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NLM Citation: du Souich C, Raymond FL, Grzeschik KH, et al. *NSDHL*-Related Disorders. 2011 Feb 1 [Updated 2018 Oct 25]. 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/

NSDHL-Related Disorders

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Created: February 1, 2011; Updated: October 25, 2018.

Summary

Clinical characteristics

The *NSDHL*-related disorders include: CHILD (*c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects) syndrome, an X-linked condition that is usually male lethal during gestation and thus predominantly affects females; and CK syndrome, an X-linked disorder that affects males.

- CHILD syndrome is characterized by unilateral distribution of ichthyosiform (yellow scaly) skin lesions and ipsilateral limb defects that range from shortening of the metacarpals and phalanges to absence of the entire limb. Intellect is usually normal. The ichthyosiform skin lesions are usually present at birth or in the first weeks of life; new lesions can develop in later life. Nail changes are also common. The heart, lung, and kidneys can also be involved.
- CK syndrome (named for the initials of the original proband) is characterized by mild to severe cognitive impairment and behavior problems (aggression, attention deficit hyperactivity disorder, and irritability). All affected males reported have developed seizures in infancy and have cerebral cortical malformations and microcephaly. All have distinctive facial features, a thin habitus, and relatively long, thin fingers and toes. Some have scoliosis and kyphosis. Strabismus is common. Optic atrophy is also reported.

Diagnosis/testing

The diagnosis of CHILD syndrome is established in a proband by identification of an *NSDHL* pathogenic variant that results in loss of functional NSDHL protein. The diagnosis of CK syndrome is established in a proband by identification of a "hypomorphic" *NSDHL* pathogenic variant that results in partial loss of functional NSDHL protein.

Management

Treatment of manifestations:

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- *CHILD syndrome.* No one therapy described to date appears to ameliorate the cutaneous findings for every reported individual with CHILD syndrome. Lactic acid 12% skin creams or lotions can reduce itching, and urea skin creams can reduce dryness. Treatment of an inflammatory nevus by grafting skin obtained from a contralateral unaffected region has been successful. Oral aromatic retinoids (etretinate) used to ameliorate cutaneous symptoms have been found to be of limited use and not well tolerated. Topical statins may be beneficial for the treatment of inflammatory nevus. Scoliosis and joint contractures are treated with braces and/or corrective surgery.
- *CK syndrome.* Behavior modification and/or drug therapy to control aggression and help with ADHD symptoms; anti-seizure medication to control seizures.

Surveillance:

- *CHILD syndrome.* Monitoring for new cutaneous lesions and musculoskeletal deformities such as scoliosis and joint contractures.
- *CK syndrome.* Monitoring for the effectiveness of AEDs in controlling seizures and for the development of scoliosis/kyphosis.

Genetic counseling

The *NSDHL*-related disorders are inherited in an X-linked manner. No affected male has reproduced.

- CHILD syndrome is usually male lethal during gestation. Affected females have a 50% chance of transmitting the *NSDHL* pathogenic variant in each pregnancy; however, the expected live-born distribution of persons at risk for CHILD syndrome is 33% unaffected females, 33% affected females, and 33% unaffected males.
- CK syndrome is diagnosed in males. Heterozygous females have a 50% chance of transmitting the *NSDHL* pathogenic variant in each pregnancy; males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will have normal physical features, intellect, and brain imaging but may display behavioral problems such as irritability and aggression.

Testing of at-risk female relatives and prenatal testing for pregnancies at increased risk for an *NSDHL*-related disorder are possible if the pathogenic variant has been identified in the family.

GeneReview Scope

NSDHL-Related Disorders: Included Phenotypes [1]
• CHILD syndrome • CK syndrome

For synonyms and outdated names see Nomenclature.
1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

An *NSDHL*-related disorder **should be suspected** in an individual with features of CHILD (*c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects) syndrome (typically in females) and CK syndrome (intellectual disability and associated features in males; CK = initials of the original proband) as follows.

CHILD syndrome

- Unilateral distribution of ichthyosiform nevus

- Limb defects ipsilateral to the skin lesions
- Punctate calcifications of cartilaginous structures
- Visceral malformations
- Central nervous system anomalies

CK syndrome [du Souich et al 2009, McLarren et al 2010, Preiksaitiene et al 2015]

- Central nervous system (CNS) findings: mild to severe intellectual disability, microcephaly, cerebral cortical malformations, spasticity, and seizures
- Characteristic craniofacial features: almond-shaped and upslanted palpebral fissures, prominent nasal bridge, high arched palate, crowded dentition, micrognathia, and plagiocephaly
- Asthenic habitus

Establishing the Diagnosis

Male proband. The diagnosis of an *NSDHL*-related disorder **is established** in a male proband with the identification of a hemizygous pathogenic variant in *NSDHL* by molecular genetic testing (see Table 1).

Female proband. The diagnosis of an *NSDHL*-related disorder **is usually established** in a female proband with the identification of a heterozygous pathogenic variant in *NSDHL* by molecular genetic testing (see Table 1).

Note: Animal models show that male conceptuses with a severe *NSDHL* loss-of-function allele die early in gestation, explaining the fact that with few exceptions individuals with CHILD syndrome are female [Bornholdt et al 2005, Bittar et al 2006].

