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Chediak-Higashi Syndrome

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Summary

Clinical characteristics

Chediak-Higashi syndrome (CHS) is characterized by partial oculocutaneous albinism (OCA), immunodeficiency, a mild bleeding tendency, and late adolescent- to adult-onset neurologic manifestations (e.g., learning difficulties, peripheral neuropathy, ataxia, and parkinsonism). While present in nearly all individuals with CHS, these clinical findings vary in severity.

Of note, all individuals with CHS are at risk of developing neurologic manifestations and hemophagocytic lymphohistiocytosis (HLH).

Individuals with severe childhood-onset presentations are considered to have "classic" CHS, whereas individuals with milder adolescent- to adult-onset presentations are considered to have "atypical" CHS. Because of the considerable overlap between classic CHS and atypical CHS, the disorder is best understood as a continuum of severe to milder phenotypes, with the universal feature being the pathognomonic giant granules within leukocytes observed on peripheral blood smear.

Diagnosis/testing

The clinical diagnosis of CHS is established in a proband with suggestive clinical findings by identification of the pathognomonic giant granules within leukocytes on peripheral blood smear and/or biallelic pathogenic variants in *LYST* on molecular genetic testing.

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Management

Targeted therapy: The only targeted therapy currently available is hematopoietic stem cell transplantation (HSCT). HSCT can correct the hematologic and immunologic manifestations of CHS but does not appear to protect against the development of neurologic manifestations.

Supportive care: Multidisciplinary care is recommended, including specialists in ophthalmology and low vision services, infectious disease for management and prevention, hematology (to manage the bleeding disorder, HSCT, and treatment of HLH), neurology and physiatry, physical therapy, occupational therapy, and (for children) neuropsychology or developmental pediatrics to address educational and emotional needs or (for adults) neuropsychology.

Surveillance: To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, routinely scheduled follow-up evaluations by the multidisciplinary specialists are recommended.

Agents/circumstances to avoid: Live vaccines given the risk of infection due to immunodeficiency; all nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, ibuprofen) given the risk of exacerbating the bleeding tendency.

Evaluation of relatives at risk: It is appropriate to evaluate the older and younger sibs of a proband as early as possible. Early diagnosis may provide the opportunity to perform HSCT prior to the development of HLH.

Pregnancy management: Although data are limited, to date females with CHS report uneventful pregnancy, labor, and delivery. However, because of concerns about bleeding during delivery and the postpartum period, developing a plan prior to delivery to address this issue is recommended.

Genetic counseling

CHS is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *LYST* 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 *LYST* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

Chediak-Higashi syndrome (CHS) is characterized by partial oculocutaneous albinism (OCA), immunodeficiency, a mild bleeding tendency, and late adolescent- to adult-onset neurologic manifestations (e.g., learning difficulties, peripheral neuropathy, ataxia, and parkinsonism). All individuals are at risk of developing hemophagocytic lymphohistiocytosis (HLH).

While present in nearly all individuals with CHS, these clinical findings vary in severity. Individuals with severe presentations (see *GeneReview* Scope) are considered to have "classic" CHS, whereas individuals with milder presentations are considered to have "atypical" CHS. Because of the considerable overlap between classic CHS and atypical CHS, the disorder is best understood as a continuum of severe to milder phenotypes, with the universal feature being the pathognomonic giant granules within leukocytes observed on peripheral blood smear.

***GeneReview* Scope: Chediak-Higashi Syndrome Clinical Continuum**

Severity	Age at Diagnosis	OCA	HLH [1] Risk	Immune Deficiency	Bleeding Diathesis	Neurologic Involvement
Severe: Classic CHS	Earlier in life (childhood)	Mild to moderate	Higher	Frequent, severe, & unusual infections	Similar across phenotypic continuum	
Milder: Atypical CHS	Later in life (adolescent- or adult-onset)	Absent to mild	Lower	May be only mild or no unusual infections		

Based on Introne et al [2017], Kuptanon et al [2023]
CHS = Chediak-Higashi syndrome; HLH = hemophagocytic lymphohistiocytosis; OCA = oculocutaneous albinism
1. Also called "accelerated phase"

Diagnosis

Suggestive Findings

The diagnosis of Chediak-Higashi syndrome (CHS) **should be suspected** in a proband with any of the following clinical features, supportive laboratory findings, and family history.

