



Autophagy as an Emerging Common Pathomechanism in Inherited Peripheral Neuropathies

*Mansour Haidar and Vincent Timmerman**

Peripheral Neuropathy Research Group, Institute Born Bunge, University of Antwerp, Antwerpen, Belgium

The inherited peripheral neuropathies (IPNs) comprise a growing list of genetically heterogeneous diseases. With mutations in more than 80 genes being reported to cause IPNs, a wide spectrum of functional consequences is expected to follow this genotypic diversity. Hence, the search for a common pathomechanism among the different phenotypes has become the holy grail of functional research into IPNs. During the last decade, studies on several affected genes have shown a direct and/or indirect correlation with autophagy. Autophagy, a cellular homeostatic process, is required for the removal of cell aggregates, long-lived proteins and dead organelles from the cell in double-membraned vesicles destined for the lysosomes. As an evolutionarily highly conserved process, autophagy is essential for the survival and proper functioning of the cell. Recently, neuronal cells have been shown to be particularly vulnerable to disruption of the autophagic pathway. Furthermore, autophagy has been shown to be affected in various common neurodegenerative diseases of both the central and the peripheral nervous system including Alzheimer's, Parkinson's, and Huntington's diseases. In this review we provide an overview of the genes involved in hereditary neuropathies which are linked to autophagy and we propose the disruption of the autophagic flux as an emerging common pathomechanism. We also shed light on the different steps of the autophagy pathway linked to these genes. Finally, we review the concept of autophagy being a therapeutic target in IPNs, and the possibilities and challenges of this pathway-specific targeting.

Keywords: autophagy, hereditary neuropathies, Charcot-Marie-Tooth, neurodegeneration, proteostasis

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*Correspondence:

Vincent Timmerman
vincent.timmerman@uantwerpen.be

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INTRODUCTION

Disruption of intracellular homeostasis is at the base of most pathological conditions. Cellular health and function often relies on the maintenance of protein homeostasis by assuring that structurally abnormal proteins do not accumulate in cells, causing aggregate formation and organelle damage. The function of proteostasis is accomplished by two systems, the proteasome and the autophagy system. While the proteasome targets ubiquitinated and short-lived proteins, autophagy can degrade long-lived proteins and damaged organelles. Three main subtypes of autophagy have been identified, microautophagy, CMA, and macroautophagy. Microautophagy involves the degradation of cytosolic material inside the lysosome by direct lysosomal invagination (Mijaljica et al., 2011). CMA is a specific autophagic pathway where chaperones target proteins containing the KFERQ motif to the lysosome for degradation (Cuervo et al., 1995). Unlike CMA, macroautophagy (the main focus of this review), is a bulk degradation process characterized by the

formation of double membrane vesicles, autophagosomes, which engulf cytoplasmic material and degrade their contents by fusing with the lysosomes (Yang and Klionsky, 2010). Disruption of the macroautophagy pathway can lead to failure to clear out misfolded proteins and dead organelles, or increased accumulation of autophagic structures and has been linked to neurodegeneration (Frake et al., 2015). Mutations in key autophagy regulating genes have been shown to cause neurodegeneration (Saitou et al., 2013; Kyöstiä et al., 2015). Furthermore, mouse models with neuron-specific KO of autophagy genes frequently develop neurodegeneration (Komatsu et al., 2006). Interestingly, some of these mouse models display features of peripheral neuropathy as evident by decline in motor performance on the rota-rod, limb-clasping, and paw placement tests (Hara et al., 2006). The link between disruption at the gene level and the development of peripheral neuropathy is the main feature of IPNs. IPNs are a genetically heterogeneous disease population with over 80 affected genes discovered so far (Baets et al., 2014; Timmerman et al., 2014). While the clinical presentation of IPN patients is rather common, with length-dependent degeneration affecting the motor and/or sensory nerves, the variety of associated genes has produced various molecular phenotypes (Pareyson et al., 2014; Weis et al., 2016). Recently, more and more studies have indicated the involvement of autophagic impairment in IPN causing-mutations, and important roles for IPN related genes in autophagy. While the evidence linking IPN associated genes to autophagy can

be direct or indirect, impairment of autophagy presents as an important contributor to the neuropathic phenotype given the vulnerability of neurons, especially those of the peripheral nervous system to disrupted cellular recycling and clearance. Identifying a common pathomechanism among the different IPN-related genes would provide a great therapeutic potential for targeting these neuropathies. This review discusses the advances made so far regarding the cellular and molecular mechanisms behind the different forms of IPN due to impairment of the autophagic pathway.

AUTOPHAGY

Macroautophagy, hereafter referred to as autophagy, is a homeostatic cellular process by which protein aggregates and cellular organelles are targeted, degraded, and recycled (Figure 1). Autophagy is a multi-step process consisting of: induction, nucleation of the isolation membrane (phagophore), elongation and expansion of the phagophore into a closed double-membraned autophagosome, lysosomal docking and fusion, and degradation of autophagic cargo. The different autophagy steps, explained below, are governed by a wide array of proteins and protein complexes, most notably the group of proteins encoded by the autophagy-related (ATG) genes (Parzych and Klionsky, 2014).

Induction of Autophagy

The initiation of autophagy is regulated by the ULK complex composed of ULK1 and ULK2, and their stable interactors RB1CC1 and ATG13. The autophagy initiation complex is under the control of the nutrient-sensing, MTORC1, a serine–threonine kinase. During nutrient rich conditions MTORC1 binds to and phosphorylates ULK1/2 inhibiting their kinase activity. Removal of MTORC1 from the ULK1/2 complex, by nutrient starvation for example, allows for the activation of ULK1/2 and the proceeding of the autophagic process (Hosokawa et al., 2009).

Phagophore Nucleation

The membrane nucleation step involves the conversion of PtdIns to phosphatidylinositol 3-phosphate (PtdIns3P) by the kinase complex Class III PtdIns3K. This complex consists of PIK3C3/VPS34, BECN1, and PIK3R4/VPS15 (Petiot et al., 2000). PtdIns3P is a signal for recruiting ATG proteins in the nucleation site, by recognizing and binding to PtdIns3P. BECN1 moderates the coupling of the PtdIns3K complex with various proteins, and via its binding partners serves as a check point that can inhibit or upregulate autophagy. Among the binding partners are ATG14, UVRAG, and apoptosis regulator BCL2 proteins. BCL2 binding suppresses autophagy (Pattingre et al., 2005). UVRAG binding targets the nucleation machinery to the endosomal membranes or the cell surface and can up or downregulate autophagy depending on its other binding partners (Yang and Klionsky, 2010). ATG14 binding on the other hand targets the nucleation to the omegasome (an ER resident precursor of the autophagosome where formation of autophagic vacuoles ensues) (Axe et al., 2008).