Identification of a "hypomorphic" *NSDHL* pathogenic variant that results in partial loss of functional NSDHL protein confirms the diagnosis of CK syndrome [McLarren et al 2010].

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, exome array) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *NSDHL*-related disorders is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *NSDHL*-related disorders has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *NSDHL* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *NSDHL* 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the diagnosis of *NSDHL*-related disorders is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. **Exome array** (when clinically available) may be considered if exome sequencing is not diagnostic.

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 *NSDHL*-Related Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
NSDHL	Sequence analysis [3]	45/51 [4]
	Gene-targeted deletion/duplication analysis [5]	6/51 [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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. Extrapolated from Bornholdt et al [2005], Mi et al [2015], Preiksaitiene et al [2015], Yu et al [2018]
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. Deletion of the gene or of multiple exons has been reported [Bornholdt et al 2005, Kim et al 2005, Yu et al 2018] only in individuals with CHILD syndrome.

Clinical Characteristics

Clinical Description

CHILD Syndrome

CHILD syndrome (Figure 1) is characterized by unilateral distribution of ichthyosiform skin lesions and ipsilateral limb defects (see Bornholdt et al [2005] for a summary of features). The skin and skeletal involvement can be right-sided (seen in ~2/3 of individuals), left-sided, or bilateral [König et al 2002, Hummel et al 2003, Mi et al 2015]. Based on mouse studies and family observation, CHILD-associated *NSDHL* pathogenic variants are usually lethal to males during gestation.

Early death of affected females is usually the result of cardiovascular malformations.

A few males with CHILD syndrome have been reported [Zellweger & Uehlinger 1948, Happle et al 1996]. The male reported by Happle et al [1996] had the typical skin findings seen in females with CHILD syndrome and

was developmentally normal. He was mosaic for the c.262C>T (p.Arg88Ter) pathogenic variant in *NSDHL* [Bornholdt et al 2005].

Dermatologic findings

- **Ichthyosiform nevus.** The hallmark of CHILD syndrome is the presence of ichthyosiform skin lesions with yellow scales and a sharp demarcation in the midline of the body. The initial ichthyosiform skin lesions are evident at birth or in the first weeks of life; new lesions may develop in later life [Happle et al 1980]. The face is usually spared; scalp alopecia has been reported [Hummel et al 2003]. Most skin lesions improve spontaneously, but some can cause lifelong morbidity. Other skin lesions can develop after infancy at sites of injury such as a surgical wound.

  Histologically the skin lesions exhibit hyperkeratosis, parakeratosis, and acanthosis as well as inflammatory and lipid-laden infiltrates within the dermal papillae [Hebert et al 1987, Hashimoto et al 1995]. The skin lesions from persons with *NSDHL* pathogenic variants can be distinguished histologically and biochemically from those with chondrodysplasia punctata 2, X-linked, in which unilateral skin and skeletal lesions can occur.

  Occasionally, heterozygous females present with comparatively minor skin lesions such as Blaschko-linear inflammatory scaly lesions, patchy alopecia, or nail changes. Regardless, the specific finding of an ichthyosiform nevus should always raise the possibility of heterozygosity for an *NSDHL* pathogenic variant. In some females, an ichthyosiform nevus can be present without any associated symptoms of CHILD syndrome in a woman at risk of having a daughter with typical CHILD syndrome [Happle et al 1995]. The relative severity of disease in studied organs reflects the skewing of X-chromosome inactivation [König, unpublished results].

- **Verruciform xanthoma-like lesions.** Although rare, these types of lesions were reported in a girl age nine years with CHILD syndrome harboring a large deletion of *NSDHL* exons 3 and 4 [Yu et al 2018].

- **Nails.** Onychodystrophy and periungual hyperkeratosis are common.

Skeletal features

- **Limbs.** Ipsilateral hypoplasia of the limbs varies from shortening of metacarpals and phalanges to absence of the entire limb [Happle et al 1980]. Incomplete development or absence of vertebrae, ribs, and long bones has also been reported [Bornholdt et al 2005].
- **Other skeletal defects** (generally evident in infancy) include scoliosis and joint contractures.
- **Punctate calcifications of cartilaginous structures.** Unilateral punctate epiphyseal calcifications in the pelvis, ribs, vertebrae, and extremities have been reported [Happle et al 1980] and are usually seen in the affected limb or body part [Hashimoto et al 1995, Hummel et al 2003]. These can be visible on x-ray examination in infancy. In one child, the punctate calcifications were reported to have disappeared completely by age two years [Happle et al 1980]; however, it is not known whether this is the case for every affected child. Ipsilateral stippling has also been observed in the sella turcica and the laryngeal, nasal, and thyroid cartilage [Happle et al 1980, Grange et al 2000].

Other structural anomalies

- **CNS anomalies** include unilateral hypoplasia or underdevelopment of the brain, lissencephaly type II, and cerebellar malformation [Tang & McCreadie 1974, Schmidt-Sidor et al 2008]. Hypoplasia of cranial nerves V, VII, VIII, IX, and X and the spinal cord was identified on autopsy in the same individual reported by Tang & McCreadie [1974]. The individual reported by Schmidt-Sidor et al [2008] showed multiple left-sided brain anomalies as a consequence of disturbances in proliferation and migration. The Virchow-

Robin spaces of the left parietal lobe were locally enlarged in an affected female reported by Yu et al [2018].