Clinical features

- Oculocutaneous albinism (OCA) with residual pigmentation characterized by:
  - Signs and symptoms of low vision typical of OCA
  - Reduced iris pigmentation (manifesting as iris transillumination often only on ophthalmologic examination). Note that irides may be darker than the light blue that is often associated with OCA.
  - Reduced retinal pigmentation
  - Hair that may have a silvery-gray sheen
- A significant history of infections (particularly bacterial) of the skin and respiratory tract; also increased susceptibility to periodontal disease
- Mild bleeding tendency associated with platelet dysfunction such as epistaxis, gum/mucosal bleeding, and easy bruising
- Increased risk for hemophagocytic lymphohistiocytosis (HLH) (previously called "CHS accelerated phase"). Clinical findings and diagnostic criteria are the same as those for familial hemophagocytic lymphohistiocytosis.
- Childhood- to early adult-onset neurologic manifestations, including:
  - Learning difficulties
  - Peripheral neuropathy
  - Ataxia
  - Parkinsonism

Supportive laboratory findings

- White blood cell (WBC) giant granules (also called "inclusions"), peroxidase-positive granules primarily in polymorphonuclear neutrophils (PMNs) and to a lesser extent in lymphocytes (Figure 1c-1e), are the most reliable diagnostic criterion for CHS. Nonetheless, giant granules may be overlooked in a routinely evaluated complete blood count (CBC) unless a peripheral smear is reviewed.
  - Although the giant granules are seen using routine staining techniques, in some individuals with atypical CHS the presence of these giant granules can be less striking and thus missed by routine evaluation.

- Slide review is optimally conducted by a hematologist or other specialist with experience reviewing blood smears for the presence of abnormal granules.
- Because the finding of WBC giant granules is the most reliable clinical diagnostic criterion for CHS, the combination of any of the other hematologic findings listed below should prompt review of a peripheral blood smear to evaluate for giant granules.

- Other hematologic findings:
  - Absent or reduced number and/or irregular morphology of platelet-dense bodies (required for the secondary wave of platelet aggregation) on whole-mount electron microscopy (Figure 1a, 1b)
  - Normal or reduced number of natural killer cells with abnormal (reduced) function
  - Neutropenia
  - Normal immunoglobulins, complement, antibody production, and delayed hypersensitivity

Other. Pigment clumping on polarized light microscopy hair analysis (Figure 1f, 1g)

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis. Note: When evaluating sibs of a proband for the purpose of the family history, clinicians should have a high level of suspicion for all findings that may be associated with CHS, since presenting manifestations may vary in sibs with the same biallelic *LYST* pathogenic variants.

Establishing the Diagnosis

The **clinical diagnosis** of CHS **is established** in a proband by identification of the pathognomonic giant granules within leukocytes on peripheral blood smear (see Suggestive Findings). The **molecular diagnosis** of CHS **is established** in a proband by the identification of biallelic pathogenic (or likely pathogenic) variants in *LYST* on molecular genetic testing [Sharma et al 2020, Morimoto et al 2023] (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variant" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *LYST* variants of uncertain significance (or of one known *LYST* pathogenic variant and one *LYST* 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). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (Option 1), whereas comprehensive genomic testing does not (Option 2).

Option 1

Single-gene testing is an option when laboratory and clinical findings are strongly suggestive of the diagnosis. Sequence analysis of *LYST* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. 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.

An albinism or neutropenia panel that includes *LYST* 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