Abbreviations: ALS, amyotrophic lateral sclerosis; ATG, autophagy-related gene; BCL2, B-cell lymphoma2 (BCL2) apoptosis regulator; BECN1, beclin 1; BNIP3, BCL2 interacting protein 3; BSCL2, seipin lipid droplet biogenesis associated; CASA, chaperone-assisted selective autophagy; CCT5, chaperonin containing TCP1 subunit 5; CMA, chaperone mediated autophagy; CMAP, compound muscle action potential; CMT, Charcot-Marie-Tooth; DCTN1, dynactin subunit 1; dHMN, distal hereditary motor neuropathy; DNAJB2, DnaJ heat shock protein family (Hsp40) member B2; DNM2, dynamin2; DST, dystonin; eIF2 α , eukaryotic initiation factor 2-alpha; ER, endoplasmic reticulum; ERES, ER exit sites; FAM134B, family with sequence similarity 134 member B; FIG4, FIG4 phosphoinositide 5-phosphatase; GABARAP, GABA type A receptor-associated protein; GDAP1, ganglioside induced differentiation associated protein 1; GEF, guanine nucleotide exchange factor; HOPS, homotypic fusion and protein sorting; HSAN, hereditary sensory and autonomic neuropathy; HSP, hereditary spastic paraplegia; HSPB8, heat shock protein B8; IPNs, inherited peripheral neuropathies; iPSCs, induced pluripotent stem cells; KIF1A, kinesin family member 1A; KO, knock-out; LC3, microtubule associated protein 1 light chain 3 (MAP1LC3); LITAF, lipopolysaccharide induced TNF factor; LRSAM1, leucine rich repeat and sterile alpha motif containing 1; MFN2, mitofusin 2; MTMR2/13, myotubularin-related protein 2/13; MTORC1, mechanistic target of rapamycin 1; NCVs, nerve conduction velocities; NDRG1, N-myc downstream regulated 1; NEFL, neurofilament light; P62/SQSTM1, sequestosome 1; PARK2, parkin 2; PERK, protein kinase R (PKR)-like endoplasmic reticulum kinase; PHF23, PHD finger protein 23; PIK3C3/VPS34, phosphatidylinositol 3-kinase catalytic subunit type 3; PIK3R4/VPS15, phosphoinositide-3-kinase regulatory subunit 4; PINK1 PTEN, induced putative kinase 1; PKA, protein kinase A; PMP22, peripheral myelin protein 22; PtdIns, phosphatidyl inositol; PTPIP51, protein tyrosine phosphatase interacting protein 51; Rab11, Ras-related protein Rab-11A; RAB21, Ras-related protein Rab-7; RAB7, Ras-related protein Rab-21; RB1CC1, RB1 inducible coiled-coil 1; SEC24D, SEC24 homolog D, COPII coat complex component; SH3TC2, SH3 domain and tetratricopeptide repeats 2; SNARE, SNAP (soluble NSF attachment protein) receptor; SOD1, superoxide dismutase 1; TECPR2, tectonin beta-propeller repeat containing 2; TrkA, tyrosine kinase A; TRPV4, transient receptor potential cation channel subfamily V member 4; ULK1/2, unc-51 like autophagy activating kinase 1/2; UVRAG, UV radiation resistance associated; VAPB, VAMP associated protein B; VCP, valosin containing protein; WNK1, WNK lysine deficient protein kinase 1; WT, wild-type.

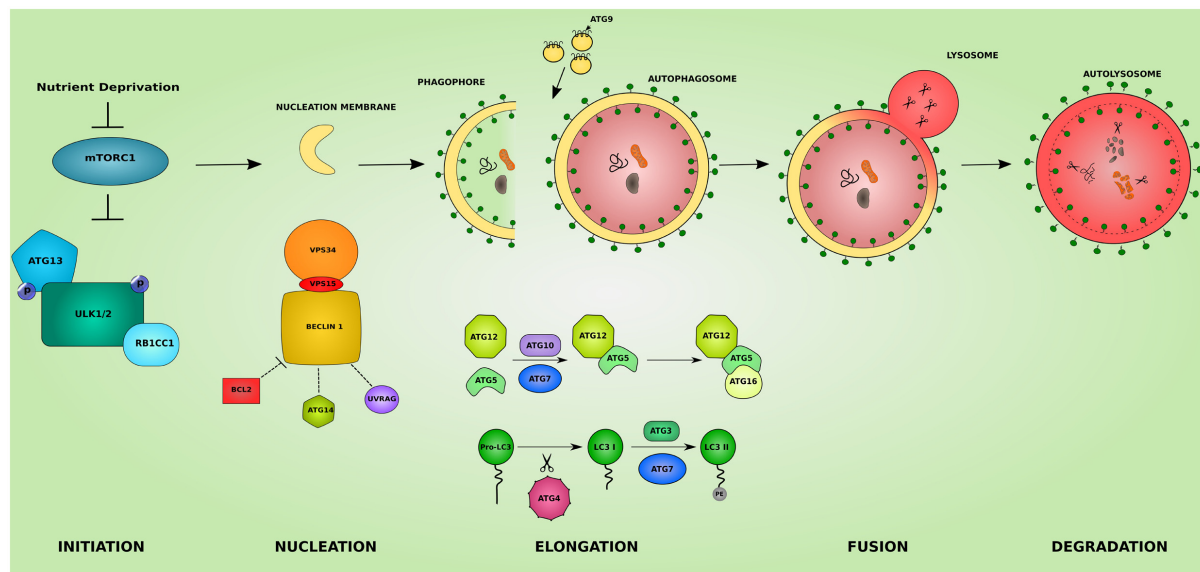


FIGURE 1 | The different steps of the autophagic pathway. The autophagic pathway consists of several steps. The initiation step is governed by the initiation complex composed of ULK1 and ULK2 (*unc-51 like autophagy activating kinase 1/2*), RB1CC1 (*RB1 inducible coiled-coil 1*) and ATG13 and under the control of the nutrient sensing *mechanistic target of rapamycin* (mTORC1) complex. After the initiation step, the nucleation of early autophagic membranes is controlled by the nucleation complex consisting of *phosphatidylinositol 3-kinase catalytic subunit type 3* (PIK3C3/VPS34), *beclin 1* (BECN1), and *phosphoinositide-3-kinase regulatory subunit 4* (PIK3R4/VPS15). BECN1 acts as an autophagy check point by interacting with ATG14, UVRAG (*UV radiation resistance associated*), and apoptosis regulator BCL2 proteins. The formed phagophore then undergoes elongation to become a fully closed double-membraned autophagosome. This step involves 2 conjugation systems resulting in the formation of ATG12-ATG5-ATG16L1 complex via ATG7 and ATG10 action, and of the autophagosomal marker LC3II via the action of ATG4, ATG7, and ATG3. The delivery of membranes to forming autophagosomes is served by ATG9-containing vesicles. The completed autophagosome then fuses with a lysosome becoming an autolysosome where its cargo is subjected to lysosomal degradation. The colors and shapes of the boxes are randomly assigned and show that they are different proteins belonging to the same complexes.

