Chapter 2

Lysosomal Dysfunctions in Hereditary Spastic Paraplegias

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Additional information is available at the end of the chapter

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Abstract

Hereditary spastic paraplegias (HSPs) comprise a heterogeneous group of inherited neurodegenerative diseases with the cardinal feature of a length-dependent degeneration of corticospinal motor axons. They are classified by their mapped genetic loci, SPG1–SPG78. Recently, lysosomal dysfunction is one of the pathomechanism for some autosomal-recessive HSPs. SPG11 is caused by loss-of-function mutations in the *SPG11* gene. Its gene product is called spatacsin, which is needed for the recycling of lysosomes from autolysosomes. SPG15 is caused by loss-of-function mutation in the *ZFYVE26* gene. The ZFYVE26 gene encodes spastizin. Mutations in spastizin impair autophagosome maturation and lead to an accumulation of immature autophagosomes. *SPG48*/*KIAA0415* encodes AP5Z1, known to be a spatacsin and spastizin interactor. Its mutations lead to loss of protein or mutated forms of protein with defective autophagy. The TECPR2 is a human ATG8-binding protein and positive regulator of autophagy, which plays a key role in major adult and pediatric neurodegenerative diseases. Mutations in the *lysosomal trafficking regulator* (*LYST*) gene have been reported to cause hereditary spastic paraplegia. The LYST protein is involved in control of the exocytosis of secretory lysosomes. Recently, Drosophila with a gene mutation of an LYST homolog was revealed to exhibit impaired autophagy.

Keywords: SPG11, SPG15, SPG48, SPG48, SPG49, Chediak-Higashi syndrome, lysosomal trafficking regulator, autophagy

1. Introduction

Lysosomal dysfunction, especially disturbance of the autophagy-lysosomal system, substantially contributes to the pathodynamics of some major neurodegenerative disorders: Alzheimer disease, Parkinson disease, Huntington disease, frontotemporal dementia,

amyotrophic lateral sclerosis, bulbospinal muscular atrophy and spinocerebellar ataxia 3, hereditary spastic paraplegias (HSPs), and so on [1].

Hereditary spastic paraplegias (HSPs) comprise a heterogeneous group of inherited neurodegenerative diseases with the cardinal feature of a length-dependent degeneration of corticospinal motor axons [2]. They are classified by their mapped genetic loci, SPG1–SPG78. To date, over 60 causative genes have been identified, transmitted by autosomal-dominant, autosomal-recessive (AR), X-linked recessive inheritances, with *de novo* mutations also described.

Several pathogenic mechanisms of HSPs were suggested by the studies in several causative genes for HSP. HSP might result from disruption of the axonal transport of molecules, organelles, and other cargos, which mainly affect the distal parts of motor neurons. Other mechanisms for developing HSP are endoplasmic reticulum formation, membrane trafficking, mitochondrial function [3], lipid metabolism, and myelination. Recently, lysosomal dysfunction is one of the pathomechanism for some autosomal-recessive HSPs: SPG11, SPG15, SPG49, SPG78, and HSP with *lysosomal trafficking regulator* (*LYST*) gene mutation [4, 5].

2. SPG11

The most prevalent autosomal-recessive (AR) HSP is SPG11. SPG11 is characterized by early onset spastic paraplegia with mental impairment and peripheral neuropathy. Brain MRI shows thin corpus callosum (TCC) [6] (**Figure 1**).