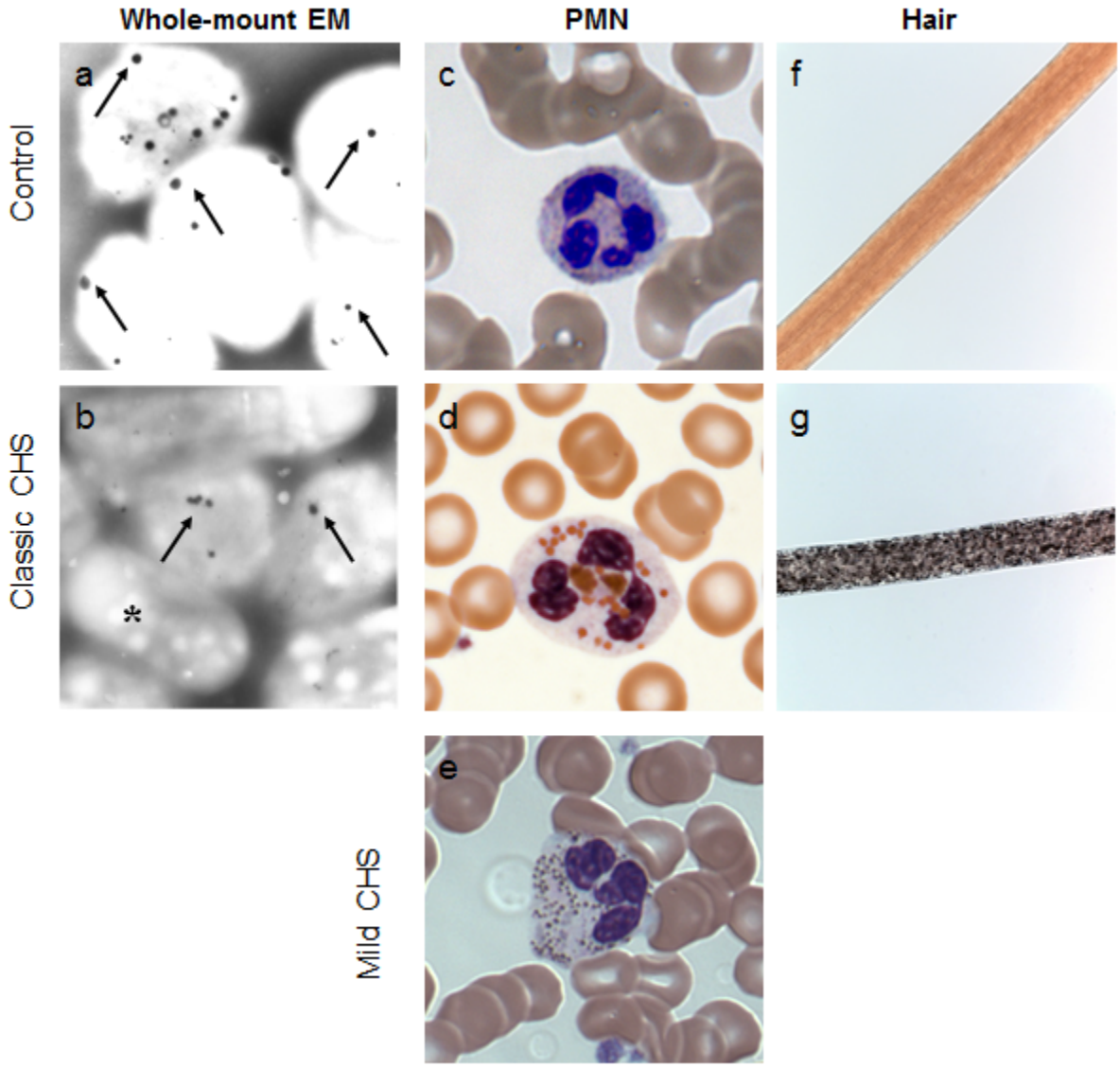

Figure 1. Examples of granules in polymorphonuclear neutrophils, platelet-dense bodies, and pigment in hair shafts for controls, classic Chediak-Higashi syndrome (CHS), and atypical CHS

a. Whole-mount electron microscopy (EM) of control platelets shows several dense bodies per platelet (arrows).

b. Some CHS platelets have no dense bodies (asterisk) and others have irregular electron-dense granules (arrows).

c. Normal control polymorphonuclear neutrophils (PMNs) contain numerous small cytoplasmic granules.

d. The blood smear derived from an individual with classic severe CHS shows PMNs that contain enlarged intracytoplasmic granules.

e. PMNs from an adult-onset, mildly affected individual with atypical CHS contain many granules that are larger than normal but smaller than those of the individual with classic CHS seen in 1d.

f. Control hair shows pigment that is evenly distributed throughout the shaft.

g. Hair of an individual with classic CHS shows an irregular distribution of large and small pigment clumps.

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. To date, the majority of *LYST* pathogenic variants reported (e.g., missense, nonsense) are within the coding region or close to canonical splices and are therefore likely to be identified by exome sequencing.

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 Chediak-Higashi Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
LYST	Sequence analysis [3]	~97% [4]
	Gene-targeted deletion/duplication analysis [5]	~2% [6]
	Unknown	~1% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Morimoto et al [2023] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Certain et al [2000], Fusaro et al [2021], Kuptanon et al [2023]
7. Several pathogenic variants were identified that were determined to lead to exon skipping by cDNA Sanger sequencing, but the exact genomic variant leading to these exon-skipping events has not been determined [Kuptanon et al 2023].

Clinical Characteristics

Clinical Description

Chediak-Higashi syndrome (CHS) is characterized by partial oculocutaneous albinism (OCA), immunodeficiency, and a mild bleeding tendency. These features are present in nearly all individuals with CHS but to a very variable degree. Affected individuals with severe presentations (i.e., OCA; early-onset, recurrent, severe infections; and a bleeding diathesis) are considered to have "classic" CHS. Individuals with milder phenotypes (e.g., later-onset, milder pigmentary, immunologic, and hematologic features) are considered to have "atypical" CHS (also referred to as "mild" or "adolescent" CHS). Both groups of individuals are at risk of developing hemophagocytic lymphohistiocytosis (HLH), previously called "the accelerated phase," with the highest risk of HLH (~85%) in individuals with classic CHS.

Over time, it has become apparent that the classification of CHS into "classic" vs "atypical" phenotypes is arbitrary, as the considerable overlap of the two groups means that this disorder is best understood as a

continuum of severe to milder phenotypes, with the universal feature being the pathognomonic giant granules within leukocytes observed on peripheral blood smear.

Although the proportion of individuals with atypical CHS is unknown [Karim et al 2002, Westbroek et al 2007], it is likely underrecognized. In some individuals with atypical CHS, the neurologic findings may be the predominant manifestation. Additionally, some individuals may not be diagnosed until the third decade of life or later [Weisfeld-Adams et al 2013, Yarnell et al 2020].

