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Chediak-Higashi syndrome

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Abstract

Purpose of review—Chediak-Higashi syndrome is a rare autosomal recessive disorder characterized by congenital immunodeficiency, bleeding diathesis, pyogenic infection, partial oculocutaneous albinism, and progressive neurodegeneration. Treatment is hematopoietic stem cell transplantation or bone marrow transplantation; however, this does not treat the neurologic aspect of the disease. Mutations in the Lysosomal Trafficking Regulator (*LYST*) gene were identified to be causative of Chediak-Higashi, but despite many analyses, there is little functional information about the LYST protein. This review serves to provide an update on the clinical manifestations and cellular defects of Chediak-Higashi syndrome.

Recent findings—More recent papers expand the neurological spectrum of disease in CHS, to include hereditary spastic paraplegia and parkinsonism. Granule size and distribution in NK cells have been investigated in relation to the location of mutations in LYST. Patients with mutations in the ARM/HEAT domain had markedly enlarged granules, but fewer in number. By contrast, patients with mutations in the BEACH domain had more numerous granules that were normal in size to slightly enlarged, but demonstrated markedly impaired polarization. The role of LYST in autophagosome formation has been highlighted in recent studies; LYST was defined to have a prominent role in autophagosome lysosome reformation for the maintenance of lysosomal homeostasis in neurons, while in retinal pigment epithelium cells, LYST deficiency was shown to lead to phagosome accumulation.

Summary—Despite CHS being a rare disease, investigation into LYST provides an understanding of basic vesicular fusion and fission. Understanding of these mechanisms may provide further insight into the function of LYST.

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Conflicts of interest

The authors have no conflict of interest to declare.

Keywords

Lysosomes; bone marrow transplantation; neurodegeneration; rare disorders; congenital autoimmune disease

Introduction

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by congenital immunodeficiency, bleeding diathesis, pyogenic infection, partial oculocutaneous albinism, and progressive neurodegeneration. It is also associated with hemophagocytic lymphohistiocytosis (HLH), or the accelerated phase, a hyperinflammatory condition that is the primary cause of mortality in CHS [1–3].

A key diagnostic feature of CHS is enlarged granules within the leukocytes on a peripheral blood smear. Neutropenia and decreased Natural Killer (NK) cell number and function may also be present [4]. Fewer than 500 cases have been reported in literature worldwide.

Biallelic mutations in *LYST* cause CHS. *LYST* is located on 1q42.3 of chromosome 1 and spans ~222 MB of DNA. Most of the mutations in *LYST* are either homozygous or compound heterozygous missense, frameshift, or nonsense. *LYST* encodes a large protein that has a putative lysosomal trafficking function. Despite the identification of mutations of *LYST* as the molecular cause of disease six decades ago, the precise function of LYST has not been established.

In this paper, we review the clinical phenotypes associated with CHS, the current approaches for therapy, and discuss the most recent updates about the function of LYST. We also provide a summary of the multiple animal and cell models generated to further understand the molecular pathology of the disease.

Clinical manifestations

CHS is an autosomal recessive disorder with varying clinical manifestations. Patients typically present with partial oculocutaneous albinism, congenital immunodeficiency, and bleeding diathesis in early childhood; however, some individuals have an atypical phenotype that may not be detected until adolescence or adulthood [5–7]. Partial oculocutaneous albinism in patients with CHS presents with varying degrees of pigmentation and can include the hair, skin, and eyes [1]. Hair color is variable, but most commonly is lighter with a silvery, or metallic sheen (Figure 1A) [1, 6]. Pigment clumping can be observed in the hair shaft of patients with CHS (Figure 1B). Reduced pigmentation may be seen in the iris and retina; however, individuals have been reported with no evidence of ocular albinism [6]. Clinically, patients may present with photophobia, nystagmus, and changes in visual acuity [1, 6]. Vision loss may be progressive [8, 9].

Giant inclusions within the cytoplasm of leucocytes are pathognomonic of CHS (Figure 1C, D). These inclusions impair leucocyte function leading to immune dysfunction. Neutropenia may be present, as well as decreased Natural Killer cell number and function. Individuals

with CHS often have recurrent infections, predominantly bacterial, typically of the skin and respiratory systems [4]; however, individuals with the atypical phenotype may not have unusual, severe, or recurrent infections.