Intellect is usually normal; some reported individuals have intellectual disability [Baden & Rex 1970].

- **Heart defects** include septal defects [König et al 2002], unilateral ventricle [Falek et al 1968], and a single coronary ostium [Tang & McCreadie 1974].
- **Lung hypoplasia,** observed in several individuals [Tang & McCreadie 1974, Bornholdt et al 2005], can cause respiratory compromise and death [Hummel et al 2003].
- **Renal findings** range from unilateral hydronephrosis to renal agenesis. The frequency of these is unknown.

Other findings. Reported additional findings include hearing loss, absence of facial muscles, and unilateral hypoplasia of the thyroid gland, adrenal glands, ovaries, and fallopian tubes [Happle et al 1980, König et al 2002]. Bilateral optic atrophy has been reported in one individual [Knape et al 2010], as have thrombocytosis and congenital bilateral dislocation of the hip [Chander et al 2010]. Small intestinal mucosal xanthoma was reported in an individual with CHILD syndrome [Ryan et al 2013].

CK Syndrome

CK syndrome (Figure 2) is an X-linked intellectual disability syndrome that affects males. Although 24 affected males from three unrelated families have been identified and fully evaluated, characterization of the syndrome remains limited.

Development. Affected males have mild to severe intellectual disability. Most cannot speak.

Behavior. Most manifest aggression, attention deficit hyperactivity disorder (ADHD), and irritability. These behaviors appear in infancy and early childhood. According to the Autism Diagnostic Review (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS), affected males do not fulfill the criteria for an autism spectrum disorder.

Neurologic findings. All affected males have developed seizures in infancy. These range from multiple daily episodes of brief unresponsiveness associated with staring and facial and/or limb twitching to prolonged generalized tonic-clonic seizures. These likely arise from cerebral cortical malformations which, by MRI examination, are most consistent with polymicrogyria (see Polymicrogyria Overview). Spasticity, tetraparesis, and development of contractures have also been reported.

Craniofacial. Affected males have a long thin face, plagiocephaly, almond-shaped and upslanted palpebral fissures, prominent nasal bridge, high palate, dental crowding, and micrognathia. The ears are normally shaped but rotated posteriorly.

Growth and skeletal. All affected males have microcephaly (<3 SD to <2 SD), a thin habitus, and relatively long, thin fingers and toes. Some have scoliosis and kyphosis. The height of affected individuals is average for parental heights.

Ocular findings. Strabismus is common. Optic atrophy is also seen.

Analyte testing associated with CHILD syndrome and CK syndrome

- When cultured in cholesterol-depleted medium, lymphoblastoid cells of individuals with CHILD syndrome and CK syndrome have increased levels of methyl- and carboxy-sterols and slightly decreased levels of cholesterol [Grange et al 2000, Hummel et al 2003, McLarren et al 2010].
- In individuals with CHILD syndrome, sterol analysis of skin flakes collected from an affected area show elevated levels of methyl- and carboxy-sterols [RI Kelley, personal communication].