Elongation and Expansion

Two ubiquitin-like conjugation systems are at the heart of the expansion of the phagophore into an autophagosome. The first system concerns the formation of ATG12-ATG5-ATG16L1 complex. ATG12 is covalently conjugated to ATG5 via the E1 activating enzyme ATG7 (Tanida et al., 1999) and the E2 conjugating enzyme ATG10 (Shintani et al., 1999). The ATG12-ATG5 complex then binds ATG16L1 through ATG5. The second ubiquitin-like conjugation reaction involves the lipidation of ATG8 (LC3) to ATG8-Phosphatidylethanolamine (LC3II). This first requires the C-terminal cleavage of LC3 by the protease ATG4. The cleaved protein (LC3I) is then processed by the E1 activating enzyme ATG7 and the E2 conjugating enzyme ATG3 yielding LC3II. LC3II remains associated with the phagophore and the mature autophagosomes until its degradation in the lysosome (Kabeya, 2000). This association makes LC3II a good marker for the study of the autophagic activity in cell and animal models. Since lipid synthesis does not occur at the phagophore, delivery of membrane from other locations in the cell is necessary for the elongation step. The task of membrane recruitment is served by ATG9, the only transmembrane protein in the ATG family. Mainly localized to the *trans*-Golgi network and the late endosomes, autophagy activation drives the trafficking of membrane delivering-ATG9 to the sites of autophagosome formation (Mari et al., 2010). Lipid delivery supplied by ATG9

allow for the elongation of the phagophore into a fully closed autophagosome.

Fusion

The complete autophagosome eventually moves to and fuses with a lysosome becoming an autolysosome and/or with an endosome forming an amphisome. The transport of autophagosomes to the lysosomes depends on microtubules. The mechanism of docking at and fusion with the lysosome is not well-understood (Chen and Klionsky, 2011), but it is thought to involve UVRAG, RAB7 GTPase and syntaxin-17 (STX17) of the SNARE machinery (Jäger et al., 2004; Liang et al., 2008; Jiang et al., 2014).

Degradation

Upon the fusion of the autophagosome with the lysosome, the autophagic cargo is degraded by various lysosomal hydrolases and proteases. The degradation products including metabolites, amino acids and fatty acids are recovered and reutilized by the cell.

Autophagy in Neurons

The morphological features that distinguish neurons from other cells are their post-mitotic nature, highly polarized structure, and extended cytoplasm into axons and dendrites that can stretch far from the cell body. The latter feature is more exaggerated in neurons supplying the peripheral nerves. The

spatial compartmentalization of neurons makes them prone to aggregation and accumulation of dead organelles and misfolded proteins. Autophagy therefore forms an essential homeostatic process for neurons. Knocking out key autophagy genes, such as ATG7 in mouse neurons leads to neurodegeneration (Komatsu et al., 2006). Defective autophagy has also been linked with numerous neurodegenerative diseases (Frake et al., 2015). The high susceptibility of neurons to autophagic impairment could explain why mutations in ubiquitously expressed genes can cause neuron-specific pathology in inherited neuropathies.

INHERITED PERIPHERAL NEUROPATHIES (IPNs)

Inherited peripheral neuropathies are a genetically heterogeneous group of disorders affecting the peripheral nerves. Depending on the affected nerves, IPNs are classified as CMT or HMSN if motor and sensory nerves are affected. If sensory and/or autonomic nerve dysfunction predominates, the neuropathy is termed (HSAN) and dHMN if motor deficits are the most prevalent (Pareyson et al., 2014).

Clinical and Inheritance Pattern Classification

Charcot-Marie-Tooth, the most common form of hereditary neuropathies affects about 1:2500. Patients with CMT share a common clinical presentation of slowly progressive muscle wasting and weakness ascending from the feet to reach the thighs and hands, reduced tendon reflexes, skeletal deformities, and sometimes sensory loss (Harding and Thomas, 1980b). In many cases, the age of onset is in the first to second decade, but infantile, early-onset and late-onset forms exist. CMT is further classified on the prevalence of myelin or axonal involvement and according to the mode of inheritance. CMT1, the demyelinating subgroup is associated with reduced NCVs to less than 35 m/s. CMT2, the axonal subgroup on the other hand, only shows slightly reduced NCV but with reduced CMAPs amplitudes. An intermediate CMT subgroup exists with NCV between 35 and 45 m/s. The mode of inheritance further subdivides CMT neuropathies into CMT4 for recessive demyelinating CMT, CMT2R for recessive axonal CMT, CMTDI, and CMTRI for dominant and recessive intermediate CMT respectively, and CMT-X for the X-linked CMT (Stojkovic, 2016).

The HSAN disorders are characterized by sensory deficits and the involvement of the autonomic dysfunction. Five types of HSAN are acknowledged depending on the inheritance pattern and the sensory abnormality (Thomas, 2005). HSAN type I is autosomal dominant with variable motor involvement. HSAN types II to VI are autosomal recessive and further classified according to the sensory involvement and the clinical presentation ranging from osteomyelitis in type II to respiratory difficulties in type VI. HSAN types III, IV, and V show congenital onset. HSAN with spastic paraplegia, also a recessive form of HSAN, presents as a sensory neuropathy with mild spastic paraplegia (Rotthier et al., 2012).

The dHMN are classified into seven subtypes depending on the age of onset, inheritance pattern, and the distribution of the deficits (Harding and Thomas, 1980a). The dHMN types I, II, V, and VII are autosomal dominant, while types III, IV, and VI are autosomal recessive and the X-linked dHMN has an X-linked inheritance. Minor sensory abnormalities are frequent to many dHMN forms, and an overlap with axonal CMT (CMT2), where mutations in the same gene can cause either phenotypes is common. The phenotypic characteristics of dHMN are very diverse with the pathology involving other organs such as the vocal cords or the respiratory system (Rossor et al., 2012).

GENE FUNCTION CLASSIFICATION

Hereditary peripheral neuropathies show overlap on the genetic level with mutations in the same gene leading to different clinical subtypes. This has recently led to attempts in classifying IPNs based on the gene function involved in neuropathy (Vallat et al., 2016). While many genes associated with neuropathy have a known function in neuronal maintenance, development, or myelination, several other genes revealed functions that were unrecognized or indirect to the caused neuropathy (Weis et al., 2016). The categorization based on gene function further highlighted the heterogeneity of inherited neuropathies. Hence, the search for a common pathomechanism among the different causal genes is starting to become a focal point in the hope of better understanding the pathology of inherited neuropathies and ultimately designing efficient therapeutic approaches. We believe that this classification is of great help for a better understanding of the molecular consequences of the disease-causative mutations. In the following sections, we shed light on the involvement of IPN-associated genes in the different steps of the autophagy pathway presenting autophagic impairment (Figure 2) as an emerging common pathomechanism (summarized in Table 1).