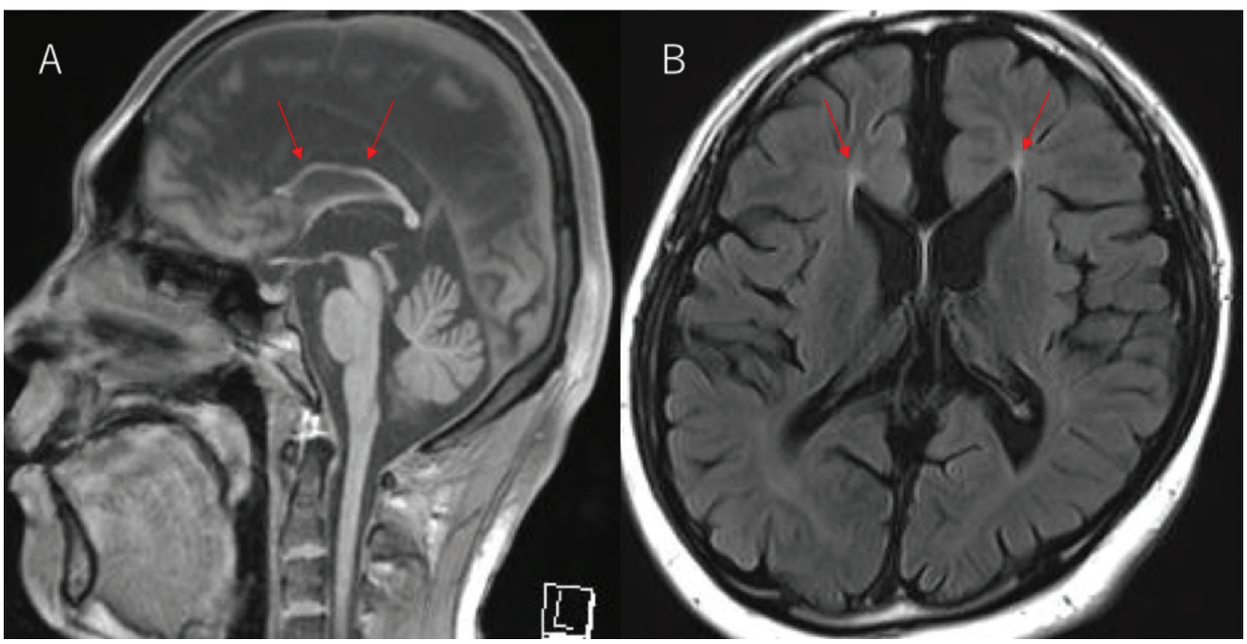

Figure 1. Brain MRI findings of the SPG11 patient. (A) Sagittal T1 image showing a thin corpus callosum, especially the anterior part. (B) Axial FLAIR image showed subtle ears of the lynx formation at the anterior periventricular portions of the lateral ventricles.

There may be upper limb involvement and nystagmus. Some patients additionally present with parkinsonism or ataxia. Patients with an amyotrophic lateral sclerosis (ALS)-like upper motor neuron-dominant phenotype but with atypically long disease duration and absence of TCC or mental impairment (ALS5) had been reported [7]. Moreover, peripheral neuropathy-dominant phenotype (Charcot-Marie-Tooth disease like) has been described recently [8].

Pathological features of SPG11 in neurons are mainly intracytoplasmic granular lysosome-like structures in supratentorial areas, and others in subtentorial areas are ubiquitin and p62 aggregates, observed in amyotrophic lateral sclerosis (ALS), except that they are never labeled with anti-TDP-43 or anti-cystatin C [9].

SPG11 is caused by loss-of-function mutations in the *KIAA1840* gene on chromosome 15q. *KIAA1840*, encoding spatacsin, is expressed ubiquitously in the nervous system, but most prominently in the cerebellum, cerebral cortex, hippocampus, and pineal gland. Its gene product is called spatacsin, which is needed for the recycling of lysosomes from autolysosomes, a process known as autophagic lysosome reformation (ALR). Loss of spatacsin (or spastizin) resulted in the depletion of free lysosomes, which are competent to fuse with autophagosomes, and an accumulation of autolysosomes, reflecting a failure in ALR. Moreover, spatacsin and spastizin were essential components for the initiation of lysosomal tubulation [10]. Fibroblasts prepared from patients with SPG11 have selective enlargement of LAMP1-positive structures, though prominent abnormal lysosomal storage was not evident [11].

In spatacsin-null mice, lysosomes are diminished in cortical neurons and Purkinje cells *in vivo*. The decreased number of lysosomes useful for fusion with autophagosomes damages autolysosomal clearance, results in the accumulation of undegraded substances, and finally causes death of particularly susceptible neurons like cortical motor neurons and Purkinje cells in knockout mice [12].

3. SPG15

SPG15 is the second most common type of hereditary spastic paraplegia with thin corpus callosum. SPG15 cases show similar symptoms to those observed in SPG11. Clinical manifestation in addition to spastic paraplegia includes intellectual disability, pigmentary retinopathy (Kjellin syndrome), cerebellar ataxia, parkinsonism, and axonal neuropathy. Brain MRI often shows thin corpus callosum.