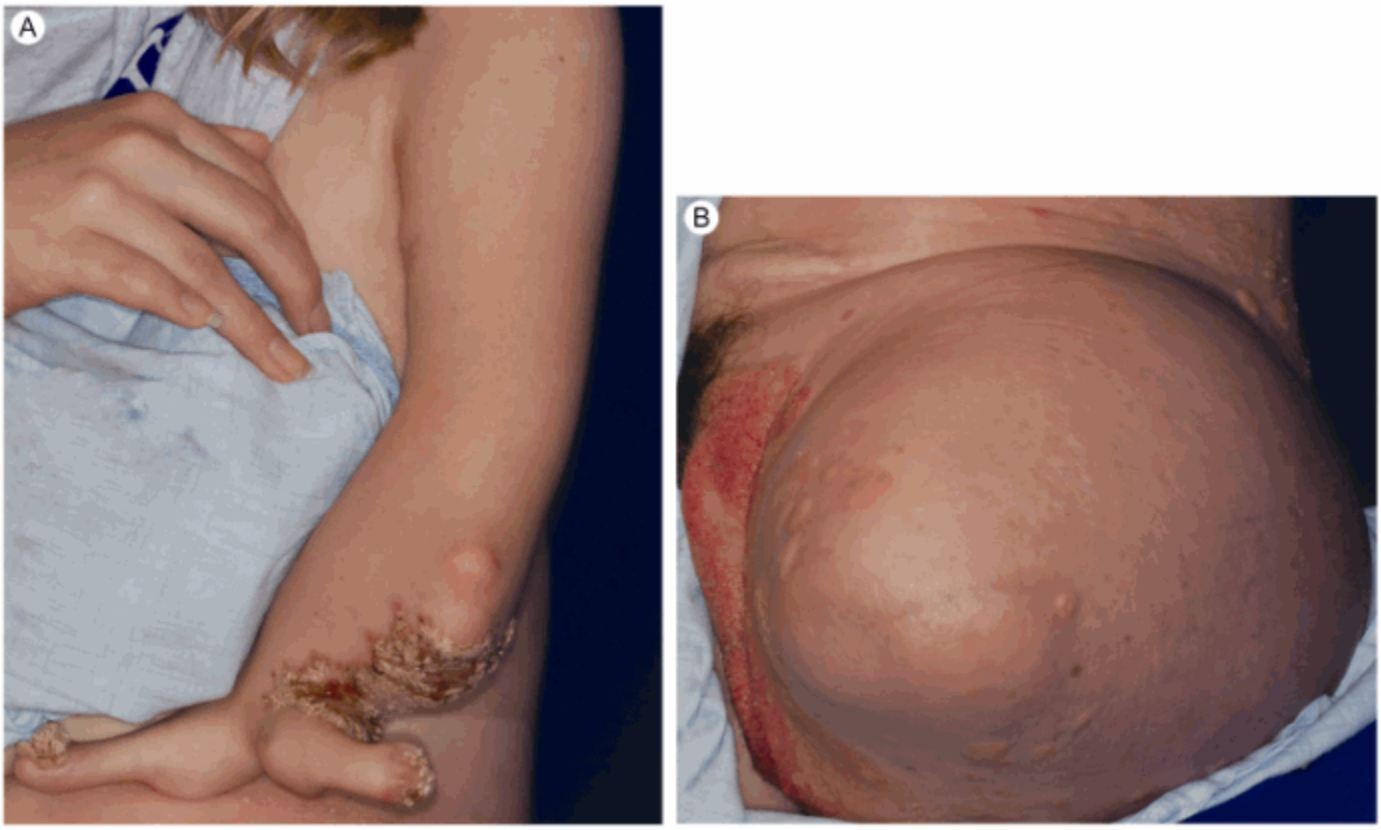

Figure 1. Photographs of a female with CHILD syndrome

A. Upper left limb. Note the forearm hypoplasia, ectrodactyly, onychodystrophy, and characteristic ichthyosiform skin lesions with yellow scales.

B. Lower left limb and groin. The leg was amputated at the knee to improve function. Note the verruciform xanthoma in the genital region.

Photographs provided by Dr Amy Paller, Department of Dermatology, Northwestern University School of Medicine

- Serum concentrations of methyl-sterol and cholesterol are almost always normal in individuals with CHILD syndrome and CK syndrome.

Heterozygous females. Females heterozygous for an *NSDHL* pathogenic variant have normal physical features, intellect, and brain imaging but display behavioral problems including irritability and aggression [Herman & Kratz 2012]. Since heterozygous females have normal plasma cholesterol and plasma 24S-hydroxycholesterol levels, du Souich et al [2012] hypothesized that methyl-sterol accumulation accounts for the behavioral and cognitive problems.

Genotype-Phenotype Correlations

CHILD syndrome. Phenotypic variability within the spectrum of CHILD syndrome does not strictly correlate with the predicted severity of *NSDHL* pathogenic variants [Bornholdt et al 2005, Mi et al 2015].

CK syndrome. The three reported pathogenic variants (c.696_698del, c.1098dup, and c.455G>A) are associated with the same phenotype in affected males.