Patients with CHS have an increased bleeding tendency. While platelet counts are typically normal, platelet dense granules are diminished or absent (Figure 1E), leading to coagulation defects characterized by increased bruisability and mucosal bleeding [10–12].

The above phenotypes have previously been used to classify CHS as either “typical” or “atypical”. Nonetheless, further delineation of the phenotypes through our natural history studies (clinicaltrials.gov, NCT00005917, Investigations into Chediak-Higashi Syndrome and Related Disorders) suggest that this classification is arbitrary because of the overlapping and variable phenotypes found in both groups.

The majority of patients with CHS experience hemophagocytic lymphohistiocytosis (HLH), or the “accelerated phase” [13, 14]. HLH is a potentially fatal, inflammatory disorder characterized by fever, cytopenias, hepatosplenomegaly, and lymphadenopathy [15]. Abnormal NK cell function or Epstein-Barr viral infection have both been suggested as triggers of HLH in patients with CHS [1,16]. HLH is initially treated with a combination of steroids and chemotherapy followed by hematopoietic stem cell transplantation (HSCT) [17]. HSCT is often considered as soon as the diagnosis of CHS is confirmed and corrects the immunologic and hematologic manifestations. Individuals with the atypical phenotype appear to be at a lower risk of HLH [1].

Neurological manifestations are characteristic of CHS. Learning disabilities can be observed in patients with CHS early during the disease course, while a more severe neurologic decline is observed later in disease progression [6, 18]. Progressive neurodegeneration is seen in most patients with CHS, but the onset and presentation are highly variable. Sensorimotor neuropathy is a common neurological manifestation that typically appears in the second and third decades of life while some patients may also develop diffuse motor neuronopathy [19]. Cerebellar ataxia is a common neurological symptom; cerebellar and cerebral atrophy may be observed later in the disease course (Figure 1F) [5–7, 20, 21]. In some severe cases, patients present with a parkinsonism phenotype [5, 22]. Additionally, adolescents and adults have also been diagnosed with CHS after presenting with complicated hereditary spastic paraplegia further expanding the neurologic phenotype [20]. Classical and atypical phenotypes cannot be distinguished neurologically [6].

Cellular defect

CHS has been regarded as a lysosomal disorder. This is in part due to the presence of the canonical enlarged lysosomes noted in primary cells from patients, including fibroblasts and melanocytes [23]. Overall, the primary cellular defect associated with CHS is the perturbation in the biogenesis of lysosomes and LRO that ultimately lead to mistargeting of membrane proteins in trans-Golgi network, endosomes, lysosomes, and plasma membrane. In patients with CHS, all cell types exhibit enlarged lysosomes or lysosome-related organelles (LRO) (Figure 2A, B). Some abnormal LROs in CHS

patient cells are melanosomes, lytic granules, basophil granules, azurophil granules, major histocompatibility complex (MHC) class II molecules, and platelet dense bodies. CHS melanocytes contain enlarged and irregularly shaped melanosomes. These melanosomes are observed to have localized pigment deposits, resulting in the abnormal pigmentation of oculocutaneous albinism [23]. MHC class II molecules first show a delay in maturation and peptide loading, then a delay in transport to the cell surface [24]. Cytotoxic T lymphocytes in patients with CHS cells contain enlarged lysosomes and have decreased cytotoxicity. Decreased cytotoxic activity is likely caused by a defect in membrane fusion and fission, as the giant granules in cytotoxic T lymphocytes are unable to secrete their contents [25].

A human NK cell model with disruption of the *LYST* gene was observed to have enlarged granules, as well as decreased cytolytic activity [26]. While function of NK cells is impaired, they are still able to deliver small amounts of granzyme B to target cells. In contrast, cytokine production and secretion are not affected by *LYST* disruption [27]. Cytotoxicity of NK cells seem to be restored following HSCT.

