ORGANELLE
REVIEW | OPEN ACCESS

Qin *et al.* Organelle (2026) 4:1
https://doi.org/10.61747/0ifp.202604001

REEP1 at the crossroads of organelle homeostasis and neurodegeneration

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Received: 15 September 2025; Revised: 1 December 2025; Accepted: 9 January 2026
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Journal homepage: https://www.organelles.org

ABSTRACT

Hereditary spastic paraplegia (HSP) is a group of inherited neurodegenerative disorders characterized by progressive spasticity and weakness of the lower limbs, primarily due to degeneration of corticospinal motor neurons. Among the genetic causes of HSP, mutations in Receptor Expression Enhancing Protein 1 (REEP1) are well established, highlighting its critical role in motor system maintenance. Beyond HSP, REEP1 mutations have also been implicated in other motor neuron and neuromuscular diseases, including distal hereditary motor neuropathies (dHMNs), Charcot–Marie–Tooth disease (CMT), and spinal muscular atrophy (SMA). REEP1 is a transmembrane protein with hydrophobic domains and a cytosolic microtubule-binding region that plays a central role in shaping and maintaining intracellular organelles, particularly the endoplasmic reticulum (ER) and mitochondria. In addition, REEP1 contributes to the homeostasis of other organelles and membrane contact sites, including mitochondrial-associated membranes (MAMs), lipid droplets, and endo-lysosomal system. Loss-of-function mutations disrupt organelle morphology and dynamics, resulting in impaired axonal transport, increased cellular stress, and selective vulnerability of motor neurons. By linking fundamental defects in organelle biology to neuromuscular phenotypes, REEP1 provides critical insight into mechanisms of motor system degeneration. This review integrates current knowledge of REEP1 protein structure and functions, emphasizing its role in maintaining organelle homeostasis, and explores how disruption of these mechanisms contributes to neuromuscular and motor neuron disease pathogenesis.

Key words: REEP1; Mitochondria; MAM; ER; HSP; Motor neuron disease

INTRODUCTION

REEP1 (Receptor Expression Enhancing Protein 1) was first identified in studies of G protein-coupled receptor trafficking, where it was shown to modestly enhance the cell surface expression of odorant receptors (ORs) in heterologous systems [1]. In olfactory sensory neurons, ORs are synthesized in the endoplasmic reticulum (ER) and transported to the cell membrane to recognize their ligands. However, these ORs are difficult to express in heterologous cell systems, implicating that olfactory neurons may have a selective molecular machinery that promotes proper sorting of ORs [2]. Since accessory proteins are required for targeting the cell membrane of some GPCRs, it was hypothesized that olfactory neurons might express cell-specific accessory proteins facilitating GPCRs to correct targeting to cell surface [3]. In an attempt to identify these accessory proteins, Saito and colleagues have identified two new protein families enhancing cell surface expression of ORs, REEP and receptor transporting protein (RTP) families [1]. Later, another study demonstrated that REEP family proteins was also associated with some bitter taste receptors expression [4].

There are six members in the REEP protein family, which can be divided structurally into two main subgroups: REEP1-4 and REEP5-6. Although all REEPs harbor paired hydrophobic domains, REEP1-4 are characterized by the presence of a shorter first hydrophobic domain, lack of a clear N-terminal cytoplasmic domain, and a longer C-terminal region compared to REEP5–6 [5]. Among these REEPs, REEP1 (also known as SPG31, Spastic paraplegia type 31) is under intensive investigation because of its close association with several neurodegenerative diseases, including hereditary spastic paraplegia (HSP) [6,7], distal hereditary motor neuropathies (dHMNs) [8], Charcot-Marie-Tooth disease (CMT) [9], and spinal muscular atrophy (SMA) [10,11]. Since the truncating nature of most genetic mutations of REEP1, it has been proposed that these mutations in REEP1 cause diseases through a loss-of-function mechanism [7,12].

As a transmembrane protein, REEP1 is composed of two hydrophobic domains inserting into intracellular membranes and a carboxy-terminal microtubule-binding domain (MTBD) facing cytosol [5,13]. Functionally, REEP1 plays numerous roles in maintaining homeostasis of many membrane-bound organelles, such as ER, trafficking vesicles, lipid droplets, as well as mitochondria [8,13–18]. Also, dysfunction of intracellular organelles, like mitochondria and ER, have been consistently reported in REEP1-related neurodegenerative diseases and experimental models [6,16–18]. In this review, we first describe the association of REEP1 with membrane-bound organelles, then review in detail the possible mechanisms by which REEP1 causes organelle dysfunction in various neurodegenerative diseases.

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The Article Processing Charge for this work was funded by the authors.

Association between REEP1 and organelles

REEP1 was initially reported to localize to the ER membrane, but subsequent studies revealed its presence at the mitochondrial inner and outer membranes, lipid droplets and mitochondria-associated membranes (MAMs) (**Figure 1**) [1,18,19]. Loss of REEP1 disrupts ER architecture and mitochondrial integrity, underscoring its essential role in maintaining homeostasis across intracellular membrane-bound organelles [6,16,18,19].