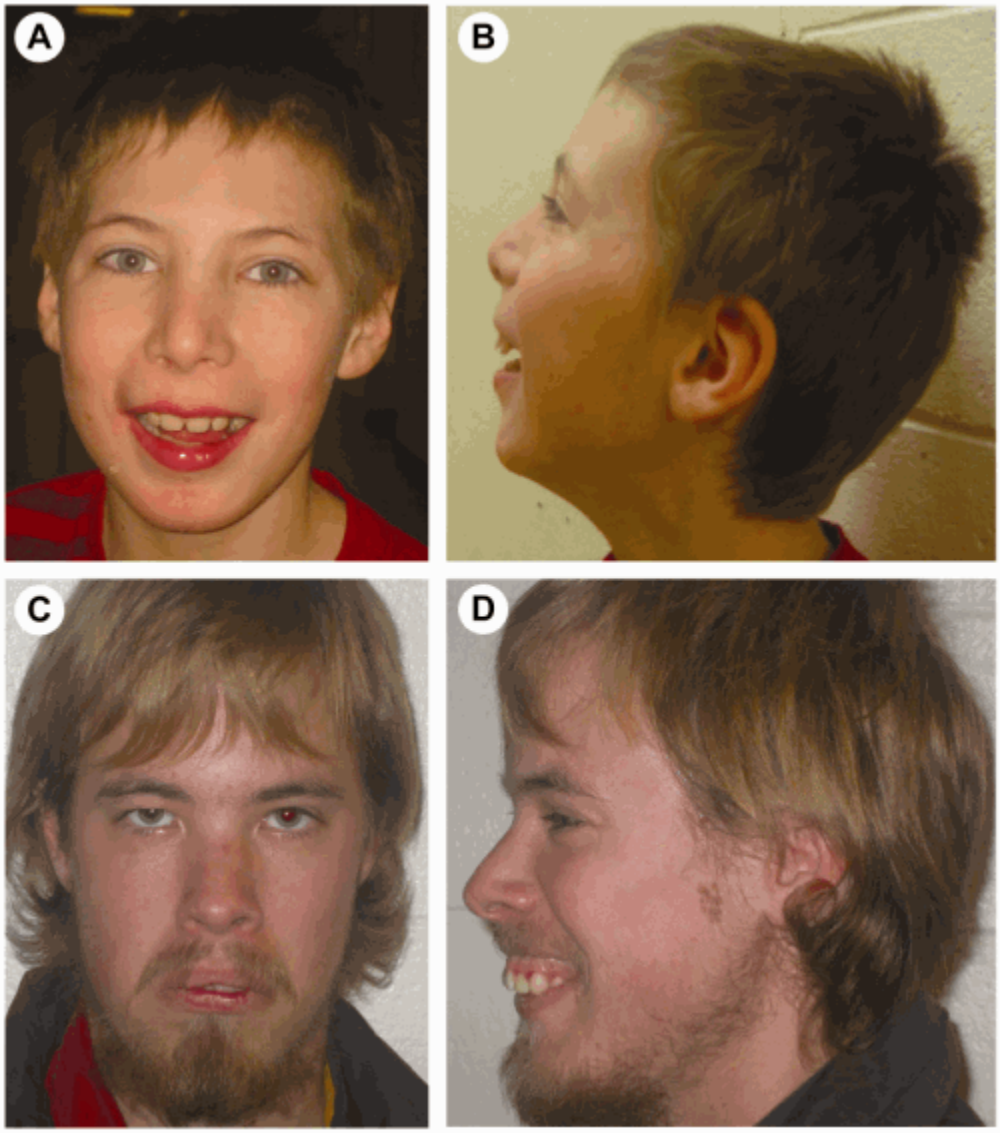

Figure 2. A male age 11 years (A, B) and a male age 22 years (C,D) with CK syndrome. Note the long thin face, epicanthal folds, almond-shaped palpebral fissures, prominent nasal bridge, and micrognathia. The long thin face becomes more apparent with age.

Penetrance

Incomplete penetrance has not been reported for CHILD syndrome; therefore, the penetrance is probably very high. Of note, expressivity is highly variable; in affected females, CHILD syndrome may manifest as minor skin changes only.

Penetrance is probably 100% in males with CK syndrome.

Nomenclature

CHILD is an acronym for *c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects. CHILD syndrome was first reported in 1903 by Dr Otto Sachs [Bittar & Happle 2004].

CK syndrome represents the initials of the original proband. CK syndrome was first described by du Souich et al [2009].

Prevalence

The prevalence of CHILD syndrome is unknown; more than 60 individuals have been reported thus far.

The prevalence of CK syndrome is unknown; it is thought to be rare.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

See Table 2 (CHILD syndrome) and Table 3 (CK syndrome).

Table 2. Disorders to Consider in the Differential Diagnosis of CHILD Syndrome

DiffDx Disorder	Gene(s)	MOI	Clinical Features of the DiffDx Disorder	
			Overlapping	Distinguishing
Chondrodysplasia punctata 2	*EBP*	XL	• Affects males • Skin manifestations: congenital generalized ichthyosiform nevus consisting of bilateral linear or patchy whorls of follicular hyperkeratosis • Asymmetric shortening of limbs	• Skeletal abnormalities: ◦ Short stature ◦ Epiphyseal stippling • Ocular anomalies
Schimmelpenning-Feuerstein-Mims syndrome (SFMS) (OMIM 163200)	*HRAS* *KRAS* *NRAS*	See footnote 1.	Skin lesions, which are w/o erythema or scaling, typically follow the lines of Blaschko & involve the face.	• Systematized sebaceous nevus syndrome • Cerebral anomalies • Coloboma of the iris, choroid, or eyelids • Conjunctival lipodermoid
Incontinentia pigmenti	*IKBKG*	XL	• Embryonic lethal in many males • Skin lesions present as erythema & then blisters at birth, progress to a wart-like rash (Stage II), swirling macular hyperpigmentation following lines of Blaschko (Stage III), & finally linear hypopigmentation by adulthood (Stage IV)	• Alopecia • Hypodontia • Onychogryposis • Peripheral neovascularization in eyes • Seizures • ID

DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. SFMS is sporadic and variable in severity [Wiedemeyer & Hartschuh 2009]. Somatic mosaic pathogenic variants in *HRAS*, *KRAS*, or *NRAS* have been reported in lesional tissue of some individuals.