SPG15, the second most autosomal-recessive HSP, is caused by loss-of-function mutation in the *ZFYVE26*/*SPG15* gene. The ZFYVE26 gene encodes a large protein of 2539 amino acid residues termed spastizin.

In zebrafish, spastizin, together with spatacsin, is essential for proper establishment of the motor neuron axonal network; these proteins are indeed necessary for outgrowth and proper targeting of motor neuron axons [13].

Spastizin interacts with the autophagy-related Beclin 1-UVRAG-Rubicon multiprotein complex and is involved in autophagosome maturation. Mutations in spastizin disrupt its interaction with Beclin 1 and thus with the complex, damaging autophagosome maturation and resulting in a retention of immature autophagosomes in patient's fibroblasts. Similarly, a deposition of autophagosomes was detected in SHSY5Y cells and in primary hippocampal neurons after spastizin silencing, thus indicating that autophagy impairments by spastizin deficiency give rise to both neuronal and non-neuronal cells [14].

Spastizin is expressed in the identical organs as spatacsin (SPG11) and partially coexists with microtubules, mitochondria, and the nucleus. Spastizin is also observed at the midbody during cytokinesis. The spastizin interacts with spatacsin and with KIAA0415 (SPG48), a member of the AP5 complex. Mutations lead to loss of protein or mutated forms of protein with defective autophagy [14].

Zfyve26 knockout mice developed normally by 12 months of age acquire a spastic and ataxic gait disorder accompanied by neuron loss in the motor cortex and the cerebellum, consistent with the clinical phenotype of SPG15 patients [15]. High-density LAMP1-positive membrane-bound vesicles and lipopigment accumulate in neurons of *Zfyve26* knockout mice [15].

4. SPG48

Two siblings in the one French family have pure adult-onset spastic paraplegia and urinary incontinence with hyperintensity of the cervical spinal cord (C3-4,7) in one sibling as the only distinguishing magnetic resonance imaging (MRI) feature [16]. Thereafter, clinical features included not only prominent spastic paraparesis but also sensory and motor neuropathy, ataxia, dystonia, parkinsonism, and myoclonus. Skin fibroblasts from SPG48 patients tested positive for periodic acid Schiff (PAS) and intrinsic fluorescence material, while electron microscopic analysis indicated lamellar material concordant with abnormal storage of lysosomal material [17].

An insertion/deletion mutation has been identified in *SPG48*/*KIAA0415* in two HSP families. *KIAA0415* encodes a presumptively helicase (AP5Z1), localized in both nucleus and cytoplasm, participated in DNA double-strand break repair processes, and interacted with spatacsin and spastizin. Especially, spatacsin is phosphorylated upon DNA damage by protein kinases ataxia telangiectasia mutated (ATM) or ATR (ATM and Rad3-related) [16]. A recent study showed that the protein is a member of the adaptor protein 5 complex (AP5) that is implicated in vesicle formation and sorting (as AP4) [18].

5. SPG49

A homozygous truncating mutation in SPG49/TECPR2 (tectonin beta-propeller repeat containing 2) was identified in a new form of complicated HSP [19]. This HSP is characterized by

early onset of spastic paraplegia, motor development delaying, mental retardation, dysmorphic features (short stature, round face, low anterior hairline, dental crowding, short broad neck, mild brachycephalic microcephaly, a chubby appearance), cerebellar dysarthria, ataxia, episodes of central apnea, and TCC on brain MRI.

TECPR2 protein has been established to be a binding partner of the mammalian Atg8 protein family, including LC3, and a probable positive regulator of autophagosome formation [20]. Using fibroblast of affected SPG49 patients and knockdown of TECPR2 using siRNA in cultured cell lines, loss of TECPR2 was found to result in a decreased number of autophagosomes and reduced delivery of LC3 and p62 for lysosomal degradation [19]. Recent study showed that TECPR2 is involved in maintaining functional endoplasmic reticulum exit sites, which may serve as scaffolds for the formation of autophagosomes [21].