Table 2. Chediak-Higashi Syndrome: Phenotypic Continuum

Feature	Degree of Involvement [1]
Oculocutaneous albinism	Ranges from mild/moderate in classic CHS to mild/absent in atypical CHS
Immunodeficiency / increased risk of infection	Ranges from infantile onset of frequent and often severe infections in classic CHS to absence of a noticeable increase in severity or frequency of infections in atypical CHS
Bleeding tendency	Similar bleeding diathesis in all individuals with CHS
Neurologic involvement	Wide-ranging and nonspecific features in all individuals with CHS.
Hemophagocytic lymphohistiocytosis [2]	Occurs in the majority of individuals with CHS who have not undergone hematopoietic stem cell transplantation.

Based on Introne et al [2017], Kuptanon et al [2023]
1. The same CHS-related features are present in nearly all individuals with classic and atypical CHS but to a very variable degree.
2. Also called "accelerated phase"

Partial oculocutaneous albinism (OCA). Pigment dilution, which can involve eyes, hair, and skin, is highly variable.

Reduced iris pigmentation and iris transillumination may be subtle. Affected individuals may have decreased retinal pigmentation and nystagmus. Visual acuity varies from normal to moderately reduced.

The hair has a "silvery" or metallic appearance. Pigment clumping within the shaft of the hair is generally observed by light microscopy (Figure 1g) [Smith et al 2005].

Skin pigment dilution may not be appreciated unless compared to the pigmentation of family members. Individuals with darker skin tone may observe areas with scattered hyper- and hypopigmentation.

Although partial OCA was once thought to be a diagnostic criterion for CHS, at least two individuals with atypical CHS had no evidence of OCA [Introne et al 2017].

Immunodeficiency. Frequent infections usually begin in infancy and are often severe in classic CHS. Individuals with atypical CHS may not have a noticeable increase in severity or frequency of infections.

Bacterial infections are most common, with *Staphylococcus* and *Streptococcus* species predominating; viral and fungal infections can also occur [Introne et al 1999]. Infections of the skin and upper respiratory tract are the most common.

Periodontitis, an important manifestation of immunologic dysfunction [Thumbigere Math et al 2018, de Arruda et al 2023], can be the clinical finding that leads to the correct diagnosis [Bailleul-Forestier et al 2008].

Neutropenia may be present and, in some individuals, cycles between normal absolute neutrophil counts and neutropenia (also called "cyclic neutropenia").

Bleeding tendency. The bleeding diathesis in CHS, a result of absent or severely reduced platelet-dense granules, is present in both classic and atypical CHS. Clinical manifestations are generally mild and include epistaxis, gum/mucosal bleeding, and easy bruising. The bleeding diathesis may also be subtle (i.e., generally not requiring

medical intervention) and thus may not be identified as a health concern by affected persons. However, with trauma or invasive procedures, bleeding may be more severe and prolonged.

Neurologic involvement. Despite successful hematologic and immunologic outcomes with allogenic hematopoietic stem cell transplantation (HSCT) to treat hematologic findings, neurologic involvement nonetheless manifests by early adulthood.

Neurologic features are similar across the CHS phenotypic spectrum; thus, individuals with classic and atypical CHS cannot be distinguished neurologically [Introne et al 2017]. Due to the wide range of neurologic features that can occur, findings among affected individuals are variable and nonspecific. Likewise, age of onset and disease progression also vary. While learning difficulties may be present in childhood and can be considered developmental in nature, other neurologic signs and symptoms are generally not observed until late adolescence or early adulthood and are progressive. Neurologic findings can include:

- Learning difficulties in childhood [Introne et al 2017, Shirazi et al 2019]
- Sensory neuropathy. Onset in late adolescence or early third decade and slowly progresses to sensorimotor neuropathies and/or diffuse motor neuronopathy [Lehky et al 2017]
- Cerebellar dysfunction. Onset in late adolescence or early adulthood [Introne et al 2017]
- Optic neuropathy. Onset in late adolescence or early adulthood [Desai et al 2016]
- Spastic paraplegia. Onset in early to middle adulthood [Shimazaki et al 2014, Koh et al 2022]
- Tremor, which can include kinetic and postural tremor
- Parkinsonism, including L-dopa-responsive parkinsonism, may occur as early as the second or third decade [Bhambhani et al 2013, Weisfeld-Adams et al 2013]
- Progressive cognitive decline late in the disease course

Hemophagocytic lymphohistiocytosis (HLH; also known as the "accelerated phase") occurs in the majority of individuals with CHS who have not undergone HSCT [Lozano et al 2014] and can occur at any age. Although individuals with atypical CHS are thought to be at lower risk of HLH than individuals with classic CHS, the frequency of occurrence in atypical CHS is unknown.

Originally thought to be a malignancy resembling lymphoma, the "accelerated phase" is now known to be HLH characterized by multiorgan inflammation. Manifestations include fever, lymphadenopathy, hepatosplenomegaly, anemia, neutropenia, and thrombocytopenia.

