**	By neurologist	To incl assessment of muscle tone, muscle strength of upper & lower limbs, neck & trunk, & deep tendon reflexes for hypotonia & hypo-/areflexia that often occur w/muscle weakness
	Seizures		• EEG if seizures are a concern • Brain MRI for possible focal epileptic focus

Table 6. continued from previous page.

System/Concern	Evaluation	Comments
Musculoskeletal complications / Limitations on ADL	By physical medicine & rehab physician / PT & OT	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • PT to improve gross motor skills • OT to improve fine motor skills
	By orthopedist	To incl exam of: • Hips & x-ray for subluxation • Spine & x-ray for scoliosis • Joints for contractures
Developmental delay / Intellectual disability	By developmental pediatrician / clinical psychologist	To incl assessment of • Developmental performance • Adaptive & cognitive eval • Need for early intervention / special education support
Speech delay	By speech-language pathologist	To incl assessment of language & need for ongoing speech-language therapy
Behavioral issues	By developmental pediatrician &/or mental health professional	For persons age >12 months: screening for behavior concerns incl possible ASD, ADHD, &/or sleep disturbance
Ichthyosis	By dermatologist	As needed for skin lesions
Cardiomyopathy	By cardiologist	Assessment for possible cardiomyopathy
Hearing loss	By audiologist	• To assess degree & nature of hearing loss • To refer to otolaryngologist
Feeding issues	By dietitian / speech-language pathologist	• For dietary advice • For videofluoroscopic swallowing study • For referral to gastroenterologist
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *CHKB*-MD to facilitate medical & personal decision making
Family support & resources	Social support eval	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; PT = physical therapy; OT = occupational therapy

1. Medical geneticist, certified genetic counseling, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *CHKB*-MD.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in pediatric neurology, orthopedics, physical therapy,

occupational therapy, developmental pediatrics, mental health, speech-language pathology, cardiology, audiology, and clinical genetics (see Table 7).

Table 7. Treatment of Manifestations in Individuals with *CHKB*-Related Muscular Dystrophy

Manifestation/Concern	Treatment	Considerations/Others
Muscle weakness / Limitations on ADL	Physical medicine & rehab / PT & OT	• Incl stretching & training to avoid contractures & falls • Consider need for positioning & mobility devices, disability parking placard / permit card.
Seizures	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]
Scoliosis / Hip subluxation	Per treating orthopedist	Bracing as indicated by treating orthopedist; corrective surgery if indicated
Preoperation assessment	Per evaluating anesthesiologist	• Assess respiratory & cardiac status (w/attention to possible cardiomyopathy). • Malignant hyperthermia precautions given history of rhabdomyolysis in some persons
Developmental delay / Intellectual disability	Per evaluating developmental pediatrician / clinical psychologist	• Assess need for early intervention & referral for multidisciplinary specialists. • Assess need for early referral for special education support.
Speech development	Per treating speech-language pathologist	Consider eval for alternative means of communication for persons who have expressive language difficulties.
Behavioral issues	Standardized treatment w/behavioral therapy &/or medical treatment per experienced developmental pediatrician / mental health professional	Many medications may be effective to improve attention, hyperactivity, and emotional issues; none has been demonstrated effective specifically for this disorder.
Ichthyosis	Per treating dermatologist	Topical treatment for skin hydration & to ↓ scaling
Cardiomyopathy	Standardized treatment w/cardiac medication per experienced cardiologist	Many cardiac medications may be effective; none has been demonstrated effective specifically for this disorder.
Hearing loss	Hearing aids may be helpful per treating otolaryngologist.	Communication & hearing services through early intervention or school district
Feeding issues	• Dietary plan by dietitian • Feeding plan per treating gastroenterologist or feeding team	Consider gastrostomy feeding if oral feeding is unsafe.
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.	• Consider involvement in adaptive sports or Special Olympics. • Ongoing assessment of need for palliative care involvement &/or home nursing

ADL = activities of daily living; ASM = anti-seizure medication
1. Caregiver education on the disease state and medication use, including possible side effects

Surveillance

Surveillance recommendations – which include evaluations to monitor existing neurologic features and assess for the emergence of new findings/concerns – are intended to promote development, mitigate comorbidities, and optimize function while maximizing quality of life (see Table 8).