Mutations in LYST cause Chediak Higashi Syndrome

The *LYST* gene consists of 53 exons and a 13.5 Kb mRNA transcript that encodes a 429 kDa protein (Figure 3A). There is no systematic review about biallelic *LYST* mutations associated with Chediak Higashi syndrome. Nonetheless, mutations seem to be scattered all throughout the gene and are a combination of point/missense mutations, insertion/deletion, or frameshift variants [1, 3, 5, 7, 23, 28–46]. A few reports identify canonical splice-site mutations and association with uniparental isodisomy [47, 48].

Domains of LYST

To date, no crystal structure for LYST has been identified. Several *in silico* studies have identified functional domains through homology comparison [46, 49]. These domains include the pleckstrin homology (PH) [49], beige and CHS (BEACH) domains; and several WD40 domains [46] (Figure 3B). The N-terminal region of LYST has been regarded to have a series of alternating hydrophobic helices and regions that resemble ARM and HEAT repeat motifs [46] that are involved with vesicular transport. The PH domain is usually a homology domain in BEACH domain containing proteins. PH domains have diverse functions and are involved in targeting proteins to the membrane or a subcellular location, or to an interaction with a binding partner. The BEACH domain has been subsequently identified in other human proteins (LRBA, NBEA, NBEAL1, NBEAL, NSMAF, WDRFY2, and WDR81). Using NBEA to analyze the crystal structure of BEACH, it has been proposed that the combined PH-BEACH motifs may present a single continuous structural unit involved in protein binding, as studies have provided evidence for the requirement of both domains for activity [49].

The WD40 domain is involved in mediating protein-protein interactions [50] involved in targeting proteins to subcellular compartments; this domain is usually seen in proteins that function as adaptor/regulatory modules in signal transduction, pre-mRNA processing and cytoskeleton assembly. A single paper correlated the domains of LYST and associated

cellular phenotype [51]. Overexpression of the carboxy-terminal part of LYST, which contained the BEACH and WDR40 domains, in cells showed enlarged lysosomal phenotype. Similarly, expression of a part of the amino terminal domain (specifically, FM2, which includes amino acids 736–1410) resulted to the same dominant negative cellular phenotype [51]. A more recent paper investigated granules in NK cells in relation to the location of mutations in *LYST*. Patients with mutations in the N-terminal region where the putative ARM/HEAT domain is had markedly enlarged granules but less in number; these granules could polarize to the synapse but could not fuse with the plasma membrane. On the other hand, patients with mutations in the BEACH domain had more granules, but the granules seemed to be normal in size or slightly enlarged; these granules had markedly impaired polarization [27].

In yeast hybrid studies [52], the N-terminal domain of LYST has been shown to interact with Casein kinase II β subunit (CKIIβ) and hepatocyte growth factor (HRS), two proteins implicated in vesicular trafficking and signal transduction. Interestingly, HRS is known to bind to the SNARE protein complex, which regulates vesicle docking and fusion. LYST was also shown to interact with Calmodulin (CALM), which is a Ca^{++}-binding protein also involved in vesicular trafficking and signal transduction. These studies support the hypothesis that LYST is involved with vesicular trafficking.

Animal Models

Several animal models of CHS, or a disease resembling CHS, have been characterized. A spontaneous murine mutant was identified in 1960, colloquially known as the "*beige* mouse," in reference to its altered beige coat color, is the most well studied animal model of CHS [3, 4, 46, 53]. Examination of the *beige* mouse revealed enlarged cellular granules and propensity to infection, recapitulating human CHS [54]. A knockout mouse model [55], Aleutian mink [56], Japanese black cattle [57], Brangus cattle [58], blue fox [59], Beige rat [60, 61], Persian cat [62], Corn snake [63], *Orcinus orca* [64, 65], *Drosophila mauve* [66], *Caenorhabditis elegans* models [67], have all been characterized with varying phenotypical manifestations (Table 1). The *Lyst* knockout mouse, Aleutian mink, and lavender corn snake all present with a diluted coat color and enlarged lysosomes or LROs, but they do not exhibit any other clinical manifestations of CHS. The Persian cat, blue fox, Japanese black cattle, *Drosophila mauve,* and both beige rat models also exhibit abnormal coat color and enlarged LROs; however, they additionally present with bleeding diathesis and immunodeficiency, similar to patients with CHS and the beige mouse. The *C. elegans* model, however, is characterized to have lysosomes smaller than the wild type, as well as changes in autofluorescence and gut granule morphology.