Table 3. Disorders to Consider in the Differential Diagnosis of CK Syndrome

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping	Distinguishing
Lujan syndrome	*MED12*	XL	• ID • Marfanoid habitus • Long narrow face • Slender habitus w/long, thin fingers & toes • Long nose w/a high narrow bridge • High arched palate • Micrognathia • Low-set posteriorly rotated ears	• Macrocephaly • Maxillary hypoplasia • Short & deep philtrum • Thin upper lip • Retrognathia • Nasal speech • Generalized hypotonia • Abnormalities of the corpus callosum • Joint hypermobility & pectus excavatum
Snyder-Robinson syndrome	*SMS*	XL	• ID • Slender body • Long thin face • Long fingers & toes • High arched palate • Kyphoscoliosis	• Prominent lower lip • Diminished muscle bulk • Osteoporosis • Hypotonia • Unsteady gait
Zinc finger DHHC domain-containing 9-associated ID (OMIM 300799)	*ZDHHC9*	XL	• Thin habitus • Long face & digits • Moderate ID	Joint hypermobility
Smith-Fineman-Myers syndrome (OMIM 309580)	*ATRX*	XL	• ID • Severe speech delay • Microcephaly • Narrow face • Slanted palpebral fissures	• Short stature • Ptosis • Infantile hypotonia • Development of hypertonia in adolescence to early adulthood
Renpenning syndrome (OMIM 309500)	*PQBP1*	XL	• ID • Microcephaly	• Short stature • Heart defects • Cleft palate • Microphthalmia
X-linked ID with epilepsy (OMIM 300423)	*ATP6AP2*	XL	• Moderate to severe ID • Generalized tonic-clonic seizures • Scoliosis	• Progressive gait disturbance • *Pes planus*
Christianson syndrome	*SLC9A6*	XL	• ID • Microcephaly • Epilepsy	Ataxia
Shprintzen-Goldberg syndrome	*SKI*	AD	• Mild to moderate ID • Brain anomalies	• Craniosynostosis • Distinctive dysmorphic features • Skeletal abnormalities • Cardiovascular & abdominal wall defects • Myopia • ↓ subcutaneous fat • Cryptorchidism in males

Table 3. continued from previous page.

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping	Distinguishing
Methylmalonic aciduria and homocystinuria, cblC type (early-onset form) (See Disorders of Intracellular Cobalamin Metabolism.)	*MMACHC*	AR	• DD • Seizures • Microcephaly • Long face	• Hypotonia • Congenital heart malformation • Pigmentary retinopathy • Anemia • Dysmorphic features incl long face, high forehead, flat philtrum, & large, floppy, & low-set ears
Chromosome 17p13.3 microduplication syndrome (OMIM 613215)	See footnote 1.	AD	• ID • Marfanoid habitus • Microcephaly [2] • Dysgenesis of the corpus callosum, & other subtle brain defects	• Hypotonia • Dysmorphic features incl frontal bossing, low-set ears, broad nasal bridge, downslanting palpebral fissures, & triangular-shaped chin
Chromosome 3q27.3 microdeletion syndrome	See footnote 3.	AD	• ID • Slender habitus • Severe speech delay • Scoliosis • Long, thin fingers • Long face	• Psychosis w/mood disorders • Absent/↓ fat deposits • Thin, dry, atopic skin

The X-linked inheritance, intellectual disability, and asthenic habitus of CK syndrome overlap with several disorders. Recognizing that the physical features of CK syndrome could overlap with non-X-linked disorders, evidence of X-linked inheritance is a critical diagnostic criterion. For completeness, however, other non-X-linked disorders that share similar phenotypes are included here in the differential diagnosis.

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. 17p13.3 microduplications are grouped into two classes determined by the presence or absence of three genes: *YWHAE*, *PAFAH1B1*, and *CRK* [Bruno et al 2010]. Class I microduplications (presence of *YWHAE* but not *PAFAH1B1*) are associated with autistic features, speech and motor delays, and subtle dysmorphic features. Class II microduplications (presence of *PAFAH1B1* and sometimes *CRK* and *YWHAE*) are associated with intellectual disability and hypotonia and similar dysmorphic features to the class I microduplication.

2. Microcephaly is characteristic of individuals with duplication of *PAFAH1B1* but not of *YWHAE* or *CRK*.

3. Thevenon et al [2014] reported on seven individuals with chromosome 3q27.3 microdeletions; five individuals had clinical information available. Two small regions of overlap, SRO1 and SRO2, were common to all five individuals and were systematically associated with facial dysmorphism and neurobehavioral problems. Five deleted genes in the SRO1 area (*MASP1, ADIPOQ, ST6GAL1, SST*, and *BCL6*) were of interest, *SST* likely being responsible for psychiatric disorders and *ADIPOQ* possibly associated with the thin habitus. Seven genes were contained in the SRO2 area: *FETU8, KNG1, HRG, DGKG, TBCCD1, AHSG, and CRYGS. AHSG* was thought to be a good candidate for the skeletal phenotype and/or the intellectual disability.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with **CHILD syndrome**, 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 CHILD Syndrome

System/Concern	Evaluation	Comment
Integument	Dermatologic eval	
Musculoskeletal	Referral to orthopedist &/or radiologic exam of trunk & extremities	As needed to evaluate for skeletal malformations incl scoliosis
Neurologic	• Referral to neurologist • EEG • Brain MRI exam • Developmental eval	Evaluate for seizures.
Cardiac	Echocardiogram	Evaluate for congenital heart disease.
Pulmonary	Chest imaging	Evaluate for lung hypoplasia.
Genitourinary	Abdominal & pelvic ultrasound exam	Evaluate for renal or other genitourinary anomalies.
Other	Consultation w/clinical geneticist &/or genetic counselor	

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

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with CK Syndrome

System/Concern	Evaluation	Comment
Developmental	Psychoeducational eval	To define delays & facilitate appropriate interventions
Psychiatric	Referral to psychiatrist	If behavioral problems are present
Neurologic	• Referral to neurologist • EEG	Evaluate for seizures.
Musculoskeletal	X-ray exam &/or referral to orthopedist	Evaluate for scoliosis/kyphosis.
Ophthalmologic	Referral to ophthalmologist	Evaluate ocular findings incl strabismus & optic atrophy.
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