Table 8. Recommended Surveillance for Individuals with *CHKB*-Related Muscular Dystrophy

System/Concern	Evaluation	Frequency
Muscle weakness	Assess for progression of weakness.	Every 6-12 mos
Seizures	Assess response to medications.	Every 3-6 mos
Development	Monitor developmental progress & educational needs.	At each visit
Speech development	Assess for response to interventions & new manifestations	Every 6-12 mos
Behavioral	Behavioral assessment for response to therapy & any new findings	
Ichthyosis	Assess response to treatment & possible new changes.	
Cardiomyopathy	Cardiac assessment & monitoring	• Every 6 mos, if stable • Every 2-3 mos, if adjusting medications
Musculoskeletal complications / Limitations on ADL	• Physical medicine, OT/PT assessment of mobility, self-help skills • Orthopedics assessment for scoliosis &/or hip subluxation	Every 6-12 mos
Hearing loss	Audiologic assessment & monitoring	
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

ADL = activities of daily living

Agents/Circumstances to Avoid

Avoid strenuous exercise and viral infection, as in some affected individuals these may exacerbate muscle weakness.

Evaluation of Relatives at Risk

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

Pregnancy Management

Because of the small number of individuals reported to date with adolescent-onset LGMD, the risk of dilated cardiomyopathy in this milder phenotype is unknown. Nonetheless, it would be advisable for women of childbearing age who are considering pregnancy to undergo cardiac evaluation prior to becoming pregnant and to discuss pregnancy-related risks with her cardiologist and a high-risk obstetrician.

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

CHKB-related muscular dystrophy (*CHKB*-MD) – comprising congenital muscular dystrophy (CMD) and adolescent-onset limb-girdle muscular dystrophy (LGMD) – is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *CHKB* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *CHKB* 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 a 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) 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 *CHKB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- To date, individuals with *CHKB*-related CMD are not known to reproduce.
- Unless an individual with *CHKB*-related adolescent-onset LGMD has children with an affected individual or a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *CHKB*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CHKB* pathogenic variant.

Carrier Detection

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

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 carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CHKB* pathogenic variants have 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.

- **Cure CMD**

  Phone: 562-444-5656

  www.curecmd.org

- **Muscular Dystrophy Association (MDA) - USA**

  Phone: 833-275-6321

  www.mda.org

- **Muscular Dystrophy UK**

  United Kingdom

  Phone: 0800 652 6352

  musculardystrophyuk.org

- **Congenital Muscle Disease International Registry (CMDIR)**

  The CMDIR is a global partnership of patient advocacy organizations, researchers, and clinicians, all working toward the same goal: to find treatments for congenital muscle disease.

  CMDIR/Cure CMD

  www.cmdir.org

- **Human Disease Gene Website Series - Registry**

  CHKB

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. CHKB-Related Muscular Dystrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

CHKB	22q13.33	Choline/ethanolamine kinase	CHKB homepage - Leiden Muscular Dystrophy pages	CHKB	CHKB

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 CHKB-Related Muscular Dystrophy (View All in OMIM)

602541	MUSCULAR DYSTROPHY, CONGENITAL, MEGACONIAL TYPE; MDCMC
612395	CHOLINE KINASE, BETA; CHKB

Molecular Pathogenesis

Biallelic pathogenic variants in *CHKB* lead to the loss of function of choline kinase beta (the enzyme that catalyzes the first step in phosphatidylcholine biosynthetic pathway). The resulting decrease in cellular phosphatidylcholine content, especially in the mitochondrial membrane, seems to make mitochondria functionally defective and unable to use fatty acids for mitochondrial beta-oxidation [Tavasoli et al 2022], especially those in the center of the cells. Such dysfunctional mitochondria are eliminated by mitophagy, whereas the mitochondria remaining at the periphery of the myofibers are enlarged (most likely by a compensatory mechanism), thereby developing a "megaconial" appearance [Mitsuhashi et al 2011a, Mitsuhashi & Nishino 2011, Marchet et al 2019]. Such quantitative and functional loss of mitochondria impair cellular function in skeletal muscles, cardiac muscles, the brain, and possibly the skin as well.

Mechanism of disease causation. Loss of function of choline kinase beta, the enzyme encoded by *CHKB*.