IPN Genes and Autophagy Initiation PMP22 (Peripheral Myelin Protein 22)

The PMP22 is a myelin glycoprotein which plays an important role in the formation and maintenance of compact myelin hence participating in the formation of the myelin sheath (Li et al., 2012). Autophagy is also involved in myelination of sciatic nerves by regulating the structural plasticity of Schwann cells (Jang et al., 2015). Mutations in *PMP22* are responsible for more than 50% of all inherited neuropathies. Duplication of *PMP22* causes the most common demyelinating neuropathy, CMT1A (Lupski et al., 1992; Timmerman et al., 1992). Point mutations in *PMP22* cause CMT1E neuropathy, while a heterozygous deletion cause hereditary neuropathy with liability to pressure palsies (HNPP) (Nicholson et al., 1994; Russo et al., 2011). CMT1A and CMT1E patients show variable clinical severity but the main features of the diseases include slowly progressive weakness and atrophy of the distal limb muscles, *pes cavus*, and reduced or absent deep tendon reflexes. In the *Trembler* CMT1E mouse models carrying a missense mutation in *Pmp22*, the mutant protein colocalizes with lysosomal markers (Notterpek et al., 1997). In the C22 mouse model of overexpression of

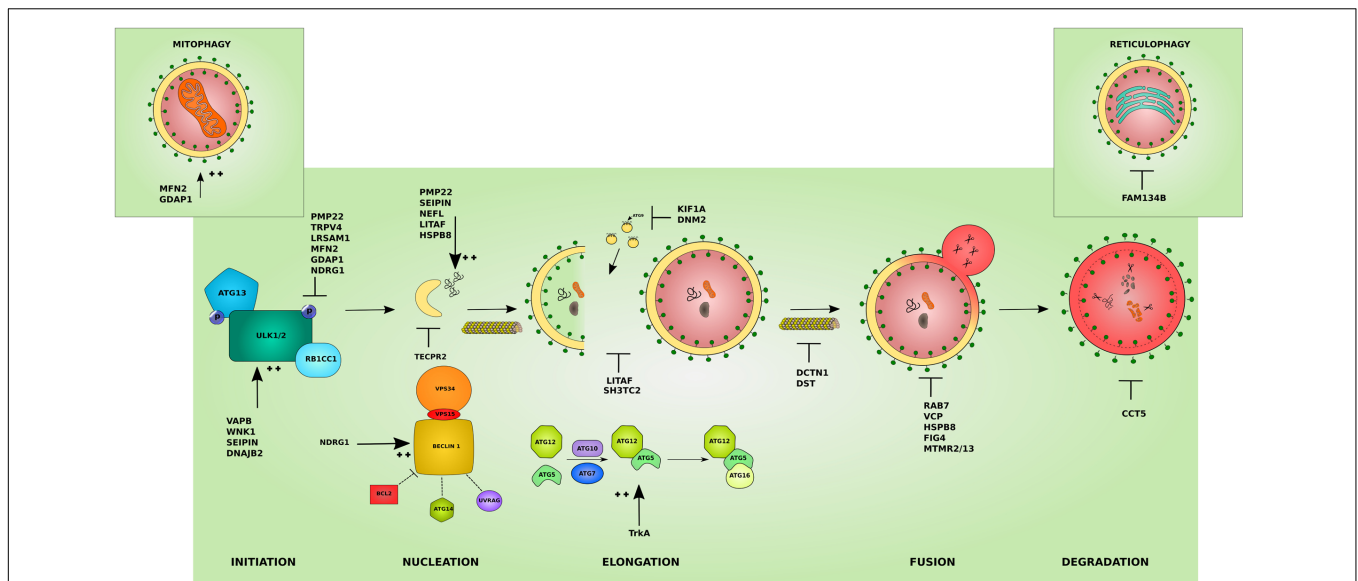


FIGURE 2 | Effects of the different IPN-associated genes on the autophagy pathway. Inherited peripheral neuropathy associated genes disrupt autophagy at various levels. Several affected proteins disrupt the initiation of autophagy by inhibiting the initiation complex these include: *peripheral myelin protein 22* (PMP22), involved in more than 50% of IPNs, *transient receptor potential cation channel subfamily V member 4* (TRPV4), and *leucine rich repeat and sterile alpha motif containing 1* (LRSAM1). Others overstimulate the initiation step such as: *VAMP associated protein B* (VAPB), *WNK lysine deficient protein kinase 1* (WNK1), *seipin lipid droplet biogenesis associated* (Seipin), and *DnaJ heat shock protein family (Hsp40) member B2* (DNJB2). Mutations affecting mitochondrial proteins can inhibit autophagy by causing an abnormal increase in mitophagy and disrupting the autophagy/mitophagy balance: *mitofusin 2* (MFN2) and *ganglioside induced differentiation associated protein 1* (GDAP1) (left inset). Mutant ER-resident *family with sequence similarity 134 member B* (FAM134B) affects its role in reticulophagy (right inset). The cyto-protective *N-myc downstream regulated 1* (NDRG1) inhibits the initiation complex or stimulates the nucleation complex depending on the physiological triggers. At the nucleation step, mutant *tectonin beta-propeller repeat containing 2* (TECPR2) disrupts the formation of early autophagocytic membranes from the ER. The elongation of the phagophore into an autophagosome is disrupted by mutations that affect the supply for forming membranes from late endosomes: *lipopolysaccharide induced TNF factor* (LITAF) and *SH3 domain and tetra-tryptophan repeats 2* (SH3TC2), and from ATG9-containing vesicles as in the microtubules associated proteins: *kinesin family member 1A* (KIF1A) and *Dynamin 2* (DNM2). This step can also be overstimulated by mutations in the *tyrosine kinase A* (TrkA) which lead to toxic increase in ATG12-ATG5 conjugates. The transport of autophagosomes to lysosomes is disrupted by mutations affecting cytoskeleton associated proteins such as *Dynactin 1* (DCTN1) and *dystonin* (DST). Mutations involving *Ras-related GTPase* (RAB7), *valosin containing protein* (VCP), *heat shock protein B8* (HSPB8), and the phosphatases: *phosphoinositide 5-phosphatase* (FIG4), and *myotubularin-related proteins* (MTMR2 and MTMR13) block the lysosomal fusion step in autophagy. Mutant *chaperonin containing TCP1 subunit 5* (CCT5) on the other hand inhibits the degradation step. In addition, several mutant proteins lead to the formation of aggregates which basal autophagy on its own might not cope with (PMP22, Seipin, LITAF, HSPB8) and *neurofilament light* (NEFL). The colors and shapes of the boxes are randomly assigned and show that they are different proteins belonging to the same complexes.

PMP22, resembling the CMT1A phenotype, aggregate formation is seen in affected nerves. This aggregation occurs together with a reduced proteasomal activity and association of the aggregates with autophagosomes (Fortun et al., 2006). Since autophagy and the proteasome can play compensatory roles in maintaining cellular homeostasis, autophagy seems to play a part in the pathomechanism of CMT1 neuropathic mouse models. With reduced proteasomal activity, basal autophagy on its own might not be enough to clear out all the aggregating mutant proteins, but induction of autophagy by external methods can aid in the degradation of toxic products. Indeed, autophagy induction in neuronal cultures from CMT1A mouse models via nutrient deprivation or rapamycin treatment decreases the aggregate formation. Autophagy induction also improves PMP22 trafficking leading to an enhancement of remyelination and indirectly increasing the expression of myelin proteins and the abundance and length of myelin internodes (Madorsky et al., 2009; Rangaraju et al., 2010). Suppression of a key autophagy protein, ATG12 by siRNA, abolishes these effects, indicating that the phenotypic improvements are mediated by autophagy

and that an intact autophagy pathway is required for proper remyelination (Rangaraju et al., 2010).