6. SPG78

The disease presentation in SPG78 patients was dominated by an adult-onset lower-limb predominant spastic paraparesis. Cognitive impairment was present in most of the cases and ranged from very mild deficits to advanced dementia with frontotemporal characteristics. Nerve conduction studies revealed involvement of the peripheral motor and sensory nerves. Only one of five patients with hereditary spastic paraplegia showed clinical indication of extrapyramidal involvement in the form of subtle bradykinesia and slight resting tremor. Neuroimaging cranial investigations revealed pronounced vermian and hemispheric cerebellar atrophy. Notably, reduced striatal dopamine was apparent in the brain of one of the patients, who had no clinical signs or symptoms of extrapyramidal involvement [22].

ATP13A2, which is causative protein of SPG78, is a lysosomal P5-type transport ATPase, the activity of which critically depends on catalytic autophosphorylation. Biochemical and immunocytochemical experiments in COS-1 and HeLa cells and SPG78 patient-derived fibroblasts demonstrated that the hereditary spastic paraplegia-associated mutations, similarly to the ones causing Kufor-Rakeb syndrome and neuronal ceroid lipofuscinosis, cause loss of ATP13A2 function due to transcript or protein instability and abnormal intracellular localization of the mutant proteins, ultimately impairing the lysosomal and mitochondrial function [22]. They confirm in fibroblast of SPG78 patients that LAMP1-positive organelles accumulate, correlating with a reduction in their proteolytic activity. These findings are similar to that of SPG11 and SPG15 [10, 11, 14]. ATP13A2 has been implicated in autophagy pathway [23].

7. HSP due to *LYST* mutation

We encountered an autosomal-recessive (AR) HSP family with cerebellar ataxia and neuropathy whose gene locus was not linked to previously reported AR-HSP loci. We have identified a novel

homozygous missense mutation in the *lysosomal trafficking regulator* (*LYST*) gene, a nuclear gene encoding for a protein involved in intracellular trafficking [24]. *LYST* is described as the causative gene for Chediak-Higashi syndrome (CHS, OMIM #214500), which is a rare autosomal-recessive syndrome characterized by hypopigmentation, severe immune-deficiency, a bleeding tendency, and progressive neurological dysfunction [25]. We describe a CHS family including two patients who show variable degrees of spastic paraplegia, cerebellar ataxia, and neuropathy, whereas they exhibit no apparent skin hypopigmentation and blood or immune system abnormalities (**Figure 2**).

The study included two patients in a Japanese consanguineous family (**Figure 2**). Neurologic examination was performed in two patients. Detailed clinical and laboratory findings of the two patients were shown in **Table 1** and **Figures 3** and **4**. Blood examinations revealed peroxidase-positive giant granules in granulocytes in two cases (**Figure 4**).

DNA analysis was done in two patients and two normal family members. We performed a genomewide linkage analysis employing SNP arrays with two patients' DNAs (**Figure 5A**) and exome sequencing using one patient's sample. We confirmed the mutation by Sanger sequencing of the family members (**Figure 5B**).

We identified a homozygous missense mutation (c.4189T>G, p.F1397V) in the *lysosomal trafficking regulator* (*LYST*) gene in the two patients. (**Figure 5B**). This mutation co-segregated with the disease in the family and located at the well-conserved amino acid. (**Figure 5C**). We also detected a heterozygous nonsense mutation (c. 823C>T, p.R275X) in the *BSCL2* gene in one patient (III-3), not in another one (III-1) (**Figure 5C**). *BSCL2* is the causative gene for SPG17. This mutation is deleterious [26], and we suggest that this nonsense mutation is implicated in phenotype differences between two cases: leg spasticity of III-3 is stronger than that of III-1.

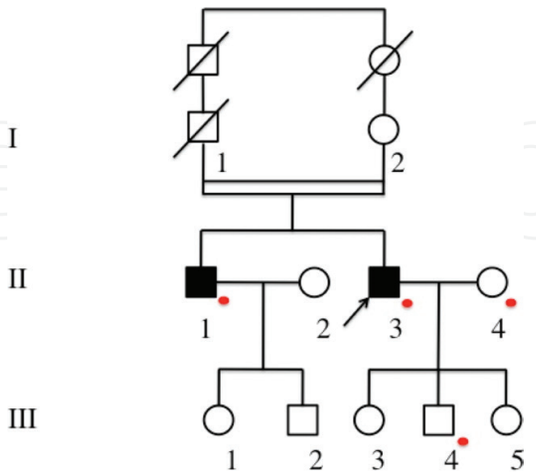

Figure 2. Family pedigree with *LYST* gene mutation. The proband (III-3) and his older brother (III-1) show the almost same clinical phenotype. Other members are all healthy except for deceased elderly ones. The parents (II-1 and 2), who were first cousins, were neurologically asymptomatic. Arrow indicates the proband, and dots indicate the persons who permit analysis of their DNAs.