Table 9. Notable *CHKB* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_005198.5 NP_005189.2	c.598delC	p.Gln200ArgfsTer11	See Genotype-Phenotype Correlations.
NM_005198.5	c.677+1G>A	--	
NM_005198.5 NP_005189.2	c.810T>A	p.Tyr270Ter	
NM_005198.5	c.1031+1G>A	--	

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 Sophelia HS Chan is a pediatric neurologist and researcher at the Paediatric Neurology Division, the Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, the University of Hong Kong. She studies rare neuromuscular diseases, including *CHKB*-related muscular dystrophy. She is the moderator for the *CHKB* page of the Human Disease Genes website.

Dr Ichizo Nishino is an adult neurologist and scientist at the National Institute of Neuroscience and National Center of Neurology and Psychiatry, Japan. His department serves as a diagnostic center for muscle diseases. He

and his team discovered *CHKB*-related megaconial congenital muscular dystrophy in 1998 and confirmed the genetic cause in 2006.

Acknowledgments

We would like to thank Prof Bert BA de Vries for including *CHKB* in the Human Disease Genes website.

References

Literature Cited

Astrea G, Romano A, Angelini C, Antozzi CG, Barresi R, Battini R, Battisti C, Bertini E, Bruno C, Cassandrini D, Fanin M, Fattori F, Fiorillo C, Guerrini R, Maggi L, Mercuri E, Morani F, Mora M, Moro F, Pezzini I, Picillo E, Pinelli M, Politano L, Rubegni A, Sanseverino W, Savarese M, Striano P, Torella A, Trevisan CP, Trovato R, Zaraieva I, Muntoni F, Nigro V, D'Amico A, Santorelli FM; Italian CMD Network. Broad phenotypic spectrum and genotype-phenotype correlations in GMPPB-related dystroglycanopathies: an Italian cross-sectional study. Orphanet J Rare Dis. 2018;26;13:170.

Bardhan M, Polavarapu K, Bevinahalli NN, Veeramani PK, Anjanappa RM, Arunachal G, Shingavi L, Vengalil S, Nashi S, Chawla T, Nagabushana D, Mohan D, Horvath R, Nishino I, Atchayaram N. Megaconial congenital muscular dystrophy secondary to novel CHKB mutations resemble atypical Rett syndrome. J Hum Genet. 2021;66:813–23. PubMed PMID: 33712684.

Brady L, Giri M, Provias J, Hoffman E, Tarnopolsky M. Proximal myopathy with focal depletion of mitochondria and megaconial congenital muscular dystrophy are allelic conditions caused by mutations in CHKB. Neuromuscul Disord. 2016;26:160–4. PubMed PMID: 26782016.

Cabrera-Serrano M, Junckerstorff RC, Atkinson V, Sivadorai P, Allcock RJ, Lamont P, Laing NG. Novel CHKB mutation expands the megaconial muscular dystrophy phenotype. Muscle Nerve. 2015;51:140–3. PubMed PMID: 25187204.

Castro-Gago M, Dacruz-Alvarez D, Pintos-Martínez E, Beiras-Iglesias A, Arenas J, Martín MÁ, Martínez-Azorín F. Congenital neurogenic muscular atrophy in megaconial myopathy due to a mutation in CHKB gene. Brain Dev. 2016;38:167–72. PubMed PMID: 26006750.

Castro-Gago M, Dacruz-Alvarez D, Pintos-Martínez E, Beiras-Iglesias A, Delmiro A, Arenas J, Martín MÁ, Martínez-Azorín F. Exome sequencing identifies a CHKB mutation in Spanish patient with megaconial congenital muscular dystrophy and mtDNA depletion. Eur J Paediatr Neurol. 2014;18:796–800. PubMed PMID: 24997086.

Chan SH, Ho RS, Khong PL, Chung BH, Tsang MH, Yu MH, Yeung MC, Chan AO, Fung CW. Megaconial congenital muscular dystrophy: Same novel homozygous mutation in CHKB gene in two unrelated Chinese patients. Neuromuscul Disord. 2020;30:47–53. PubMed PMID: 31926838.