Triggers of HLH remain unclear. Although infection with Epstein-Barr virus is thought to hasten development of HLH, this relationship has never been proven. Abnormal function of NK cells and cytolytic T cells is also believed to contribute to development of HLH [Jessen et al 2011, Gil-Krzewska et al 2016].

Prognosis. HLH and its complications are the most common cause of mortality in individuals with CHS [Lozano et al 2014].

Genotype-Phenotype Correlations

Clinical phenotypes of CHS have been correlated with classes of *LYST* pathogenic variants [Karim et al 2002, Zarzour et al 2005, Westbroek et al 2007, Morimoto et al 2023].

- Loss-of-function *LYST* pathogenic variants (e.g., nonsense, frameshift, canonical splice site, single- or multiexon deletions) are typically associated with classic CHS.
- Missense pathogenic variants and in-frame deletions of *LYST* are associated with atypical CHS; however, individuals with biallelic missense pathogenic variants with classic CHS and HLH have been reported [Sánchez-Guiu et al 2014].

Prevalence

Fewer than 500 individuals with CHS have been reported [Morimoto et al 2023, Talbert et al 2023].

Exact prevalence is difficult to determine, as some individuals have been reported in the literature more than once. In addition, the broad phenotypic spectrum that has become evident since the early descriptions of CHS suggests that many mildly affected individuals may be underrecognized or underreported.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

The diagnosis of Chediak-Higashi syndrome (CHS) should be considered in individuals with pigment dilution defects of the hair, skin, or eyes; congenital or transient neutropenia; immunodeficiency; and otherwise unexplained neurologic abnormalities or neurodegeneration. Each of these findings may be variably represented or absent in affected individuals; therefore, heightened suspicion is needed to pursue an accurate diagnosis.

Table 3. Genes of Interest in the Differential Diagnosis of Chediak-Higashi Syndrome

Gene(s)	Disorder	MOI	Clinical Features	Comment
AP3B1 *AP3D1* *BLOC1S3* *BLOC1S5* *BLOC1S6* *DTNBP1* *HPS1* *HPS3* *HPS4* *HPS5* *HPS6*	Hermansky-Pudlak syndrome (HPS)	AR	• OCA & a bleeding diathesis secondary to absent platelet-dense bodies • Of the HPS subtypes, *AP3B1*-related HPS (HPS2) most closely resembles CHS. In addition to the albinism & bleeding diathesis, persons w/HPS2 have congenital neutropenia, a recurrent pattern of severe bacterial infections, & pulmonary fibrosis & are at risk for HLH, although the risk is less than for CHS.	The distinction between CHS & HPS2 depends on identifying giant intracellular granules w/in the neutrophils of those persons w/CHS &/or molecular genetic testing.
DCT *LRMDA* *OCA2* *SLC24A5* *SLC45A2* *TYR* *TYRP1*	Nonsyndromic oculocutaneous albinism (OCA)	AR	• Cutaneous & ocular hypopigmentation • Impaired melanin biosynthesis leads to hypopigmentation in the skin, hair, & eyes w/characteristic ocular abnormalities.	• Neither an infectious history resulting from neutropenia nor neurologic abnormalities accompany the nonsyndromic OCA types. • OCA is common enough (~1:18,000) that it may coexist w/other conditions, incl primary immunodeficiencies.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Comment
EPG5	*EPG5*-related disorder (encompasses classic Vici syndrome)	AR	• *EPG5*-related disorder represents a continuum of variable severity • Vici syndrome (defined as a neurodevelopmental disorder w/ agenesis of the corpus callosum, cataracts, hypopigmentation, cardiomyopathy, combined immunodeficiency, microcephaly, & failure to gain weight) is at the most severe end of the spectrum. • Milder, attenuated neurodevelopmental phenotypes w/a variable degree of multisystem involvement are increasingly recognized.	• Defects of the corpus callosum & cardiac involvement are not typical for CHS. • Giant intracellular granules will not be seen in *EPG5*-related disorder.
LAMTOR2	Immunodeficiency due to defect in MAPBP-interacting protein (OMIM 610798)	AR	• Immunodeficiency syndrome identified in 4 members of a Mennonite family • Clinical features incl partial albinism, short stature, congenital neutropenia, & lymphoid deficiency.	• Neutrophils show altered azurophilic granule ultrastructure & less than normal microbicidal function of phagosomes, in contrast to the giant granules seen in neutrophils in CHS. • Neurologic dysfunction was not described in affected family members.
MLPH *MYO5A* *RAB27A*	Griscelli syndrome (GS) (OMIM PS214450)	AR	• Mild skin hypopigmentation & silvery-gray hair plus severe neurologic involvement in *MYO5A*-related GS & immunodeficiency & lymphohistiocytosis in *RAB27A*-related GS. • Hypopigmentation is the only clinical characteristic of *MLPH*-related GS.	• Platelet-dense bodies are present & platelet function is normal. • Giant granules w/in neutrophils are not present in GS.
PRF1 *STX11* *STXBP2* *UNC13D*	Familial hemophagocytic lymphohistiocytosis (fHLH)	AR	• Immune deficiency characterized by overactivation & excessive proliferation of T lymphocytes & macrophages, leading to infiltration & damage of organs incl bone marrow, liver, spleen, & brain • Familial HLH usually presents as an acute illness w/prolonged & high fever, cytopenias, & hepatosplenomegaly. • Persons w/fHLH may also exhibit liver dysfunction & neurologic abnormalities. • Although manifestations of fHLH are usually evident w/in 1st mos or yrs of life & may develop in utero, symptomatic presentation can occur throughout childhood & into adulthood.	The presentation of HLH in CHS will look the same as in fHLH; however, in CHS, giant intracellular granules w/in the leucocytes will be apparent on peripheral blood smear & bone marrow aspirate.