	III-1	III-3
Age at examination	63	53
Onset	58	48
Leg spasticity	–	+
Limb ataxia	+	+
Thigh muscle atrophy	+	+
Patellar Tendon Reflex (PTR)	–	++
Achilles Tendon Reflex (ATR)	+ –	–
Babinski sign	+	+
Vibration sense	Normal	Normal
Sphincter involvement	–	–
Mini-Mental State Examination (MMSE)	16/30	25/30
Lower limb NCV	FWCV decreased	Decreased
Sural nerve biopsy	Axonal swelling, myelin↓	(Not examined)
Brain MRI	Cerebellar atrophy	Cerebellar atrophy
Spinal MRI	Normal	Thoracic atrophy
Large granules in granulocytes	+	+
Phagocytic activity of leukocytes	98.7%	(Not examined)
NK-cell activity (18–40)	11	14

Table 1. Clinical and laboratory presentation of the two patients.

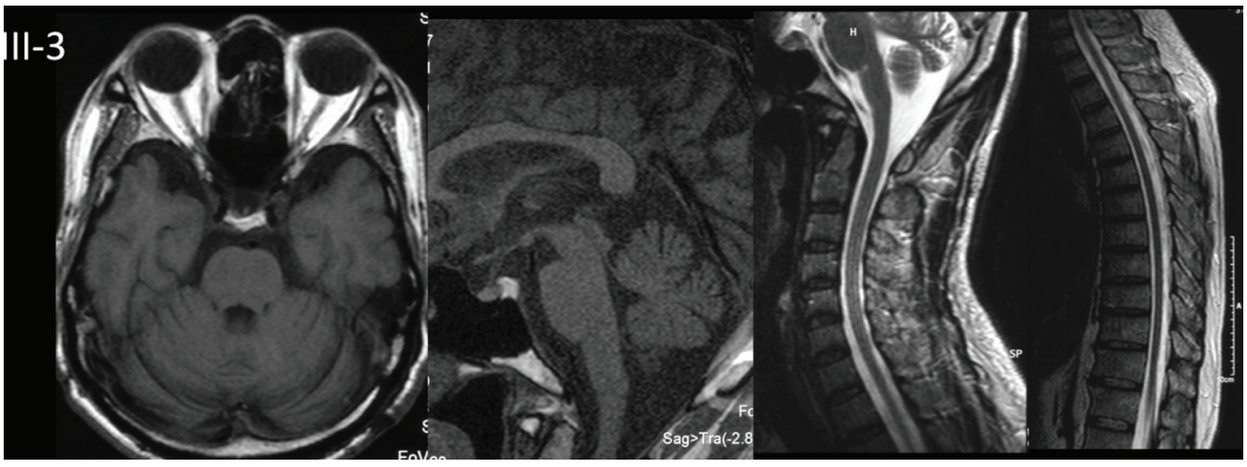

Figure 3. Brain and spinal MRI of the patient III-3. The brain MRI showed mild cerebellar atrophy, and spinal MRI disclosed mild thoracic cord atrophy.

The gene responsible for CHS was identified in 1996 and called *lysosomal trafficking regulator* (*LYST*) [27, 28]. The *LYST* gene is a large gene that has 51 coding exons and an open reading frame (ORF) of 11,403 kb [6]. The LYST protein, which is a large, putative cytosolic protein of