ER

The ER is the largest organelle in the cell and is responsible for many cellular functions, including synthesis of protein and lipids, protein folding, carbohydrate metabolism and calcium storage [20,21]. The diverse functions of the ER rely heavily on its structural complexity, which contains the numerous distinct domains existing in one continuous membrane bilayer. Morphologically, the ER forms a tubular shape or flattened cisternal structures (also called ER sheet) and spreads from the nuclear envelope to the cell cortex [22,23]. The continuity and identity of ER shape is preserved by its interaction with the cytoskeleton, proteins stabilizing membrane structures, and homotypic membrane fusion [24–26].

Numerous studies have consistently reported that extension of ER tubules move along microtubules in cells [27–30]. Microtubule-dependent ER morphology changes are driven by the activity of microtubule-associated motors and the polymerization of microtubules [24,28,29,31]. However, when ER networks are formed *in vitro* from small vesicles, an intact microtubule network is not required [32], suggesting that some other factors, rather than microtubules, are essential for ER tubules formation. To identify these components, for the first time, Voeltz and colleagues identified that the reticulons (including RTN4a and RTN4b) and DP1/Yop1p proteins generate ER tubules by inducing high curvature in the membrane [33]. Then, GTPase atlastin-1 (ATL1), homologous to yeast Sey1p, was found to mediate homotypic fusion of ER membranes to form a tubular network [34,35]. Since mutations in ATL1 (also known as SPG3A) are the second most

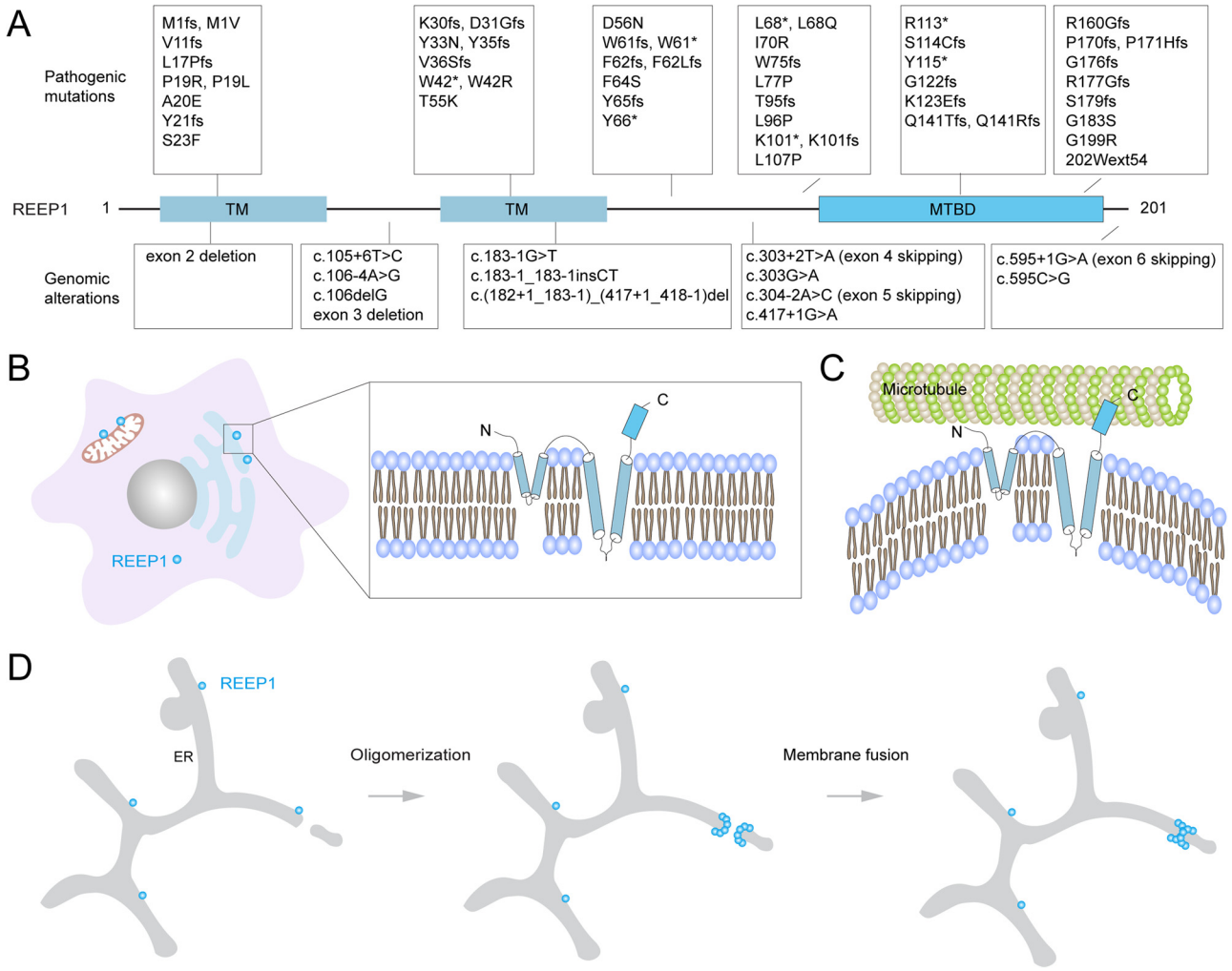

Figure 1. REEP1 mutations, localization, and function.