LYST, a protein involved in lysosomal processes

While the exact function of LYST remains unknown, a role in lysosomal trafficking has been alluded to. Cells deficient in *LYST*, both in patient-derived fibroblasts and *beige* mouse embryonic fibroblasts, show enlarged lysosomes that are mostly perinuclear. CHS lysosomes also are observed to have defects in membrane fusion and fission. Overexpression of LYST in fibroblasts produced diminished lysosomes, suggesting that LYST has a role in lysosomal

fission [68, 69]. It is suggested that if LYST acts to regulate membrane fusion and fission, it would explain the enlarged lysosomes of CHS, as well as the inability of lysosomes to fuse to the plasma membrane [68]. These findings are consistent with a previous suggestion that LYST interacts with a soluble N-ethylmaleimide-sensitive factor attachment protein receptor that is also involved in membrane fusion.

Lysotracker staining of acidic vesicles has shown that LYST deficiency does not affect the acidity of CHS patient lysosomes, however lysotracker staining in *mauve* lysosomes shows reduced signal. Another study of *mauve* flies has suggested that autophagosomes are also enlarged after starvation [70], which is in contrast with studies using patient fibroblasts that suggested that LYST does not affect lysosome degradation or trafficking of cargo via autophagy, endocytosis or retrograde transport [69]. Using *Drosophila mauve*, a more recent study revealed that LYST not only regulates LRO formation but also centrosome behavior [70].

LYST was also suggested to have a role in oxidative stress, specifically in the retinal pigment epithelium (RPE). In mice, there is impaired degradation of photoreceptor outer segment phagosomes, and this was associated with elevated oxidative stress and accumulation of cysteine cathepsins and matrix metallopeptidase (MMP) 3, ultimately resulting to reduced adhesion between the RPE and the neural retina [71]. This study could suggest a secretory function of LYST.

A more recent paper defined the role of LYST in autophagosome lysosome reformation (ALR) in facilitating fission of autolysosome tubules for the maintenance of lysosomal homeostasis [72]. Further studies will be needed to confirm these findings in animal models, to determine if the abnormality in ALR could be used as a potential readout for exploring therapy for CHS.

Treatment

Patients with HLH are treated the same as for familial HLH with a combination of steroids and chemotherapy, followed by HSCT [17, 73]. HSCT has the best outcome if performed prior to the development of HLH and is often considered as soon as the diagnosis of CHS is confirmed. Treatment with HSCT is generally effective against immunodeficiency and subsequent infection. Similarly, improvement of periodontitis in patients following HSCT has been reported [74]. If patients have already entered the accelerated phase, they generally experience a greater rate of mortality [75].

Neurological symptoms are not improved by HSCT. Patients with parkinsonism may benefit from L-dopa; adaptive equipment and rehabilitation services are recommended for patients. Patients who have not been treated with HSCT, or those at risk for recurrent infections, should have prompt treatment with antibiotics and antivirals. In individuals with recurrent infections, prophylactic antibiotics may be considered. Corrective lenses can be used to help improve visual acuity. Sun protection is important for patients with hypopigmentation to protect against UV damage [1].

Conclusion and future directions

Mutations in *LYST* are causative of Chediak-Higashi syndrome, presenting molecularly with enlarged lysosomes and LROs. While clinical manifestations can be controlled with HSCT and L-dopa, there is no approved therapy for the disease. Further investigation into the function of LYST will help us understand the mechanism of disease and could help identify therapeutic targets in the future.

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Key Points

- Biallelic mutations in *LYST* are causative of Chediak- Higashi syndrome.
- Neurologic manifestations occur frequently in CHS and are not improved with HSCT.
- CHS is a regarded as a lysosomal disorder due to the canonical enlarged lysosomes in primary patient cells.
- LYST may be involved in lysosomal homeostasis by facilitating fission of autolysosome tubules.