AR = autosomal recessive; CHS = Chediak-Higashi syndrome; HLH = hemophagocytic lymphohistiocytosis; MOI = mode of inheritance; OCA = oculocutaneous albinism

Management

No clinical practice guidelines for Chediak-Higashi syndrome (CHS) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

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

Table 4. Chediak-Higashi Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern		Evaluation	Comment
Ophthalmologic		By pediatric or adult ophthalmologist depending on age	• Assess for signs of ↓ pigment (see OCA/OA Overview) & refractive errors. • Consider OCT to provide baseline retinal fiber thickness.
Immunologic		Screening for history of frequent or unusual infections	Referral to immunologist &/or hematologist/oncologist for consideration of eval for HSCT
Bleeding disorder		By hematologist	Platelet aggregation studies &/or platelet EM for dense body analysis
Neurologic		By pediatric or adult neurologist depending on age	• Neurologic exam • Specialized testing if abnormalities identified on clinical exam
Cognitive impairment	**Child**	Developmental/educational assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / need for IEP &/or 504 plan
	Adult	Neuropsychologist	Measures of mood, memory, attention, processing speed, psychomotor speed, language fluency, executive function, & cognitive function
Hemophagocytic lymphohistiocytosis		Protocols vary by institution/ specialist (See Familial Hemophagocytic Lymphohistiocytosis.)	• History of unexplained, persistent, or recurrent fever • Assessment for hepatosplenomegaly by physical exam & ultrasound imaging • Complete blood count [1] • Ferritin concentration [2] • Soluble interleukin-2 receptor level [2] • Consideration of bone marrow biopsy [3] • Consideration of lumbar puncture • Serum triglyceride concentration [4] • Fibrinogen level [4]
Genetic counseling		By genetics professionals [5]	To inform affected persons & their families re nature, MOI, & implications of CHS to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assessment of family & social structure to determine the availability of adequate support systems	• Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

CHS = Chediak-Higashi syndrome; EM = electron microscopy; HSCT = hematopoietic stem cell transplantation; IEP = individualized education plan; MOI = mode of inheritance; OCT = optical coherence tomography
1. For evidence of cytopenia involving at least two cell lines
2. Elevated serum ferritin and soluble interleukin-2 receptor level are associated with hemophagocytic lymphohistiocytosis (HLH).
3. To assess for hemophagocytosis
4. Hypertriglyceridemia and hypofibrinogenemia are suggestive of liver dysfunction, which can be associated with HLH.
5. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for Chediak-Higashi syndrome.

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Hematopoietic stem cell transplantation (HSCT). The only targeted therapy currently available is HSCT. While HSCT will correct the hematologic and immunologic manifestations of CHS, it does not appear to protect against the development of neurologic manifestations in late adolescence and adulthood.

Preparation for HSCT is often initiated as soon as the diagnosis of CHS is confirmed. HSCT protocols vary by institution.

Best outcomes for HSCT are achieved if initiated prior to the development of hemophagocytic lymphohistiocytosis (HLH); however, if HLH occurs, treatment following the Histiocyte Society HLH-94 protocol is recommended. Once remission of HLH is achieved, HSCT may be performed.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Chediak-Higashi Syndrome: Supportive Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Skin hypopigmentation	Sunscreen	To prevent sun damage & skin cancer
Ophthalmologic	• Corrective lenses for refractive errors • Sunglasses to protect eyes from UV light	
Low vision	Low vision rehab & adaptive therapy	• Children: per educational setting • Adults: low vision clinic