De Fuenmayor-Fernández De La Hoz CP, Domínguez-González C, Gonzalo-Martínez JF, Esteban-Pérez J, Fernández-Marmiesse A, Arenas J, Martín MA, Hernández-Laín A. A milder phenotype of megaconial congenital muscular dystrophy due to a novel CHKB mutation. Muscle Nerve. 2016;54:806–8. PubMed PMID: 27169979.

De Goede C, Oh T, Joseph J, Muntoni F, Sewry C, Phadke R. Choline kinase beta-related muscular dystrophy, appearance of muscle involvement on magnetic resonance imaging. Pediatr Neurol. 2016;54:49–54. PubMed PMID: 26548592.

D'haenens E, Vergult S, Menten B, Dheedene A, Kooy RF, Callewaert B. Expanding the phenotype of B3GALNT2-related disorders. Genes (Basel). 2022;14;13:694.

Fujino H, Saito T, Matsumura T, Shibata S, Iwata Y, Fujimura H, Imura O. Autism spectrum disorders are prevalent among patients with dystrophinopathies. Neurol Sci. 2018;39:1279–82. PubMed PMID: 29594829.

Genge A, Karpati G, Arnold D, Shoubridge EA, Carpenter S. Familial myopathy with conspicuous depletion of mitochondria in muscle fibers: a morphologically distinct disease. Neuromuscul Disord. 1995;5:139–44. PubMed PMID: 7767093.

Gooch C, Dean SJ, Marzullo L. Repeatedly in rhabdomyolysis. Pediatr Emerg Care. 2021;37:e1759–e1760. PubMed PMID: 32205805.

Gutiérrez Ríos P, Kalra AA, Wilson JD, Tanji K, Akman HO, Area Gómez E, Schon EA, DiMauro S. Congenital megaconial myopathy due to a novel defect in the choline kinase Beta gene. Arch Neurol. 2012;69:657–61. PubMed PMID: 22782513.

Haliloglu G, Talim B, Sel CG, Topaloglu H. Clinical characteristics of megaconial congenital muscular dystrophy due to choline kinase beta gene defects in a series of 15 patients. J Inherit Metab Dis. 2015;38:1099–108. PubMed PMID: 26067811.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Kutluk G, Kadem N, Bektas O, Eroglu HN. A rare cause of autism spectrum disorder: megaconial muscular dystrophy. Ann Indian Acad Neurol. 2020;23:694–6. PubMed PMID: 33623274.

Libell EM, Richardson JA, Lutz KL, Ng BY, Mockler SRH, Laubscher KM, Stephan CM, Zimmerman BM, Edens ER, Reinking BE, Mathews KD. Cardiomyopathy in limb girdle muscular dystrophy R9, FKRP related. Muscle Nerve. 2020;62:626–32. PubMed PMID: 32914449.

Marchet S, Invernizzi F, Blasevich F, Bruno V, Dusi S, Venco P, Fiorillo C, Baranello G, Pallotti F, Lamantea E, Mora M, Tiranti V, Lamperti C. Alteration of mitochondrial membrane inner potential in three Italian patients with megaconial congenital muscular dystrophy carrying new mutations in CHKB gene. Mitochondrion. 2019;47:24–9. PubMed PMID: 30986505.

Misaka T, Yoshihisa A, Takeishi Y. Titin in muscular dystrophy and cardiomyopathy: urinary titin as a novel marker. Clin Chim Acta. 2019;495:123–8. PubMed PMID: 30959043.

Mitsuhashi S, Hatakeyama H, Karahashi M, Koumura T, Nonaka I, Hayashi YK, Noguchi S, Sher RB, Nakagawa Y, Manfredi G, Goto Y, Cox GA, Nishino I. Muscle choline kinase beta defect causes mitochondrial dysfunction and increased mitophagy. Hum Mol Genet. 2011a;20:3841–51. PubMed PMID: 21750112.

Mitsuhashi S, Ohkuma A, Talim B, Karahashi M, Koumura T, Aoyama C, Kurihara M, Quinlivan R, Sewry C, Mitsuhashi H, Goto K, Koksal B, Kale G, Ikeda K, Taguchi R, Noguchi S, Hayashi YK, Nonaka I, Sher RB, Sugimoto H, Nakagawa Y, Cox GA, Topaloglu H, Nishino I. A congenital muscular dystrophy with mitochondrial structural abnormalities caused by defective de novo phosphatidylcholine biosynthesis. Am J Hum Genet. 2011b;88:845–51. PubMed PMID: 21665002.