VAPB (VAMP Associated Proteins B and C)

VAMP associated proteins B and C belongs to a family of ER anchored proteins and plays a role in Golgi-mediated transport, membrane trafficking and neurotransmitter release (Lev et al., 2008). Recently the tethering complex formed by VAPB (ER) and PTPIP51 (mitochondria) has been shown to regulate the induction of autophagy through a role in mitochondria-ER calcium delivery which acts on BCL2-Beclin 1 interaction (Gomez-Suaga et al., 2017). Dominant mutations in VAPB lead to complex and atypical forms of inherited motor neuron disease (Nishimura et al., 2004). In a VAPB/ALS8 knock-in mouse model, mutant VAPB translocates from the ER to the autophagosome where it is degraded (Larroquette et al., 2015). The mislocalisation of VAPB causes ER stress and can lead to loss of VAPB functions in the ER. Absence of VAPB in the ER abolishes the VAPB-PTPIP51 tethering complex. Loosening of the ER-mitochondria contacts by loss of VAPB1-PTPIP51

can lead to overstimulation of autophagy (Gomez-Suaga et al., 2017). The dysregulated autophagy may have adverse effects on neuronal homeostasis and might be a prime pathological sign in VAPB associated neuropathies.

WNK1 (WNK Lysine Deficient Protein Kinase 1)

WNK lysine deficient protein kinase 1 is a serine/threonine kinase with the canonical function of regulating ion transport across cell membranes (Moriguchi et al., 2005). Truncating mutations in *WNK1* cause hereditary sensory and autonomic neuropathy type II (HSAN-II) (Rivière et al., 2004). HSAN-II is characterized by absence of pain sensations and patients suffer from ulcero-mutilating form of neuropathy. Little is known about the non-canonical functions of WNK1, but a role in autophagy was discovered recently. WNK1 exerts an inhibitory effect on basal and starvation-induced autophagy by interacting with UV Radiation Resistance-Associated Gene (UVRAG), a component of the main autophagy complex PI3KC3. WNK1 interaction reduces the activity of PI3KC3 and alters the phosphorylation status of ULK1 leading to inhibition of autophagy. Knocking-down WNK1 by siRNA in different cell lines leads to increased activation of autophagy (Gallolu Kankanamalage et al., 2016). WNK1 appears to play a regulatory role in autophagy by inhibiting the process, therefore truncating mutations in *WNK1*

leading to neuropathy might hinder its autophagy-related function and lead to toxic increase in autophagic flux that can have deleterious effects contributing to the neuropathology.

BSCL2 (Seipin)

The *BSCL2* gene encodes the protein seipin, a transmembrane protein that resides in the ER (Ito et al., 2008). The exact function of seipin remains elusive, though a role in lipid homeostasis and adipogenesis has been suggested (Cartwright and Goodman, 2012). Null mutations in *BSCL2* are responsible of lipodystrophy, dominant mutations on the other hand cause distal hereditary motor neuropathy (dHMN-V) and Silver syndrome. dHMN-V patients present with uncharacteristic prominent hand muscle wasting and weakness early in the course of the disease, and mild to severe plasticity of the lower limbs (Windpassinger et al., 2004). Neuropathy-causing *BSCL2* mutations have been shown to affect the glycosylation sites of BSCL2 and lead to the accumulation of the unfolded protein in the ER (Windpassinger et al., 2004). It has been confirmed that different mutations in *BSCL2* can lead to the formation of perinuclear aggregates (Hsiao et al., 2016). In a neuropathic mouse model expressing mutant seipin exclusively in neurons (seipinopathy), seipin presents in intracellular aggregates. In addition, motor neurons show accumulation of

TABLE 1 | Summary of IPN-associated genes, their clinical phenotype and the stage they impact the autophagy pathway.

Affected autophagy step/type	IPN-associated gene	Clinical phenotype
Initiation	<i>PMP22</i> (peripheral myelin protein 22)	CMT1A, CMT1E, HNPP
	<i>VAPB</i> (VAMP associated protein B)	Late onset SMA, ALS8
	<i>WNK1</i> (WNK lysine deficient protein kinase 1)	HSAN-IIA
	<i>BSCL2</i> (Seipin)	dHMN-V
	<i>LRSAM1</i> (leucine rich repeat and sterile alpha motif containing 1)	CMT2P
	<i>TRPV4</i> (transient receptor potential cation channel subfamily V member 4)	CMT2C, congenital distal SMA
	<i>NDRG1</i> (N-myc downstream regulated 1)	CMT4D
	<i>DNAJB2/HSJ1</i> [DnaJ heat shock protein family (Hsp40) member B2]	AR-dHMN
	<i>NEFL</i> (neurofilament light)	CMT2E, CMT1F
	<i>TrkA (NTRK1)</i> (neurotrophic receptor tyrosine kinase 1)	HSAN-IV, CIPA
Autophagosome formation and expansion	<i>DNM2</i> (dynamin2)	DI-CMTB
	<i>KIF1A</i> (kinesin family member 1A)	HSAN-IIC
	<i>LITAF</i> (lipopolysaccharide-induced TNF factor)	CMT1C
	<i>SH3TC2</i> (SH3 domain and tetratricopeptide repeats 2)	CMT4C
	<i>TECPR2</i> (tectonin beta-propeller repeat containing 2)	HSAN-III, HSP
	<i>DCTN1</i> (dynactin subunit 1)	dHMN-VIIb
	<i>DST</i> (dystonin)	HSAN-VI
Lysosomal fusion and degradation	<i>RAB7</i> (member RAS oncogene family)	CMT2B
	<i>CCT5</i> (chaperonin containing TCP-1 subunit 5)	HSNSP
	<i>FIG4</i> (FIG4 phosphoinositide 5-phosphatase)	CMT4J
	<i>MTMR2; MTMR13</i> (myotubularin-related proteins)	CMT4B1, CMT4B2
	<i>VCP</i> (valosin containing protein)	CMT2Y, ALS8, IBMPFD
	<i>HSPB8</i> (heat shock protein B8)	CMT2L, dHMN-I
	<i>MFN2</i> (mitofusin 2)	CMT2A
	<i>GDAP1</i> (ganglioside induced differentiation associated protein 1)	CMT4A, AR-CMT2, CMT2K
Reticulophagy	<i>FAM134B</i> (family with sequence similarity 134 member B)	HSAN-IIB

autophagy marker LC3II together with a fragmented Golgi apparatus phenotype (Guo et al., 2013). The accumulation of autophagosomes was also confirmed by electron microscopy indicating that overstimulation of autophagy by mutant seipin leads to signs of degeneration (fragmented Golgi). The increased activation of autophagy was also confirmed in cell models expressing mutant seipin (Fan et al., 2015). Together these studies show that disrupted autophagy is a hallmark of seipin-related neuropathy.