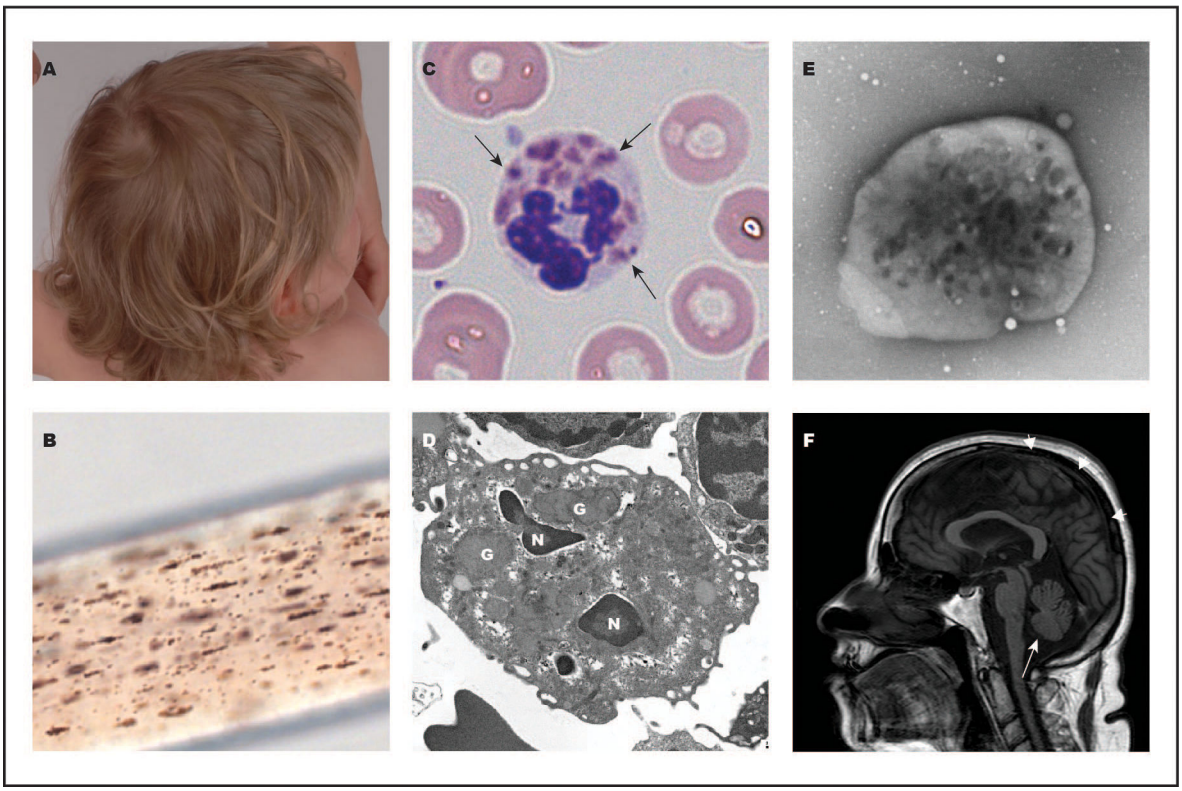

Figure 1. Clinical features of patients with Chediak Higashi syndrome.

Patients with CHS manifest with light colored or silvery hair that can have a metallic sheen (**A**); viewed under a light microscope, pigment clumping can be seen in the hair shaft (**B**). Peripheral blood smear reveals the pathognomonic giant inclusions (arrow) within the cytoplasm of leucocyte (**C**). By transmission electron microscopy (EM) of plastic-embedded leucocyte-rich samples, these giant inclusions, G, appear to be membrane bound inclusions of amorphous materials (**D**) outside the nucleus, N. Another finding that supports the diagnosis of CHS is the paucity of platelet dense granules visible by whole mount EM of unfixed platelets (**E**). Patients with CHS also present with cerebral (arrowheads) and cerebellar atrophy (arrow) later in the disease course, as seen in representative brain MRI image (**F**).