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Infections	Prompt & aggressive use of antibiotic & antiviral agents for bacterial & viral illnesses, respectively	Consideration of prophylactic antibiotics in those w/recurrent infections [1, 2]
Infection risk	Inactivated vaccine administration according to typical schedule	• Live vaccines not recommended [3] • Protection from infectious exposures as much as practical
	Routine dental cleaning & exam to prevent & monitor for periodontal disease	
Bleeding disorder	Intravenous DDAVP® (0.2-0.4 µg/kg over 15-30 mins) 30 mins prior to invasive procedures	For serious trauma or extensive bleeding, platelet transfusion may be necessary.
Neurologic	Parkinsonism	Trial of L-dopa therapy [4]
Musculoskeletal/ADL	Best provided by team comprising neurologist, physiatrist, PT, & OT	• Intensive rehab (or coordinative PT) • Canes/walkers to prevent falls • Home modifications to accommodate motorized chairs as needed • Weighted eating utensils & dressing hooks • Weight control, as obesity can exacerbate difficulties w/ambulation & mobility
Hematologic & immunologic defects	Guidelines for treatment of HLH same as for familial HLH [5, 6, 7, 8, 9]	• HLH-94 protocol is current standard of care & uses combination therapy consisting of etoposide & dexamethasone, w/ continuation phase adding cyclosporine A. • Select persons may also receive intrathecal methotrexate.
	HSCT [9, 10, 11, 12]	• Preparation for HSCT is often initiated as soon as diagnosis is confirmed. • The most favorable outcome is achieved when HSCT is performed prior to development of HLH. • If signs of HLH are present, hemophagocytosis must be brought into clinical remission before HSCT can be performed. [8]

Table 5. continued from previous page.

Manifestation/Concern		Treatment	Considerations/Other
Cognitive/ Educational	**Child**	By neuropsychologist or developmental pediatrician	Establishment or maintenance of IEP or 504 plan
	Adult	By neuropsychologist	Identification of areas that need support

HLH = hemophagocytic lymphohistiocytosis; HSCT = hematopoietic stem cell transplantation; IEP = individualized education plan; OT = occupational therapist/therapy; PT = physical therapist/therapy

1. McCusker & Warrington [2011]

2. For individuals with compromised immune systems and neutropenia who will be undergoing invasive dental procedures or procedures that cause significant bleeding, prophylaxis should be considered (see AAPD Reference Manual of Pediatric Dentistry).

3. Principi & Esposito [2014], Sobh & Bonilla [2016]

4. Bhambhani et al [2013], Introne et al [2017]

5. Better HLH control at the time of HSCT leads to better long-term outcome.

6. Recent evaluation of the HLH-2004 protocol did not find statistical evidence for superiority over the HLH-94 regimen; therefore, HLH-94 remains the standard of care [Bergsten et al 2017].

7. The remission induction rate may be as high as 71% when considering all heritable causes of HLH [Filipovich & Chandrakasan 2015].

8. This treatment is also effective at inducing remission in CHS so that HSCT can be performed [Trottestam et al 2009].

9. This is the only treatment that cures the hematologic and immunologic deficits.

10. The conditioning regimen is at the discretion of the treatment center; however, reduced-intensity conditioning regimens have demonstrated improved survival over traditional myeloablative protocols.

11. Although not specific for CHS, in a cohort of 40 individuals with genetic forms of HLH including CHS, the three-year post-HSCT survival was 92% following reduced-intensity conditioning regimens [Marsh et al 2010].

12. The overall five-year survival rate in 35 children with CHS who underwent HSCT was 62% [Eapen et al 2007].

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 6 are recommended.

Table 6. Chediak-Higashi Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Ocular	Ophthalmologic exam	At least annually or as directed by treating ophthalmologist
Skin	Dermatologic exam for routine monitoring of persons w/ hypopigmentation	At least annually
Hematology/Oncology	Post HSCT: monitoring of chimerism [1, 2] & ongoing post-transplant follow up	According to local center recommendations
	If persons have not undergone HSCT, monitor for signs of HLH using combination of: • Abdominal ultrasound • Complete blood count • Ferritin concentration • Serum triglycerides • Fibrinogen level • Soluble interleukin-2 receptor level Consider bone marrow biopsy if findings of above studies suggest HLH.	At least annually, but more frequently if changes in clinical status
Education	Monitor developmental progress & educational needs.	At each visit
Cognitive issues	By primary care physician or psychologist/neuropsychologist	If changes in clinical status

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Neurologic	Neurologic exam for signs of peripheral neuropathy, ataxia, signs suggestive of parkinsonism, or other changes from baseline daily functioning & independence	Specialized testing at discretion of treating neurologist based on clinical findings
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	At each visit
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).	

HLH = hemophagocytic lymphohistiocytosis; HSCT= hematopoietic stem cell transplantation; OT = occupational therapy; PT = physical therapy

1. Especially in those who undergo HSCT with reduced-intensity conditioning, as the incidence of mixed chimerism in the bone marrow is higher than in those who undergo traditional conditioning.

2. Recent studies suggest that 20%-30% donor chimerism is likely enough to protect against reactivation [Hartz et al 2016].