CHILD syndrome

- **Topical treatments** including lactic acid 12% creams or lotions for itching and urea creams for dry skin. Oral and topical ketoconazole were found to result in a 90% reduction of cutaneous lesions after ten days of therapy [Liu et al 2015].
- **Dermatologic surgery.** An inflammatory nevus was removed from an affected boy by dermabrasion; however, it recurred within eight months [Happle et al 1996]. König et al [2010] reported successful treatment of an inflammatory nevus by grafting skin obtained from a contralateral unaffected region.
- **Oral aromatic retinoids (etretinate)** to ameliorate cutaneous symptoms; however, this drug is often poorly tolerated [Happle et al 1980] and does not prove effective in every individual [Liu et al 2015].
- **Topical statins.** The use of lovastatin topically led to complete healing of the inflammatory CHILD nevus in a few individuals, whereas cholesterol application alone had no satisfactory effect [Merino De Paz et al 2011, Paller et al 2011]. Alexopoulos & Kakourou [2015] reported the combined topical use of simvastatin and cholesterol and showed a correction in the cutaneous phenotype of one individual. The addition of glycolic acid to cholesterol and lovastatin creams improved the penetrance of this therapy into the thick skin scales, thus improving treatment [Bergqvist et al 2018]. Bajawi et al [2018] showed remarkable

improvement of the skin lesions in one individual in response to treatment with simvastatin 2% ointment monotherapy.
- **Note:** No one therapy described to date appears to ameliorate the cutaneous findings for every reported individual with CHILD syndrome. Trying different methods until the clinician finds a successful therapy appears to be typical for most affected individuals.
- **Orthopedic abnormalities.** Treatment of orthopedic abnormalities such as scoliosis and joint contractures with braces and/or corrective surgery
- **Other** medical care as appropriate based on clinical findings

CK syndrome

- Behavior modification and/or drug therapy to control aggression and help with ADHD symptoms
- Anti-seizure medication to control seizures
- Ophthalmologic management of ocular abnormalities

Surveillance

CHILD syndrome

- Regular surveillance for cutaneous manifestations as new lesions may occur in puberty or early adulthood
- Orthopedic surveillance for musculoskeletal deformities such as scoliosis and joint contractures
- Neurologic, cardiologic, or renal surveillance depending on clinical involvement

CK syndrome

- Neurologic surveillance of seizures for readjustment of medications if necessary
- Orthopedic surveillance for scoliosis/kyphosis

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

The *NSDHL*-related disorders are inherited in an X-linked manner.

- CHILD syndrome is usually lethal to males during gestation and predominantly affects females.
- CK syndrome predominantly affects males.

Risk to Family Members – CHILD Syndrome

Parents of a proband

- A female with CHILD syndrome may have inherited an *NSDHL* pathogenic variant from her mother or the pathogenic variant may be *de novo*. Theoretically, an affected female may also have inherited the variant from a father with germline mosaicism.
- Although CHILD syndrome-associated *NSDHL* variants appear to be highly penetrant, mothers heterozygous for an *NSDHL* pathogenic variant who have only mild skin lesions, Blaschko-linear inflammatory scaly lesions, patchy alopecia, and nail changes have been reported [Bittar et al 2006]. Favorably skewed X-chromosome inactivation has been proposed to explain this milder phenotype, and theoretically could on occasion result in a phenotypically normal heterozygous female. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the mother of the proband.
- The father of an affected male will not have the disorder nor will he be hemizygous for an *NSDHL* pathogenic variant.

Sibs of a female proband. The risk to sibs depends on the genetic status of the mother.

- If the mother of the proband has an *NSDHL* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. However, since studies suggest that male conceptuses with an *NSDHL* pathogenic variant generally abort or resorb spontaneously [Cunningham et al 2005], the expected live-born distribution is 33% unaffected females, 33% affected females, and 33% unaffected males.
- If the proband represents a simplex case (i.e., a single affected family member) and if pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism.

Offspring of a female proband

- The risk to the offspring of females with CHILD syndrome must take into consideration the presumed lethality to affected males during gestation.
- At conception, the chance of transmitting the pathogenic variant in each pregnancy is 50%; however, since male conceptuses with an *NSDHL* pathogenic variant generally abort or resorb spontaneously, the expected live-born distribution is 33% unaffected females, 33% affected females, and 33% unaffected males.

Other family members. The risk to other family members depends on the status of the proband's mother: if the proband's mother has the *NSDHL* pathogenic variant, her family members may be at risk.

Risk to Family Members – CK Syndrome

Parents of a male proband

- The father of a male with CK syndrome will not have the disorder nor will he be hemizygous for the *NSDHL* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *NSDHL* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. The frequency of germline mosaicism is unknown.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo NSDHL* pathogenic variant, in which case the mother is not a heterozygote. The frequency of *de novo* pathogenic variants is unknown.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband is heterozygous for an *NSDHL* pathogenic variant, the expected chance of transmitting it in each pregnancy is 50%. However, in the three families reported to date, Preiksaitiene et al [2015] observed apparent preferential transmission of the *NSDHL* pathogenic variant: the transmission rate was approximately 82% (versus the expected 50% transmission rate). More families will have to be identified and analyzed to further substantiate this observation.
- Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will usually not be affected (see Clinical Description, CK Syndrome, **Heterozygous females**).
- If the proband represents a simplex case and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism. The frequency of germline mosaicism is unknown.