(**A**) Domain structure with disease-associated mutations of REEP1. The N-terminus contains two transmembrane domains (TM), and the C-terminus harbors a microtubule-binding domain (MTBD). (**B**) Subcellular localization of REEP1 at the ER and mitochondrial membranes. (**C**) REEP1 inserts into membranes and mediates curvature via microtubule interactions. (**D**) In the current model, REEP1 oligomerization plays a crucial functional role, as multiple studies have demonstrated that the ability of REEP1 molecules to assemble into higher-order complexes is essential for their activity in shaping the ER membrane. This oligomerization is required not only for stabilizing membrane curvature but also for facilitating membrane fusion and budding events.

frequent cause of pure hereditary spastic paraplegia (HSP), this raises the hypothesis that ER morphological defects may play an important role in disease progression of HSP. This notion is further supported by the following finding, that REEP1 interacts with ATL1 to coordinate ER shaping and microtubule dynamics [5].

Due to the difficulties to study the dynamic changes of the ER network *in vivo*, Dreier and colleagues established an *in vitro* system by mixing small membrane vesicles and cytosolic proteins to induce the formation of tubular network [32]. By adding an antibody against REEP1 in this *in vitro* system, the formation of the ER network is dramatically inhibited [32]. In addition, REEP1 overexpression in Cos7 cells induces ER tubules aligned along thickened and bundled microtubules [5]. In contrast, depletion of REEP1 increases the length and reduces the number of individual ER structures [13]. Mechanically, REEP1 forms complex with ALT1 and Spastin in tubular ER to facilitate homotypic fusion of ER membranes [5].

Unlike other proteins in DP1/Yop1p superfamily, REEP1 contains a unique C-terminal domain, which mediates the interaction of ER tubules and microtubule. HSP-related mutations lacking a C-terminal domain results in abnormal ER morphologies, including many apparent vesicles and peripheral ER sheets, as well as fewer identifiable tubular interconnections [5]. Together, these findings suggest that REEP1 mediates ER tubular network formation through both cytoskeleton interaction and homotypic membrane fusion. Of note, REEP1 and REEP2 not only show similar structure, but also demonstrate identical tissue distribution [36], implicating that REEP1 and REEP2 play a redundant role in ER shaping. Future studies with REEP1 and REEP2 double knockout cells or animal models will provide more evidence of REEPs in the regulation of ER morphology.

Mitochondria

Mitochondria are dynamic organelles that are present in most eukaryotic cells and are required for a wide range of cellular processes such as ATP production, metabolite synthesis, calcium hemostasis, and cell death [37–39]. Morphologically, mitochondria constantly alter their shape through opposite fusion and fission events, which are controlled by several large dynamin-related GTPase proteins. The key regulator in the mitochondrial fission process is dynamin-related protein1 (DRP1 or DLP1), a large GTPase mainly localized in the cytosol [40]. During fission, cytosolic DRP1 is recruited to the mitochondrial outer membrane by several receptor proteins such as MFF, FIS1, and MiD49/51, followed by oligomerization into a ring-like structure to sever the mitochondrial membrane by self-assembly and GTP hydrolysis [41–44]. On the other hand, mitochondrial fusion involves the fusion of both the outer and inner membrane, which is regulated by at least three large GTPase proteins, mitofusin 1 (MFN1) and mitofusin 2 (MFN2) for mitochondrial outer membrane fusion and optic atrophy protein 1 (OPA1) for mitochondrial inner membrane fusion [45–47]. It has been proposed that mitochondrial outer membrane fusion is mediated through interactions of the coiled-coil domains of MFN1 and MFN2 to form either homo-oligomeric or hetero-oligomeric complexes to tether membranes together [48,49].

In addition to their direct effects on mitochondrial shape, mitochondrial fusion and fission are also critical for the maintenance of the integrity and homogeneity of mitochondria. It is believed that mitochondrial fusion is an important mechanism, allowing the exchange of lipid membrane and intramitochondrial contents between different mitochondria to enable mtDNA repair and equally distribute metabolites to maintain a healthy population of mitochondria [50,51]. Due to the high levels of ROS produced and the lack of efficient DNA repair systems, mitochondria are relatively vulnerable to deleterious damage. The irreversibly damaged mitochondria need to be cleared in a timely manner, and mitochondrial fission has been shown to participate in the elimination of damaged mitochondria by autophagy [52]. Moreover, mitochondrial morphological changes coincide with OXPHOS complex assembly, cristae remodeling, and matrix space condensation [53].