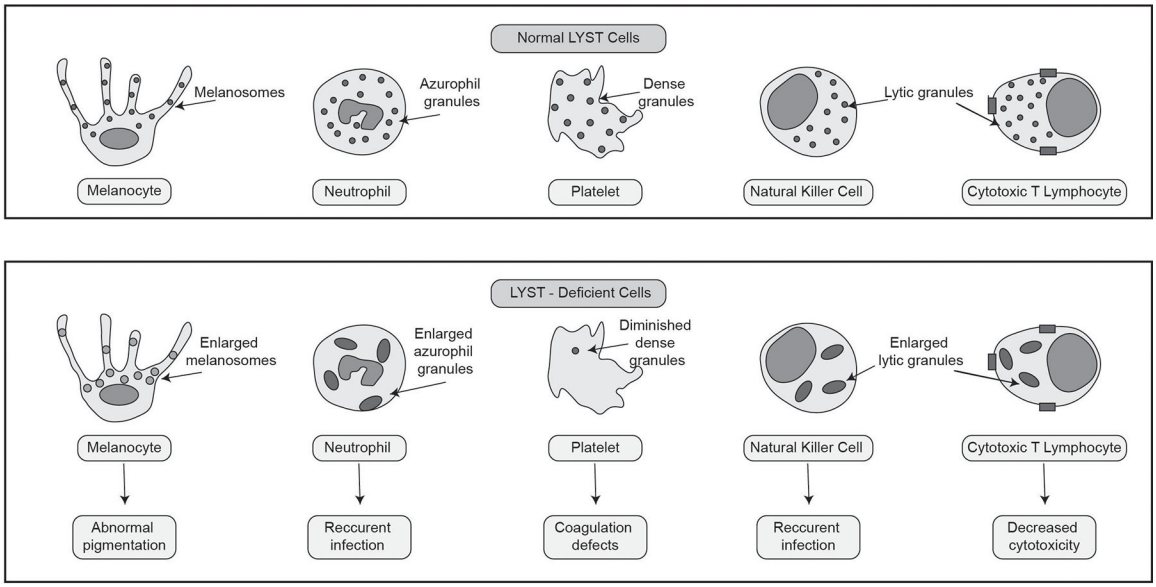

Figure 2. Defects of LYST- deficient cells.

An illustration of the comparison of cells with functional LYST and LYST-deficient cells. Cells with functional LYST and their normal lysosome-related organelles (LROs) (**A**). LYST-deficient cells and their abnormal LROs, as well as the clinical manifestation related to the LYST deficiency (**B**). Melanocytes are observed to have enlarged melanosomes, which lead to abnormal pigmentation. Neutrophils have enlarged, dysfunctional azurophil granules, presumably a factor in the recurrent infections of CHS patients. Platelets are observed to have absent or diminished dense granules, leading to coagulation defects and a propensity to bleeding. Natural killer cells and cytotoxic T lymphocytes both present with enlarged lytic granules, leading to recurrent infection and decreased cytotoxicity, respectively.

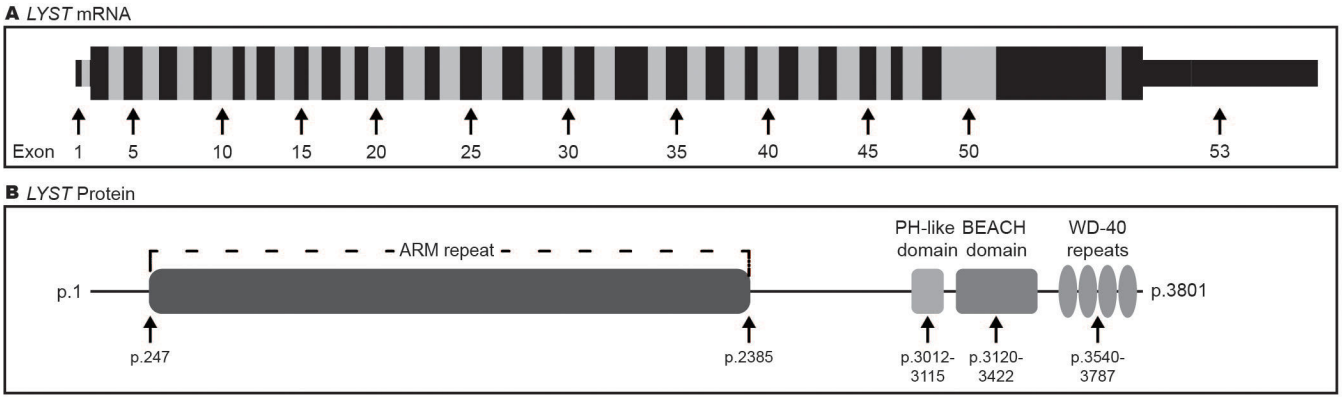

Figure 3. Domains of LYST.