LRSAM1 (Leucine Rich Repeat and Sterile Alpha Motif Containing 1)

Leucine rich repeat and sterile alpha motif containing 1 is a leucine-rich repeat protein and an E3 ubiquitin ligase. LRSAM1 is involved in cell adhesion and cargo sorting during receptor endocytosis (Amit et al., 2004). Dominant negative mutations in *LRSAM1* cause CMT2P neuropathy (Weterman et al., 2012). CMT2P patients display features of the axonal CMT2 including mild lower-limb sensorimotor neuropathy, foot deformities, and hammer toes (Weterman et al., 2012). Early studies reported a function for LRSAM1 in endocytosis and retrovirus budding (Amit et al., 2004). Later it was shown to recognize, ubiquitinate and guide several bacteria strains to autophagy (bacteriophagy) (Huett et al., 2012). LRSAM1 is also a potential interactor of LC3 family protein GAPARAPL2 (GABA type A receptor-associated protein) (Ng et al., 2011), and is also involved in the autophagy pathway via interaction with PHD finger protein 23 (PHF23), a negative regulator of autophagy (Wang et al., 2014). A role for LRSAM1 in the general autophagic pathway is evident by the fact that LRSAM1 overexpression increases autophagic flux by increasing the formation of LC3-GFP puncta in cultured cell lines, while silencing it causes a decrease in autophagic flux (Wang et al., 2014). LRSAM1 appears to play a regulatory role in the activation of autophagy probably through the interaction with other signaling proteins. Though the exact connection between LRSAM1, interactors and general autophagy remains unclear, loss of function mutations may disrupt the role of LRSAM1 in autophagy.

TRPV4 (Transient Receptor Potential Cation Channel Subfamily V Member 4)

Transient receptor potential cation channel subfamily V member 4 is a member of the TRP cation channels, and has an important role in sensing temperature, osmotic pressure, and mechanic stimuli (Köttgen et al., 2008). Mutations in *TRPV4* cause CMT2C, a hereditary motor and sensory neuropathy with diaphragm and vocal cord paresis (Dyck et al., 1994). Alterations in *TRPV4* can have toxic consequences in neuronal cells due to changes in calcium concentrations (Deng et al., 2010). *TRPV4* can induce autophagy through the AKT-pathway and potentially via regulation of calcium levels and osmotic pressure (Zhan et al., 2015). Furthermore, inhibition of *TRPV4* by siRNA leads to inhibition of autophagy (Zhan et al., 2015). Therefore, dysregulation of autophagy is a potential pathomechanism in *TRPV4* associated neuropathies, as a direct effect of mutant *TRPV4* or as one of the neurotoxic consequences

due to the disruption in calcium concentrations by *TRPV4* mutants.

NDRG1 (N-myc Downstream Regulated 1)

N-myc downstream regulated 1 is mainly involved in cyto-protective stress response through regulation of p53 protein (Chen et al., 2010). In addition, it plays a role in immunity, development, differentiation and an important role in cancer (Fang et al., 2014). Mutations in *NDRG1* cause CMT4D neuropathy characterized with severe reduction in NCVs, skeletal and foot deformities and sensory loss (Kalaydjieva et al., 2000). *NDRG1* inhibits basal and ER Stress induced autophagy via suppression of protein kinase-like endoplasmic reticulum kinase (PERK)/eIF2 α axis (Sahni et al., 2014). Upregulation of *NDRG1* has also been shown to initiate BNIP3 and Beclin mediated autophagy (Han et al., 2014). Autophagy regulation seems to be a part of the cyto-protective function of *NDRG1*. It may therefore play a role in fine tuning autophagy levels by acting on different autophagy inducing or inhibiting pathways. Though a link between CMT4D-causing *NDRG1* mutations and autophagy is yet to be established, mutations in *NDRG1* might influence autophagy regulation by *NDRG1*.

DNAJB2 [DnaJ Heat Shock Protein Family (Hsp40) Member B2, HSJ1]

HSJ1, a co-chaperone protein, is involved in binding ubiquitylated chaperone clients and their loading onto the Hsc70 chaperone, thus preventing aggregation and aiding proteasome sorting (Westhoff et al., 2005). HSJ1 consists of two isoforms with distinct intracellular localization. HSJ1a is cytoplasmic and nuclear, while HSJ1b localizes to the ER (Westhoff et al., 2005). In addition to its function in the proteasome system, HSJ1 has been shown to be involved in the recruitment of the autophagy marker protein LC3 to damaged mitochondria aiding in mitochondrial autophagy (mitophagy) (Rose et al., 2011). Recessive mutations in *HSJ1* affecting both isoforms can cause CMT2T neuropathy or purely motor AR-dHMN (Gess et al., 2014). HSJ1a, the cytoplasmic isoform has been shown to enhance autophagy and decrease aggregation (Novoselov et al., 2013; Sanchez et al., 2016). Furthermore, deletion mutations in HSJ1b isoform, have been shown to lead to neurodegeneration and irregular increase in the autophagy marker LC3 due to increase in HSJ1a expression (Sanchez et al., 2016). These studies present HSJ1 as a moderator of autophagy and proteasome activity and show that mutations in *HSJ1* could disrupt this balance leading to impaired clearance of ubiquitylated proteins and autophagy.

NEFL (Neurofilament Light)

Neurofilament light is part of the axoskeleton (neurofilaments) of large myelinated axons of the central and peripheral nerves. The main role of neurofilaments is maintaining fiber caliber and subsequently the conduction velocities of myelinated axons (Perrot et al., 2008). Mutations in *NEFL* can cause CMT2E/1F neuropathy with distal weakness and wasting of the lower limbs, and occasional cerebellar dysfunction, tremor, and hearing loss (Mersianova et al., 2000; Pareyson

et al., 2014). CMT causing NEFL mutations have been shown to cause aggregate formation in cell culture and *in vitro* models. Activation of PKA, alleviates the aggregation phenotype (Sasaki et al., 2006). PKA is a known regulator of autophagy mostly exerting an inhibitory effect through phosphorylation of ATG13 an essential protein in the Ulk1 autophagy-initiation complex (Stephan et al., 2009), and of LC3 (Cherra et al., 2010). Therefore, the aggregation phenotype of NEFL might be a by-product of abnormality in the autophagy pathway which is restored by the activation of PKA. Furthermore, NEFL has been shown to interact with the PI3-phosphatase MTMR2 (Previtali et al., 2003). This interaction might be essential for the potential role of MTMR2 in autophagy through its regulation of endosomal vesicle trafficking or through its interaction with MTMR13, a direct regulator of autophagosome-lysosome fusion (see IPN Genes and Lysosomal Fusion and Degradation).