Using HSP patient-derived skin fibroblasts (a small nucleotide deletion leading to frameshifts and premature termination codons, p.V36SfsX4), Goizet and colleagues for the first time reported that REEP1 mutant cells showed significantly longer mitochondria compared to heathy control skin fibroblasts [12]. Interestingly, the elongated mitochondrial network observed in patient fibroblasts is similar to that described in a patient with microcephaly, abnormal brain development, optic atrophy, and hypoplasia caused by a heterozygous dominant-negative mutation in the DRP1 [54], indicating that REEP1 and DRP1 may be in the same pathway to regulate mitochondrial fission. In the following study, the same group demonstrated that the expression of phosphorylated DRP1-S637 was greatly increased in HSP patient skin fibroblasts (carrying REEP1 mutations, including c.106delG, p.V36Sfs*4; c.166G>A, p.D56N; c.124T>C, p.W42R) and REEP1 mutations (D56N and W42R) overexpressed Hela cells, though the level of DRP1 was not altered [17]. These HSP-related disease mutations (D56N and W42R) promoted their transport to mitochondria and facilitated the phosphorylation of DRP1. Inhibition of DRP1 phosphorylation by H89 (inhibitor of PKA) greatly rescued the elongated mitochondrial morphology observed in patients' fibroblasts [17]. Alternatively, as mitochondrial fission always happens at mitochondria-ER contact sites [55], the abnormal ER morphology may also contribute to the tubular-like mitochondria in REEP1 mutant patient fibroblasts [17]. The detailed mechanism of how REEP1 mutations activate potential kinase to phosphorylate DRP1 needs to be explored in future studies.

Since mitochondrial dynamic changes closely relate to its function, abnormalities in mitochondrial respiration are also observed in REEP1-related neurodegenerative diseases. Hewamadduma and colleagues firstly described the deficiencies of complex I and IV in the muscle of a HSP patient carrying REEP1 truncating mutation (p.R113X) [56]. Consistently, the following study observed mild myogenic features and reduction of COX staining in the muscle REEP1 mutant HSP patient, as well as reduced mitochondrial respiration and complex IV activity both in patient muscles and fibroblasts [12]. One recent study also found that REEP1 associates with complex IV subunit NDUFA4 and plays an important role in the regulation of the integrity and function of complex IV. Together, these findings imply that REEP1 deficiency-mediated mitochondrial dysfunction plays a critical role in neurodegeneration.

Mitochondria-associated membranes

Mitochondria-associated membranes (MAMs) are specialized subdomains of the ER, which are reversibly tethered to the mitochondrial outer membrane. MAMs provide a scaffold for crosstalk between the ER and mitochondria, and play a pivotal role in many physiological processes such as calcium homeostasis [57], lipid transport [58], organelle biogenesis [59], and organelle stress regulation [60]. Additionally, abnormalities in MAMs are closely related to a wide spectrum of diseases, such as type 2 diabetes [61], Alzheimer's disease (AD) [62], Parkinson's disease (PD) [63], and ALS [64].

Studies over the past few decades have demonstrated that several regulatory protein complexes are involved in the maintenance and

modulation of mitochondria-ER interactions. Considering the self-assembly properties of MFN2, it has been reported that mitochondrial MFN2 forms homodimers with ER-residing MFN2 to mediate mitochondria and ER tethering [65]. In addition, the interaction between mitochondrial protein PTPIP51 (protein tyrosine phosphatase-interacting protein-51) and ER protein VAPB (vesicle-associated membrane protein) represents another important mechanism of ER–mitochondria tethering [66]. The IP3R (inositol 1,4,5-trisphosphate receptor) and VDAC1 (voltage-dependent anion channel 1) interaction is also found to be enriched in the MAMs and via chaperone GRP75 (glucose regulated protein 75) to facilitate mitochondria and ER communication. Lastly, platforms formed by FIS1 and BAP31 at MAMs are important for the recruitment of procaspase 8 and the transfer of the apoptotic signal from mitochondria to ER. Beyond these regulatory proteins, it is also reported that REEP1 plays a role in facilitating mitochondria and ER tethering [18].

REEP1 is enriched in MAMs fraction and an ER localization sequence. Based on a split-Renilla Luciferase 8 (RLuc8) reassembly assay, by which to quantitatively measure the level of ER-mitochondria interactions in live cells, it has been found that REEP1 facilitates the interaction between the ER and mitochondria, while HSP-related mutations (P19R, A20E, REEP1$^{1–115}$, REEP1$^{1–139}$, and REEP1$^{1–176}$) are less effective to induce their interactions [18]. Although the precise mechanisms remain elusive, there are several potential roles of REEP1 in ER and mitochondria tethering. First, as REEP1 forms oligomers through hydrophobic domains, it is highly possible that mitochondrial and ER localized REEP1 connects two organelles directly [5,67]. Second, REEP1 may facilitate ER and mitochondrial interaction through other factors on the mitochondrial outer membrane. Supporting this notion, the recent study has found that REEP1 associates with VDACs, which are important factors in MAMs formation [19]. Finally, as membrane shaping protein, REEP1 may also help MAMs formation through bending ER membranes, allowing it to wrap around mitochondria [18]. There are still other possible mechanisms for REEP1-mediated ER-mitochondria tethering, and future studies will be directed at elucidating the precise mechanisms.