Agents/Circumstances to Avoid

Avoid the following:

- Live vaccines given the risk of infection due to immunodeficiency
- All nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, ibuprofen) given the risk of exacerbating the bleeding tendency

Evaluation of Relatives at Risk

For early diagnosis and treatment. It is appropriate to evaluate the older and younger sibs of a proband as early as possible. Early diagnosis may provide the opportunity to perform HSCT prior to the development of HLH. Evaluations include:

- Molecular genetic testing if the *LYST* pathogenic variants in the family are known;
- Examination of peripheral blood for the presence of giant granules in white blood cells if the *LYST* pathogenic variants in the family are not known. (Note: Although the giant granules are seen using routine staining techniques, in some individuals with atypical CHS the presence of these giant granules can be somewhat subtle. A hematologist or a clinician experienced in reviewing blood smears for the presence of these giant granules should review the slide.)

For hematopoietic stem cell donation. Any relative considering stem cell donation should undergo molecular genetic testing to clarify their genetic status so that informed risk vs benefit discussions for both recipient and donor can be incorporated into transplant donor-option decision making. Whenever possible, related donors who do not have a familial *LYST* pathogenic variant are preferred.

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

Pregnancy Management

Based on the limited number of pregnancies in females with CHS reported in the literature to date, pregnancy, labor, and delivery were uneventful [Price et al 1992, Weisfeld-Adams et al 2013]. The infants were healthy.

Bleeding during delivery and the postpartum period are a concern; thus, prior to delivery developing a plan to deal with possible bleeding is recommended.

Therapies Under Investigation

A natural history study at the NIH (Study of Chediak-Higashi Syndrome, NCT00005917) is currently enrolling individuals for longitudinal studies but not offering new therapy.

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.

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

Chediak-Higashi syndrome (CHS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are usually heterozygous for a *LYST* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *LYST* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband. Two individuals with CHS caused by uniparental disomy of chromosome 1 have been reported [Dufourcq-Lagelouse et al 1999, Manoli et al 2010].
- 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 *LYST* 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.
- Sibs who inherit the same biallelic *LYST* pathogenic variants as the proband may present with discrepant phenotypes [Morimoto et al 2023].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with CHS are obligate heterozygotes (carriers) for a *LYST* pathogenic variant.

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

Carrier Detection

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

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *LYST* 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.

- **MedlinePlus**
  Chediak-Higashi syndrome
- **Hermansky-Pudlak Syndrome Network, Inc.**
  Phone: 800-789-9HPS
  Fax: 516-624-0640
  Email: info@hpsnetwork.org
  www.hpsnetwork.org
- **International Patient Organization for Primary Immunodeficiencies (IPOPI)**
  United Kingdom
  Phone: +44 01503 250 668

Fax: +44 01503 250 668

Email: info@ipopi.org

ipopi.org

- **National Organization for Albinism and Hypopigmentation (NOAH)**

  Phone: 800-473-2310 (US and Canada); 603-887-2310

  Fax: 603-887-6049

  Email: info@albinism.org

  www.albinism.org

- **European Society for Immunodeficiencies (ESID) Registry**

  Email: esid-registry@uniklinik-freiburg.de

  ESID Registry

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. Chediak-Higashi Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
LYST	1q42.3	Lysosomal-trafficking regulator	LYST database LYSTbase: Mutation registry for Chediak-Higashi syndrome (previously known as CHS1base) Albinism Database Mutations of the Chediak-Higashi Syndrome gene - LYST	LYST	LYST

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 Chediak-Higashi Syndrome (View All in OMIM)

214500	CHEDIAK-HIGASHI SYNDROME; CHS
606897	LYSOSOMAL TRAFFICKING REGULATOR; LYST

Molecular Pathogenesis

LYST encodes the cytoplasmic protein lysosomal-trafficking regulator (LYST), also called CHS1. It has been hypothesized that LYST has a role in the regulation of membrane fusion events and lysosomal size [Tanabe et al 2000, Tchernev et al 2002, Möhlig et al 2007, Morimoto et al 2007]. Studies in *Drosophila* have suggested that LYST plays a role in regulating lysosome-related organelle (LRO) formation and in facilitating centrosome maturation and positioning [Lattao et al 2021]. Another study suggested LYST involvement in autophagosome lysosome reformation facilitates fission of autolysosome tubules for lysosomal homeostasis [Serra-Vinardell et al 2023]. However, the precise biologic role of LYST remains unknown.

Mechanism of disease causation. Loss of function

Variants of uncertain significance (VUS). As the use of broader genomic sequencing increases, identification of VUS is also rising. For individuals identified to have VUS in *LYST*, it is important to correlate the genetic findings with the clinical features following a comprehensive evaluation, specifically taking into consideration the finding of giant granules within leukocytes on the peripheral blood smear (see Suggestive Findings). If a blood smear is unavailable, light microscopy of the hair showing the characteristic pigment clumping throughout the hair shaft may aid in interpretation of VUS.

Chapter Notes

Author Notes

Dr Toro is a movement disorder neurologist who works with the National Institutes of Health Undiagnosed Diseases Program.

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