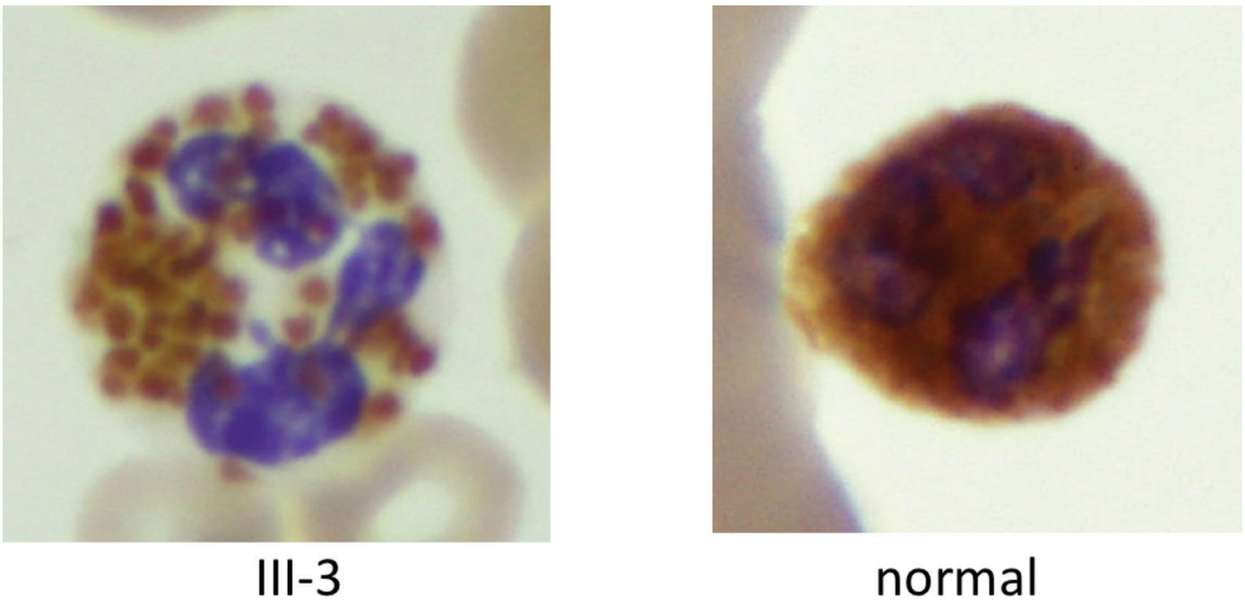

Figure 4. Peripheral blood leukocyte of patient III-3 (peroxidase stain). We found peroxidase-positive large granules in the patient's granulocytes compared with normal control WBC. These patients had no symptoms according to immunodeficiency or bleeding tendency.

425 kDa (3801 amino acids), is ubiquitously expressed and involved in control of the exocytosis of secretory lysosomes [28, 29]. The LYST protein has a BEACH (named after BEige And Chediak-Higashi) domain (amino acid numbers 3132–3422) [28], Trp-Asp (WD) 40 repeats (amino acid numbers 3477–3778), and a concanavalin (Con)A-like lectin domain (amino acid numbers 1390–1691) [30]. The LYST protein has been proposed to act as a scaffold protein in the mediation of fusion or a fission event of vesicles [31]. The mutation in this family (p.F1397V) is located within the ConA-like lectin domain. This domain could be involved in oligosaccharide binding associated with protein traffic and sorting along the secretory pathway [30].

Dysfunctional secretion of enlarged lysosome-related organelles, including lysosomes, melanosomes, and cytolytic granules, has been observed in cells with mutations in *LYST*. Small interfering RNA knockdown of LYST in human cell lines replicates the *LYST*-mutant phenotype of large lysosomes [32]. They found no evidence that autophagy or endocytic degradation was affected by LYST depletion. Autophagosomes are formed in normal size and volume and are able to form the large fused lysosomes, resulting in normal degradation rates. The large lysosomes are fully functioned in degrading endogenous proteins. LYST did not affect retrograde trafficking of toxins as well as the localization of transporters of lysosomal proteins, adaptor protein-3 (AP-3), and cation-independent mannose-6-phosphate receptor (CI-MPR). The large lysosomes quantitative analysis demonstrates that LYST depletion results in reduction in vesicle content per cell; meanwhile, the total enzymatic amount and vesicular pH are unaffected, indicating a role for LYST in lysosomal fission and/or fusion events [32].