Lipid droplets

Lipid droplets (LDs) are lipid storage organelles, consisting of a core of neutral lipids surrounded by a monolayer of phospholipids, in which regulatory proteins are embedded. LDs are highly dynamic organelles and play roles in lipid metabolism, energy homeostasis, as well as preventing lipotoxicity. For this reason, LD dysfunction is closely associated with many diseases, such as obesity, diabetes, and neurodegenerative diseases [68]. Since LDs derive from the ER membrane [69], ER-resident morphogenesis proteins-regulated membrane curvature is required for LD biogenesis and to modify their dynamics. For example, depletion of ATL1 or expression of a dominant-negative mutant causes a reduction of LDs size in a fly model [15,16]. Because REEP1 and ATL1 cooperate in controlling ER shape [70], it is not surprising that REEP1 is also involved in LD dynamics.

In line with the important role of atlastin on LDs dynamics in *Drosophila* fat bodies, Klemm and colleagues further explore how atlastin affects LDs size in mammalian tissue culture cells [15]. Although overexpression of ATL1 in Cos7 has no effect on LDs size, co-expression of ATL1 with REEP1 will greatly increase the size of LDs [14]. Consistent with this, when co-expressed together in HEK293 cells, both REEP1 and ATL1 greatly increase the size of LDs compared when expressed alone, suggesting that REEP1 corroborates a synergistic effect with ATL1 on LD dynamic regulation [14,15]. The following study from Beetz group also confirms that only wild-type REEP1, but not HSP-related mutant (A20E and p.102_139del), increased LDs size when co-expressed with ATL1 [14]. In REEP1 knockout mice, it consistently reported that loss of REEP1 induces lipoatrophy and defects in LDs formation in adipose tissues. In addition, mouse embryonic fibroblasts (MEFs) and neurons isolated from these mice also showed fewer and smaller LDs [16]. Notably, removing the N-terminus or introducing missense variants (P19L, P19R, A20E, S23F, and W42R) disrupts ER targeting of REEP1, leading to their accumulation on LDs. This supports the requirement of the N-terminus for proper ER localization and ER–LD dynamics [14]. Another recent study showed that Spastin controls LDs dynamics through modulating transcripts levels and subcellular location of Seipin and REEP1 [71].

Endo-lysosomal vesicles

The endo-lysosomal system is a series of organelles in the endocytic pathway, in which cell surface cargoes are internalized, recycled, and degraded. Depending on their functions and roles in the system, distinct types of endosomal compartments have been identified, including early endosomes, late endosomes, and recycling endosomes [72]. During the maturation process, endosomes will fuse with lysosomes, which are considered to be the final organelles in endocytic pathways, where proteolytic degradation takes place [73]. As the existence of numerous contact sites between the ER and endo-lysosomal vesicles, it has been thought that normal ER structure is important for dynamics and transportation of these vesicles [74,75]. Disruption of ER morphology can result in abnormal structures and the dysfunction of both endosomes and lysosomes. For example, ER-localized isoform of spastin (M1-spastin) interact with endosomal IST1 (increased sodium tolerance protein 1) at ER–endosome contacts to promote endosomal tubule fission. Loss of M1-spastin causes defective lysosomal enzyme traffic accompanied by abnormal lysosomal morphology [76]. Consistent with a critical role for ER-mediated endosomal tubule fission in controlling lysosome function, Allison and colleagues also found an increase in the proportion of neurons with enlarged lysosomes in the neurons from a REEP1 knockout mouse model [76]. The abnormal lysosomes had an ultrastructural appearance strikingly similar to those observed in the Spastin knockout model, with the presence of stacked linear arrays of membranous material [76]. Thus, these studies highlight a role for ER-shaping proteins in regulating ER–endo-lysosome connections. However, because REEP1 does not localize to endosomes or lysosomes, this effect is unlikely to involve a direct role, but instead occurs indirectly through its regulation of ER morphology and function.

REEP1 and neurodegenerative diseases

The majority of REEP1 genetic mutations have been identified in families with hereditary spastic paraplegia (HSP) and are classified as SPG31 (**Figure 1**). However, REEP1 mutations have also been reported in other neurodegenerative disorders, including hHMNs, CMT, SMA, and ALS. The clinical features, imaging findings, and electrophysiological profiles of these disorders show partial overlap, making it challenging to determine whether the associated REEP1 mutations act through shared pathogenic mechanisms. Here, we will describe the disease phenotypes linked to REEP1 mutations and explore the potential underlying pathomechanisms (**Figure 2**).

HSP

Hereditary spastic paraplegias (HSPs, also known as SPGs) are clinically and genetically heterogeneous groups of neurodegenerative