IPN Genes and Autophagosome Formation and Expansion

TrkA (NTRK1) (Neurotrophic Receptor Tyrosine Kinase 1)

Tyrosine kinase A, a nerve growth factor (NGF) receptor, is essential for neuronal survival and regulation of neuronal death (Miller and Kaplan, 2001). TrkA has been associated with regulating the interplay between autophagy and apoptosis mainly in cancer cells (Hansen et al., 2007; Dadakhujaev et al., 2009). Overexpression of TrkA leads to an increase in the amount of ATG5-ATG12 conjugates and ultimately to an increase in autophagy marker LC3II (Dadakhujaev et al., 2009). Mutations in *TrkA* cause HSAN-IV neuropathy with congenital insensitivity to pain (CIPA) marked by absence of reaction to noxious stimuli and self-mutilating behavior (Indo et al., 1996). Recently, mutant TrkA has been shown to cause accumulation of autophagosomes. This accumulation proved to be a result of aberrant activation of autophagy and over saturation of the lysosomes rather than a deficit in autophagosome-lysosome fusion. Neurons expressing TrkA mutant show increased cell toxicity and dystrophic neurites as a result of autophagosomes accumulation by the abnormal autophagy activation (Franco et al., 2016).

DNM2 (Dynamain2)

Dynamain2 is one of the three isoforms of dynamin. DNM2 is a mechano-GTPase involved in endocytosis, Golgi function and vesicle trafficking (González-Jamett et al., 2013). DNM2 has been shown to play essential roles in autophagy. One of its main roles has been the autophagic lysosomal reformation, supplying nascent protolysosomes and hence maintaining the autophagic flux (Schulze and McNiven, 2014; Klionsky et al., 2016). Recently, DNM2 has been shown to interact with another protein Bif-1 to mediate the generation of Atg9-containing vesicles delivering Atg9 to autophagosome formation sites and promoting the formation of autophagosomes (Takahashi et al., 2016). Dominant mutations in *DNM2* have been linked with the intermediate form of CMT (DI-CMTB) with NCVs ranging from normal to 25 m/s (Züchner et al., 2005). A mutant

DNM2 mouse model shows signs of neuropathy and a decreased autophagic flux indicated by lower levels of LC3II expression and P62-positive bodies [a selective autophagy marker also known as sequestosome1 (SQSTM1)] (Durieux et al., 2012). These studies suggest that mutations in *DNM2* leading to neuropathy affect its function in the formation of autophagosomes and present autophagy impairment as a pathomechanism of *DNM2*-linked neuropathy.

KIF1A (Kinesin Family Member 1A)

Kinesin family member 1A is a kinesin motor protein essential for the transport of vesicles in neuronal axons in anterograde fashion (Lo et al., 2011). Mutations in *KIF1A* can cause hereditary sensory and autonomic neuropathy type 2 (HSAN-II) (Rivire et al., 2011). HSAN-II patients suffer from frequent occurrence of unrecognized injuries and fractures of hands and feet due to loss in all peripheral sensations including pain and temperature. Autonomic symptoms include severe feeding problems in infants and common gastroesophageal reflux. Recently, it was shown that *KIF1A* controls the localization of ATG-9 and regulates the spatial distribution of autophagosomes in developing neurons of *Caenorhabditis elegans* (Stavoe et al., 2016). Maintaining ATG9 trafficking is essential for proper autophagosome formation (Lamb et al., 2016). The effects on autophagy in mutant *KIF1A* patients or cell/mouse models remains to be studied, but it is not inconceivable that impairment of autophagy due to disruption in ATG9 trafficking in *KIF1A* mutants is one of the pathomechanisms of neuropathy due to *KIF1A* mutations.

LITAF (Lipopolysaccharide-Induced TNF Factor)

Lipopolysaccharide-induced TNF factor, has been mainly linked with inflammatory functions, namely the secretion of cytokines such as TNF upon lipopolysaccharide stimulation (Tang et al., 2006). It has also been implicated in tumor suppression pathways and p53-induced apoptotic pathway (Zhou et al., 2011; Liu et al., 2012). LITAF seems to have different functions in different cell types. A role for LITAF in the positive regulation of autophagy has been shown in B cells. LITAF regulates LC3 expression and colocalizes with autophagosomes in B cells. Furthermore, overexpression of LITAF stimulates autophagy while silencing LITAF decreases the autophagic flux in these cells (Bertolo et al., 2013). Mutations in *LITAF* cause the dominant demyelinating CMT1C neuropathy (Street et al., 2003). In HEK293 cell models expressing CMT1C associated LITAF mutant protein, the mutant proteins cause mislocalisation of LITAF from early endosomes to the cytosol, destabilize LITAF and cause it to be aggregation prone. The aggregating mutant LITAF is then degraded by the proteasome and by autophagy (Lee et al., 2011). In neuroblastoma cell lines expressing WT and mutant forms of LITAF, CMT-causing LITAF mutants are mislocalised to the mitochondria, while the WT form traffics through the secretory pathway to the late endosome/lysosome (Lacerda et al., 2014). Late endosomes and lysosomes are essential for supplying the maturing autophagosome and for degrading the lysosomal content (Murrow et al., 2015). The trafficking function of LITAF might be related to its effect on autophagic flux, mislocalisation of

mutant LITAF can therefore have a negative effect on the integrity of the endo/lysosomes and consequently on the autophagic process.

SH3TC2 (SH3 Domain and Tetratricopeptide Repeats 2)

SH3TC2 encodes the Src homology 3 domain and tetratricopeptide repeats 2 protein. Little is known about the function of SH3TC2. However, the several motifs it contains suggest protein-protein interaction functions. Recessive mutations in *SH3TC2* cause a form of demyelinating neuropathy, CMT4C, characterized with severe scoliosis (Senderek et al., 2003b). Wild-type SH3TC2 has been shown to localize to recycling endosomes in rat Schwann cells, while the CMT causing mutant forms mistarget SH3TC2 away from the recycling endosomes (Roberts et al., 2010). SH3TC2 interacts with the small GTPase Rab11. The SH3TC2/Rab11 interaction is disrupted in mutant SH3TC2 in cultured cell lines (Roberts et al., 2010). Interestingly, KO of SH3TC2 in a transgenic mouse model decreases the expression of Rab11 in nerves of these mice (Stendel et al., 2010). Rab11 has been described as a positive regulator of autophagy. ULK1 and ATG9 localize in part to Rab11 positive recycling endosomes. Rab11 dependent vesicular transport from the recycling endosomes contributes to the forming autophagosomes and regulates starvation induced autophagy (Longatti et al., 2012). So by disrupting Rab11 interaction and expression levels and mistargeting SH3TC2 away from the recycling endosomes, *SH3TC2* CMT-associated mutations could disrupt the contribution of recycling endosomes to autophagosome formation.