The *LYST* gene consists of 53 exons and a 13.5 Kb mRNA transcript (**A**) that encodes a protein of 3801 amino acids (**B**). Several functional domains have been identified in the LYST amino acid sequence. An Armadillo (ARM) repeat resides at the amino terminus from amino acids 247–2385. The pleckstrin homology (PH) domain is located at amino acids 3012–3115. The beige and CHS (BEACH) domain follows the PH domain from amino acids 3120–3422. A WD-40 repeat is located at the carboxyl terminus, amino acids 3540–3787.

Table 1.

Animal models of Chediak-Higashi syndrome

Organism	Molecular Change	Manifestation
Beige mouse [3, 4, 46, 53]	*Beige* gene homologous with human *LYST* Spontaneous mutation on beige critical region onmouse chromosome 13 5-kilobase deletion	Hypopigmentation in coat & eye color Enlarged melanosomes & lysosomes Abnormal chemotaxis Prolonged bleeding time with normal platelet count
Lyst Knockout mouse [55]	*Lyst* targeted mutation 1b Homozygous null *Lyst* mutation	Decreased coat pigmentation
Aleutian mink [56]	Mink *LYST* gene homologous with human *LYST* Frameshift mutation on mink chromosome 2	Diluted coat color Undetectable clinical manifestations
Japanese black cattle [57]	Bovine *LYST* gene homologous with human *LYST* Nucleotide substitution, resulting in amino acidsubstitution Bovine chromosome 28	Partial albinism Inherited bleeding disorder Abnormal granules in leukocytes Decreased number of dense granules
Brangus cattle[58]	Unknown genetic mutation Possible autosomal recessive inheritance	Partial albinism Enlarged lysosomes in neutrophils, eosinophils & renaltubular epithelial cells Irregular distribution of melanin granules in hair Severe infection Increased bleeding tendency
Blue fox [59]	Unknown	Enlarged granules in hair & white blood cells Increased bleeding tendency
DA-beige rat [60]	*Beige* mutation homologous with human *LYST* Deletion of exons 28–30 of rat *Lyst*	Diluted coat color Enlarged granules in neutrophils & eye melanosomes Prolonged bleeding time NK activity impaired
ACI/N-*Lyst*beige rat [61]	Deletion in *Lyst* gene Deletion of *Lyst* exons 28–30	Beige coat color Giant granules in leukocytes, mast cells, eosinophils &melanocytes Slightly enlarged granules in neutrophils & lymphocytes Prolonged bleeding time
Persian cat [62]	Feline *LYST* gene 20-kilobase segmental duplication in *LYST* exons 30–38	Hypopigmentation in coat & eye color Enlarged granules in neutrophils, eosinophils & basophils Enlarged melanin granules in hair & skin Increased bleeding tendency
Lavender corn snake [63]	Single nucleotide polymorphism Premature *LYST* stop codon Loss of 602 amino acids Recessive single locus variant	Enlarges lysosomal-related organelles (melanosomes) Diluted pigmentation resulting in lavender phenotype No other clinical phenotype
Orcinus orca [64, 65]	Unknown – likely runs of homozygosity	Albinism, enlarged granules in peripheral blood neutrophils. Postmortem analysis showed mediastinal abscesses, pyometra, pneumonia, influenza, salmonellosis, nephritis
Drosophila mauve[66]	*Mauve* gene encodes *DrosophilaLYST*	Enlarged lysosomes Defect in innate immunity Decreased number of eye pigment cells Enlarged eye pigment cells
Caenorhabditis elegans[67]	*lyst-1* mutation homologous to human *LYST* Might facilitate association with RAB5 & GFP	Decreased lysosome size Expression of *lyst-1* in intestines, neurons, andpharyngeal cells Altered autofluorescence Changes in gut granule morphology & number