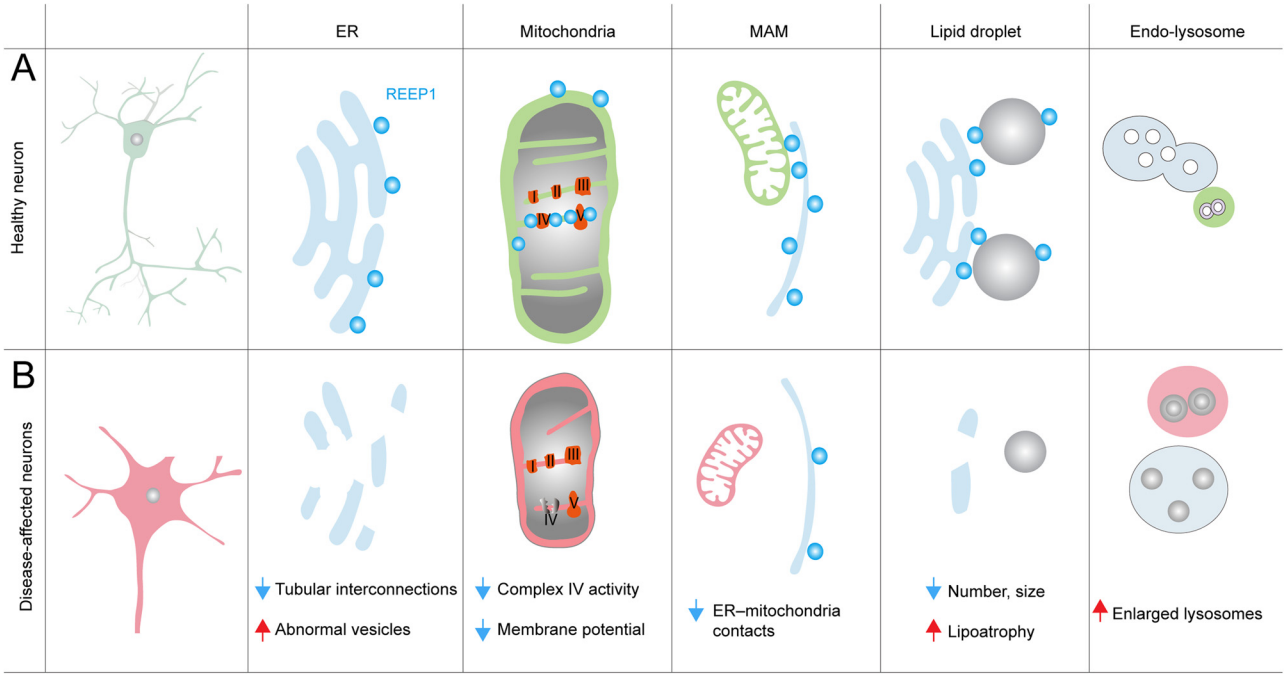

Figure 2. REEP1 and organelle dysfunction in neurodegenerative disease.

(**A**) In healthy motor neurons, REEP1 localizes to the ER membrane, where it facilitates membrane curvature through interactions with microtubules. It is also present on the inner mitochondrial membrane, stabilizing respiratory complex IV. At ER–mitochondria contact sites, REEP1 mediates inter-organelle communication and contributes to lipid droplet and endolysosome homeostasis. (**B**) In disease conditions, loss of REEP1 function leads to abnormal ER morphology, impaired mitochondrial respiration, disrupted ER–mitochondria contacts, and dysregulation of lipid droplet and endolysosome dynamics.

diseases causing progressive spasticity and weakness in the lower limbs [77]. The predominant pathological feature of HSP is the axonal degeneration of neurons of the pyramidal motor system. Motor neurons are the principal category of cells that degenerate in HSP, even though oligodendrocytes, astrocyte and microglial cells also contribute to the pathology of HSP [78].

SPGs are transmitted with all classical modes of inheritance, including autosomal dominant (AD-SPG), autosomal recessive (AR-SPG), X-linked (XL-SPG) or mitochondrial maternal transmission. Among them, AD-SPG is the most prevalent form of SPGs and accounts for approximately 70% of cases [79]. Mutations in the genes encoding for Spastin, Atlastin-1, or REEP1 are estimated to account for up to 50% of the AD-SPG cases [80]. As the third-most common mutated gene in AD-SPG, more than 70 REEP1-related HSP pedigrees have been identified from AD-SPG patients, which include small insertions, deletions or splice site mutations (**Figure 1**). These mutations result in shifts of the open-reading-frame followed by premature termination of translation and haploinsufficiency [6,7,12,56,81,82]. Loss of REEP1 protein expression disrupts ER structure, organization, and function, and impairs its interactions with other organelles, such as mitochondria, ultimately contributing to axonal degeneration (**Figure 2**) [13,16,83].

dHMNs

Distal hereditary motor neuropathies (dHMNs) are inherited disorders characterized by selective motor axon degeneration, leading to progressive distal weakness and atrophy with minimal sensory involvement, which predominantly affect lower motor neurons [84,85]. dHMN is genetically heterogeneous, with over 30 causative genes identified, including HSPB1, HSPB8, BSCL2, IGHMBP2, SETX, GARS, DYNC1H1, DCTN1, ATP7A, TRPV4, REEP1, and SLC5A7, accounting for approximately 20% of cases, while the genetic basis remains unknown in the remaining ~80%. These genes encode proteins involved in diverse cellular pathways, including cytoskeletal integrity, axonal transport, RNA processing, and mitochondrial function [86].