Mitsuhashi S, Nishino I. Phospholipid synthetic defect and mitophagy in muscle disease. Autophagy. 2011;7:1559–61. PubMed PMID: 22024749.

Mitsuhashi S, Nishino I. Megaconial congenital muscular dystrophy due to loss-of-function mutations in choline kinase β. Curr Opin Neurol. 2013;26:536–43. PubMed PMID: 23945283.

Nishino I, Kobayashi O, Goto Y, Kurihara M, Kumagai K, Fujita T, Hashimoto K, Horai S, Nonaka I. A new congenital muscular dystrophy with mitochondrial structural abnormalities. Muscle Nerve. 1998;21:40–7. PubMed PMID: 9427222.

Oliveira J, Negrão L, Fineza I, Taipa R, Melo-Pires M, Fortuna AM, Gonçalves AR, Froufe H, Egas C, Santos R, Sousa M. New splicing mutation in the choline kinase beta (CHKB) gene causing a muscular dystrophy detected by whole-exome sequencing. J Hum Genet. 2015;60:305–12. PubMed PMID: 25740612.

Pascual-Morena C, Cavero-Redondo I, Reina-Gutiérrez S, Saz-Lara A, López-Gil JF, Martínez-Vizcaíno V. Prevalence of neuropsychiatric disorders in Duchenne and Becker muscular dystrophies: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2022;103:2444–53. PubMed PMID: 35839922.

Quinlivan R, Mitsuahashi S, Sewry C, Cirak S, Aoyama C, Mooore D, Abbs S, Robb S, Newton T, Moss C, Birchall D, Sugimoto H, Bushby K, Guglieri M, Muntoni F, Nishino I, Straub V. Muscular dystrophy with large mitochondria associated with mutations in the CHKB gene in three British patients: extending the clinical and pathological phenotype. Neuromuscul Disord. 2013;23:549–56. PubMed PMID: 23692895.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Tavasoli M, Lahire S, Sokolenko S, Novorolsky R, Reid SA, Lefsay A, Otley MOC, Uaesoontrachoon K, Rowsell J, Srinivassane S, Praest M, MacKinnon A, Mammoliti MS, Maloney AA, Moraca M, Pedro Fernandez-Murray J, McKenna M, Sinal CJ, Nagaraju K, Robertson GS, Hoffman EP, McMaster CR. Mechanism of action and therapeutic route for a muscular dystrophy caused by a genetic defect in lipid metabolism. Nat Commun. 2022;13:1559. PubMed PMID: 35322809.

Vanlander AV, Muiño Mosquera L, Panzer J, Deconinck T, Smet J, Seneca S, Van Dorpe J, Ferdinande L, Ceuterick-de Groote C, De Jonghe P, Van Coster R, Baets J. Megaconial muscular dystrophy caused by mitochondrial membrane homeostasis defect, new insights from skeletal and heart muscle analyses. Mitochondrion. 2016;27:32–8. PubMed PMID: 26855408.

Wang CH, Bonnemann CG, Rutkowski A, Sejersen T, Bellini J, Battista V, Florence JM, Schara U, Schuler PM, Wahbi K, Aloysius A, Bash RO, Béroud C, Bertini E, Bushby K, Cohn RD, Connolly AM, Deconinck N, Desguerre I, Eagle M, Estournet-Mathiaud B, Ferreiro A, Fujak A, Goemans N, Iannaccone ST, Jouinot P, Main M, Melacini P, Mueller-Felber W, Muntoni F, Nelson LL, Rahbek J, Quijano-Roy S, Sewry C, Storhaug K, Simonds A, Tseng B, Vajsar J, Vianello A, Zeller R, et al. Consensus statement on standard of care for congenital muscular dystrophies. J Child Neurol. 2010;25:1559–81. PubMed PMID: 21078917.

Yis U, Baydan F, Karakaya M, Hız Kurul S, Cirak S. Importance of skin changes in the differential diagnosis of congenital muscular dystrophies. Biomed Res Int. 2016;2016:3128735. PubMed PMID: 27123443.

License