Offspring of a male proband. To date, no male with CK syndrome has reproduced.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes for the pathogenic variant, and the aunts' offspring, depending on their sex, may be at risk of being heterozygotes for the pathogenic variant or of being affected.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note: Heterozygous females may have a range of clinical manifestations (see Clinical Description, CK Syndrome, **Heterozygous females**).

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, 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, heterozygous, or at risk of being heterozygous.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *NSDHL* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for an *NSDHL*-related disorder are possible.

Biochemical testing is theoretically possible, although it has not been reported for *NSDHL*-related disorders. Additionally, limb deficiency or another skeletal anomaly detected by fetal ultrasound suggests the possibility of recurrence; however, mild manifestations may not have detectable limb findings.

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.

- **National Library of Medicine Genetics Home Reference**
  Congenital hemidysplasia with ichthyosiform erythroderma and limb defects
- **Foundation for Ichthyosis and Related Skin Types, Inc. (FIRST)**
  Phone: 215-997-9400; 800-545-3286
  www.firstskinfoundation.org
- **Rare Disease Foundation (RDF)**
  4500 Oak Street
  Room C234
  Vancouver British Columbia V6H 3N1
  Canada
  Phone: 866-348-6677
  Email: families@rarediseasefoundation.org
  www.rarediseasefoundation.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. NSDHL-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NSDHL	Xq28	Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating	NSDHL @ LOVD	NSDHL	NSDHL

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 NSDHL-Related Disorders (View All in OMIM)

300275	NAD(P)H STEROID DEHYDROGENASE-LIKE PROTEIN; NSDHL
300831	CK SYNDROME; CKS
308050	CONGENITAL HEMIDYSPLASIA WITH ICHTHYOSIFORM ERYTHRODERMA AND LIMB DEFECTS

Gene structure. *NSDHL* comprises eight exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants

- **CHILD syndrome.** Well-studied CHILD-associated *NSDHL* variants result in loss of function of the protein and many are null alleles. Approximately 21 different pathogenic variants have been reported [König et al 2000, Saito & Ishiko 2008, Schmidt-Sidor et al 2008, Avgerinou et al 2010, Mi et al 2015]; they include missense, nonsense, frameshift, and splice site variants and deletions of all or portions of the gene [Bornholdt et al 2005, Kim et al 2005]. The following pathogenic variants have been seen more than once: p.Gly205Ser, p.Tyr349Cys, and p.Ala105Val.
- **CK syndrome.** CK syndrome-associated variants cause partial loss of enzyme function. The two pathogenic variants identified to date are a 3-bp in-frame deletion [McLarren et al 2010] and a pathogenic frameshift variant altering the carboxyl terminus of *NSDHL* [Tarpey et al 2009]. Both are temperature-

sensitive pathogenic variants that decrease protein stability at 37° C [McLarren et al 2010]. Recently, a p.Gly152Asp missense variant was shown to segregate with CK syndrome in a Lithuanian family [Preiksaitiene et al 2015].

Table 6. *NSDHL* Pathogenic Variants Discussed in This *GeneReview*

Phenotype	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
CHILD syndrome	c.262C>T [1]	p.Arg88Ter	NM_001129765.1 NP_001123237.1
	c.613G>A	p.Gly205Ser	
	c.1046A>G	p.Tyr349Cys	
	c.314C>T	p.Ala105Val	
CK syndrome	c.455G>A	p.Gly152Asp	
	c.696_698delGAA	p.Lys232del	
	c.1098dupT	p.Arg367SerfsTer33	

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.
1. Identified as a mosaic mutated allele in a male with CHILD syndrome (See Clinical Description.)

Normal gene product. The NSDHL enzyme, which localizes to the surface of the endoplasmic reticulum and to lipid droplets, is a member of a multiprotein complex and functions as a C4 demethylase in post-squalene cholesterol biosynthesis [Gachotte et al 1998, Mo et al 2002, Caldas & Herman 2003]. The protein contains 362 amino acids.

Abnormal gene product

- In **CHILD syndrome**, *NSDHL* pathogenic variants result in substantial or complete loss of functional NSDHL protein. Some pathogenic variants result in deletion of all or portions of NSDHL protein, whereas pathogenic nonsense and frameshift variants are likely to be loss-of-function variants [Rebbapragada & Lykke-Andersen 2009, McLarren et al 2010]. CHILD syndrome-associated missense variants studied by Lucas et al [2003] fail to complement in the yeast complementation system.
- In **CK syndrome**, *NSDHL* pathogenic variants result in severely reduced steady-state levels of NSDHL protein and thus lead to a partial loss of NSDHL protein function. In yeast complementation studies, these pathogenic variants complement as well as the wild type human NSDHL protein because the mutated proteins are stable at 30° C [McLarren et al 2010].

Chapter Notes

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Revision History

- 25 October 2018 (sw) Comprehensive update posted live

- 25 November 2015 (me) Comprehensive update posted live
- 27 June 2013 (me) Comprehensive update posted live
- 16 February 2012 (cd) Revision: deletion/duplication analysis for *NSDHL* available clinically
- 1 February 2011 (me) Review posted live
- 9 January 2010 (cb) Original submission

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