In a three-generation family with both autosomal-dominant dHMN and dHMN type V (dHMN/dHMN-V), whole-exome sequencing of two affected members identified a splice-site alteration in REEP1 (c.304-2A>G), that results in skipping of the in-frame exon 5 [8]. The resulting mRNA is predicted to be expressed at normal levels but to encode an internally truncated protein (p.102_139del). Overexpression of the truncated protein REEP1 (p.102_139del) markedly disrupts the tubular ER network, producing abnormal spherical structures (perinuclear "clumps") that co-localize with atlastin-1 (ATL1). Moreover, only the p.102_139del mutation, but not HSP-related mutation p.Ala20Glu, alters the subcellular distribution of atlastin-1 [8]. These observations suggest that REEP1 mutations may lead to upper and lower motor neuron degeneration through distinct pathogenic mechanisms. However, these observations are only based on protein overexpression in HeLa cells rather than in neuron-related cell types; further studies are needed to investigate the potential pathogenic mechanisms in more relevant neuronal models or *in vivo* systems.

CHARCOT-MARIE-TOOTH

Charcot–Marie–Tooth disease (CMT) is the most common inherited peripheral neuropathy, characterized by progressive distal muscle weakness and atrophy, sensory loss, and foot deformities [87]. It

primarily affects peripheral motor and sensory neurons, resulting in length-dependent axonal degeneration or demyelination [88]. More than 100 causative genes have been identified to date, involving pathways such as myelin maintenance (PMP22, MPZ), mitochondrial dynamics (MFN2), axonal transport (NEFL), and protein quality control [89]. Based on the underlying genetic defects, CMT is classified into numerous subtypes, including CMT1, CMT2, CMT3, CMT4, CMT5, CMT6, X-linked CMT, and intermediate CMT [90].

In autosomal dominant CMT type 2 (CMT2), a heterozygous nonstop variant in REEP1 has been identified. This nonstop variant produces an abnormal C-terminal extension (REEP1$^{1–255}$) that drives REEP1 self-aggregation. When fused to GFP (GFP$^{1–255}$), the variant markedly increases aggregation of the fusion protein compared with GFP alone. Similarly, co-expression of the mutant (REEP1$^{1–255}$) with wild-type REEP1 induces aggregation of the wild-type protein, demonstrating a dominant, aggregation-prone effect of the nonstop variant [9]. Together with prior evidence of an aggregation-prone REEP1 deletion variant in dHMNs [8], these findings suggest that REEP1 mutations in CMT likely act through a loss-of-function mechanism.

SMA

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by progressive degeneration of α–motor neurons in the anterior horn of the spinal cord, leading to symmetrical muscle weakness and atrophy [91]. Clinically, SMA presents across a broad spectrum, from severe neonatal-onset forms (Types 0–I) to milder, adult-onset forms (Type IV), with earlier onset generally associated with faster disease progression [92]. In over 95% of cases, SMA results from homozygous deletions or loss-of-function mutations in the SMN1 (survival motor neuron 1) gene [93]. Additionally, rare non-SMA forms arise from mutations in genes such as VRK1, IGHMBP2, DYNC1H1, and BICD2, often presenting with overlapping or distinct clinical features [94].

In one family, a homozygous splice donor mutation in REEP1 (c.303 + 1-7GTAATAT>AC, p.F62Kfs23*; NM_022912) was found to cosegregate with the disease phenotype. This variant resulted in complete skipping of exon 4 and the introduction of a premature stop codon. Clinically, affected individuals exhibited a phenotype resembling spinal muscular atrophy with respiratory distress type 1 (SMARD1), characterized by early-onset diaphragmatic paralysis, distal arthrogryposis, and pronounced upper motor neuron involvement, including marked hyperreflexia [10]. In another SMA family, a homozygous pathogenic missense variant in REEP1 (NM_022912: c.124T>C; p.Trp42Arg) was identified within a 59 Mb region of homozygosity [11]. Together, these findings suggest that REEP1 loss-of-function variants can cause a severe congenital distal SMA with combined lower and upper motor neuron involvement.

OTHER NEURODEGENERATIVE DISEASE

Although only a few studies have investigated REEP1 in other neurodegenerative diseases, evidence suggests that REEP1 mutations may also be associated with amyotrophic lateral sclerosis (ALS) and early-onset atypical parkinsonism [95,96]. ALS is a progressive neurodegenerative disorder characterized by the degeneration of upper and lower motor neurons, whereas early-onset atypical parkinsonism presents with parkinsonian motor symptoms before the age of 50, often accompanied by atypical clinical features. In ALS, a mutation at REEP1 c.182 + 8C>G, located within an intronic region, has been reported; however, its impact on REEP1 expression or function remains unclear [95]. In patients with early-onset atypical parkinsonism, a 3.9-Mb deletion at 2p11.2 encompassing REEP1 has been identified, and the resulting disease phenotype is likely attributable to loss of REEP1 expression [96].

CURRENT AVAILABLE MODELS OF REEP1

Several *in vivo* and *in vitro* models have been developed to investigate the function of REEP1 and its role in HSP and other REEP1-relalted disorders. In mouse models, a REEP1 knockout line has been generated [13]. Mice with a hemizygous deletion of exon 2 exhibit reduced REEP1 expression and develop a gait abnormality that closely resembles human HSP. Homozygous knockout mice show a complete loss of REEP1 expression and present with an earlier onset and more severe phenotype, supporting that REEP1 protein levels are critical for maintaining normal motor function [13]. Interestingly, another study treated REEP1 knockout mice with salubrinal, a specific inhibitor of ER stress, which increased neuromuscular connections and improved motor function [97]. These findings suggest that targeting downstream ER stress pathways may represent a potential therapeutic strategy for HSP.