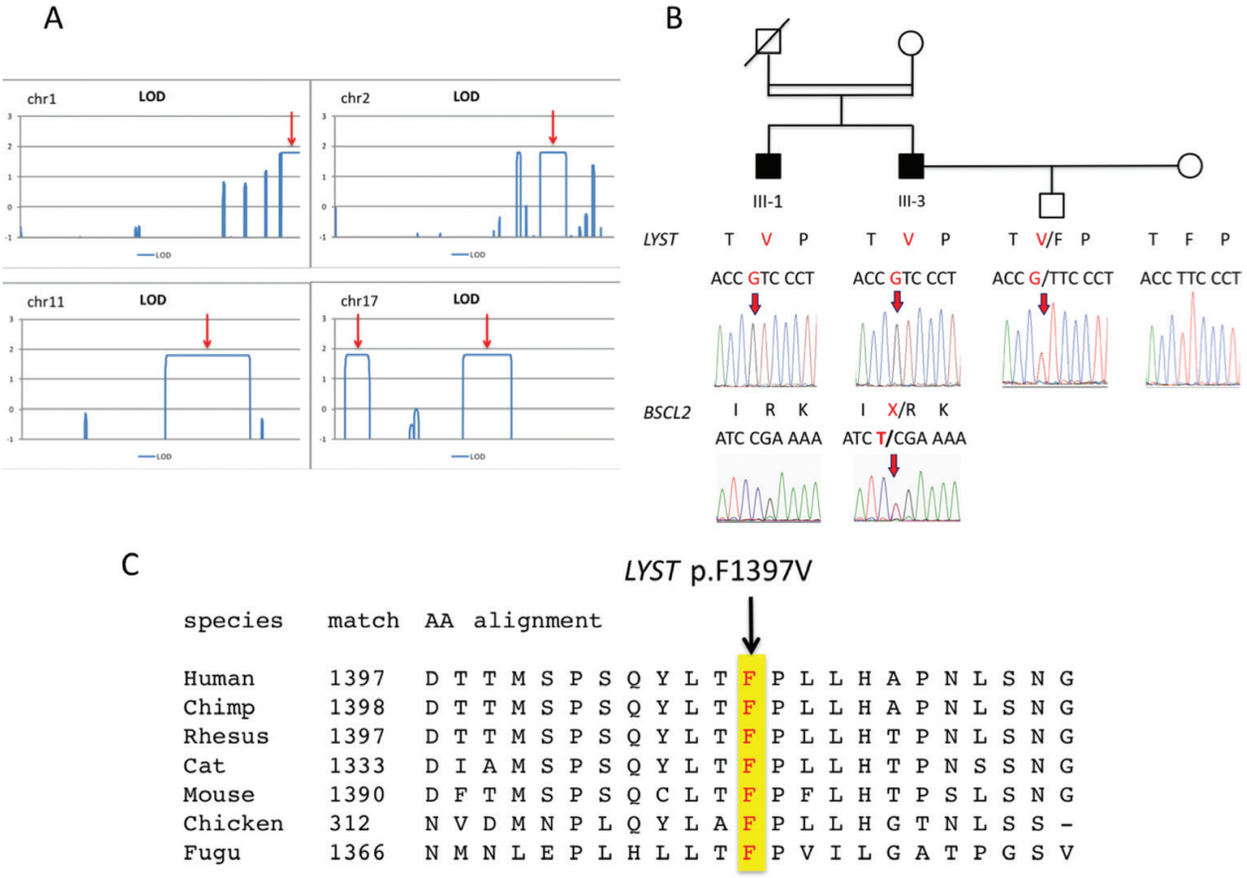

Figure 5. Linkage analysis and mutation of the *lysosomal trafficking regulator* (*LYST*) gene in the patients. (A) Linkage analysis. Linkage analysis involving SNPs revealed the highest LOD scores (about 1.8) in parts of chromosomes 1, 2, 11, and 17 (arrows). These four areas were thought to be candidate areas in which the causative gene was located. (B) Sanger sequencing confirmed the homozygous nonsense mutation (c.4189T>G, p.F1397V) of the LYST gene identified in the proband (III-3) and the affected brother (III-1). This mutation co-segregated with the disease in this family. This *LYST* mutation was not found in 200 Japanese control DNAs. In one patient (III-3), we identified a heterozygous nonsense mutation (c.823C>T, p.R275*) of the *BSCL2* gene, the causative one for SPG17, whereas no mutation in III-1. (C) This mutation located at the highly conserved residues within the BEACH (named after BEige And Chediak-Higashi) and concanavalin A (ConA)-like lectin domain.

Nevertheless, Drosophila with gene mutation of *LYST* homolog revealed impaired autophagy [33]. The roles of LYST in autophagy remain controversial [34].

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