In *Drosophila* models, loss of REEP1 consistently leads to ER dysfunction and neurodegeneration, and re-expression of either human or fly REEP1 rescues these defects and enhances neuronal resistance to ER stress [98]. Notably, this study also evaluated REEP1 function under a pathological condition involving Tau overexpression [98]. Loss of REEP1 markedly shortened lifespan in flies expressing Tau, whereas restoring REEP1 expression reversed these defects. Moreover, in the rescue lines, elevated REEP1 expression extended survival even beyond that of wild-type REEP1 strains, suggesting that increased REEP1 levels may be beneficial for organismal survival [98].

Although no human iPSC- or organoid-based studies have directly manipulated REEP1 to date, patient-derived fibroblasts carrying REEP1 mutations (c.106delG, p.V36Sfs*4; c.166G>A, p.D56N; c.124T>C, p.W42R) exhibit impaired mitochondrial function, indicating multi-organelle involvement in REEP1-related disease [17]. Overall, additional REEP1 disease-associated point-mutation animal models will be necessary to further dissect the molecular mechanisms of REEP1-related disorders. In parallel, human iPSC-derived motor neurons will provide a valuable platform for uncovering the pathogenic mechanisms underlying REEP1-related neurodegeneration.

CONCLUSION

REEP1 mutations are most frequently associated with HSP but also occur in hHMNs, CMT, SMA, and ALS. These disorders exhibit overlapping clinical and electrophysiological features, suggesting possible shared mechanisms. Experimental studies consistently demonstrate that REEP1 dysfunction perturbs ER and mitochondrial structure, leading to defects in membrane shaping and organelle interaction. Cellular and animal models further highlight abnormalities in axonal transport, ER stress responses, and mitochondrial dynamics (Figure 3). Given that loss of REEP1 disrupts multiple organelles, several studies have explored genetic approaches to reintroduce functional REEP1, which have been shown to improve dysregulated organelle activities, including ER and mitochondrial function [19,97,98]. These findings demonstrate that restoring functional REEP1 can reverse organelle defects and rescue motor neuron degeneration, supporting the idea that targeting REEP1-related pathways may represent a promising therapeutic

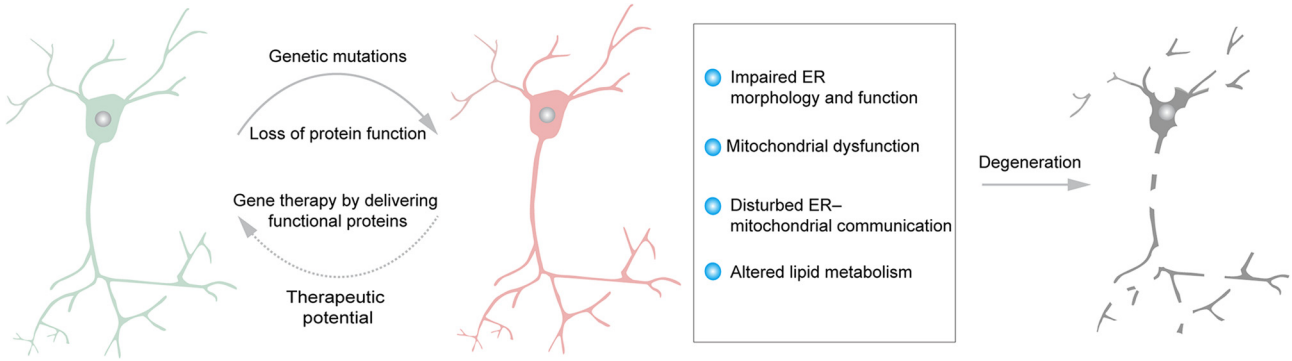

Figure 3. Pathological mechanisms of REEP1-associated disorders.
Genetic mutations in REEP1 lead to reduced protein levels or loss of normal protein function. This causes impaired ER morphology and function, mitochondrial dysfunction, disrupted ER–mitochondrial communication, and altered lipid metabolism, ultimately resulting in degeneration of neuronal cells, particularly motor neurons. Targeting REEP1-related pathways is a promising therapeutic direction. Efforts to restore organelle function by delivering functional REEP1 protein have already been explored, highlighting the therapeutic potential of this approach.

strategy for REEP1-associated disorders. However, the molecular pathways linking these defects to the spectrum of clinical phenotypes remain incompletely understood. Continued experimental exploration of REEP1 function in organelle biology will be essential to unravel the pathomechanisms underlying REEP1-associated neurodegeneration.

AUTHOR CONTRIBUTIONS

S.Q. and J.G. wrote the manuscript. L.V. provided comments and assisted with English editing.

FUNDING

This work was supported by an NIH/NIA grant (J.G., 1R03AG094840-01).

COMPETING INTERESTS

The authors declare no competing interests.

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