TECPR2 (Tectonin Beta-Propeller Repeat Containing 2)

Tectonin beta-propeller repeat containing 2 was initially identified as human ATG8-interacting protein (Behrends et al., 2010). TECPR2 possesses an LC3 interacting motif (LIR) through which it binds to LC3B and LC3C family proteins. TECPR2 LIR-dependent binding leads to its association with cellular trafficking components such as HOPS and SEC24D. This interaction ultimately maintains a functional ERES and efficient ER export. TECPR2 depletion causes a decrease in ERES number and a delayed ER export. Maintaining a functional ERES provides a scaffold for autophagosome formation (Stadel et al., 2015). Mutations in *TECPR2* leading to the translation of a truncated and unstable version of TECPR2 cause a form of HSP (Oz-Levi et al., 2012) and hereditary sensory and autonomic neuropathy (HSAN-III) (Heimer et al., 2016). The latter presents with intellectual disability and, spasticity, and chronic respiratory disease. Skin fibroblasts from TECPR2-related HSP patients show a decreased number of LC3 and P62 proteins marking a decreased autophagic flux (Oz-Levi et al., 2012). These fibroblasts also show delayed ER export (Stadel et al., 2015), an indication that the function of TECPR2 in maintaining ER export and the formation of early autophagosome intermediates is disrupted by HSP-causing mutations, presenting autophagy disruption as a likely pathomechanism in HSP neuropathy.

IPN Genes and Autophagosome Transport

DCTN1 (Dynactin Subunit 1)

Dynactin subunit 1 is the largest subunit of the dynactin complex. The dynactin complex has been associated with a large range of cellular functions including mitosis, ER-Golgi transport, lysosomes and endosomes movement as well as interacting with dynein for cargo transport (Schroer, 2004). Mutations in *DCTN1* disrupt axonal transport and lead to hereditary motor neuropathy (dHMN-VIIb) with breathing difficulty due to vocal fold paralysis and progressive facial weakness (Puls et al., 2003). *DCTN1* knock-down shows motor neuron degeneration associated with autophagosomes accumulation due to impaired transport of autophagosomes along the axons (Ikenaka et al., 2013). Similarly, in a mouse model of mutant *DCTN1*, abnormal accumulation of autophagosomes has been shown in motor neurons and linked to the motor neuropathy phenotype (Wiesner et al., 2015). This presents autophagy impairment as a pathomechanism leading to motor neuropathy for *DCTN1* mutations.

DST (Dystonin)

The dystonin gene encodes several dystonin protein isoforms which are cytoskeletal cross-linking proteins that can interact with different organelles, microtubules, and protein complexes (Ferrier et al., 2013). Mutations in *DST* cause hereditary sensory and autonomic neuropathy (HSAN-VI) also known as familial dystonomia and presenting with alacrima, depressed deep tendon reflexes, and lingual fungiform papillae (Edvardson et al., 2012). In a mouse model of dystonia, mutant *DST* disrupts the autophagic process as evident by the accumulation of LC3 and P62 proteins. This impairment is attributed to the failure of autophagosome-lysosome fusion suggesting that dystonin is required to transport the autophagosomes to the lysosomes for maturation into autolysosomes (Ferrier et al., 2015). Interestingly, expression of the non-mutated form of dystonin restores the autophagy deficits revealing that the autophagy deficit is a direct effect of the mutated dystonin (Ferrier et al., 2015).

IPN Genes and Lysosomal Fusion and Degradation

RAB7 (Member RAS Oncogene Family)

Ras-related protein Rab-21 is a small GTPase functioning in vesicular trafficking, more specifically in the transport from early to late endosomes and from late endosomes to lysosomes (Stenmark, 2009). RAB7 is recruited to autophagosomes and is required for the fusion of autophagosomes and lysosomes (Jäger et al., 2004). Mutations in *RAB7* cause CMT2B neuropathy characterized by distal muscle wasting and weakness and frequent foot ulcers and infections (Verhoeven et al., 2003). Dominant negative mutations retard the recruitment of RAB7 to autophagosomes, and prevent the progression of autophagy by impairing autolysosome formation (Gutierrez et al., 2004).

CCT5 (Chaperonin Containing TCP-1 Subunit 5)

A subunit of the TCP-1 containing chaperonin complex (CCT), an ATP-dependent chaperone responsible for folding unfolded proteins including actin and tubulin. Recessive mutations in *CCT5* cause a mutilating hereditary sensory and autonomic neuropathy with spastic paraplegia (HSNSP) (Bouhouche et al., 2006). Studies have shown that CCT can prevent mutant huntingtin (htt) aggregation *in vitro* (Darrow et al., 2015). Recently, it was shown that the function of CCT in preventing aggregation of mutant proteins is mediated by autophagy (Pavel et al., 2016). CCT is required for lysosomal biogenesis and functioning and for autophagosome-lysosome fusion, possibly via interaction with cytoskeleton proteins. Disruption of CCT integrity by knock-down or by mutations in *CCT5* disrupts autolysosome formation and cargo degradation (Pavel et al., 2016).

FIG4 (FIG4 Phosphoinositide 5-Phosphatase)

FIG4 phosphoinositide 5-phosphatase is a phospholipid phosphatase responsible for the generation and turnover of the PtdIns(3,5)P₂ phosphoinositide (Di Paolo and De Camilli, 2006). Mutations in *FIG4* cause Yunis-Varon syndrome, familial epilepsy with polymicrogyria, and the severely demyelinating Charcot-Marie-Tooth type 4J neuropathy (CMT4J) (Chow et al., 2007; Katona et al., 2011; Vaccari et al., 2015). In a *FIG4* deficient neuropathic mouse model, sensory and motor neurons as well as Schwann cells seem to be affected (Katona et al., 2011; Vaccari et al., 2015). Neurons show decrease of PtdIns(3,5)P₂ levels, a sign of impaired *FIG4* enzymatic activity, and enlargement of late endosomes and lysosomes. Enlargement of late endosomes and lysosomes can hinder the fusion capacity of autophagosomes with lysosomes. Indeed these mice show accumulation of autophagic markers LC3II and P62 in their sciatic nerve. This accumulation is independent of an increase in the autophagic flux (Ferguson et al., 2010; Vaccari et al., 2015). Thus abolishing the enzymatic activity of *FIG4* by missense mutations or haploinsufficiency seems to affect the progression of autophagic degradation by preventing the fusion between autophagosomes and the then enlarged late endosomes/lysosomes (Vaccari et al., 2015).

MTMRs (Myotubularin-Related Proteins)

Myotubularin-related proteins are PI3-phosphatases consisting of catalytically active or inactive members. Mutations in *MTMR2* and *MTMR13* (also called SET-binding factor 2) cause the demyelinating CMT4B1 and CMT4B2 neuropathies respectively with early-onset glaucoma (Azzedine et al., 2003). *MTMR2* is a catalytically active phosphatase which dephosphorylates phosphatidylinositol 3-phosphate (PI(3)P) and bisphosphate PI(3,5)P₂. *MTMR13* on the other hand is an inactive phosphatase but it has been shown to associate with *MTMR2* (Robinson and Dixon, 2005). *MTMR2* has been linked with regulation of the late endocytic pathway and vesicular transport through its putative substrate PI(3,5)P₂ (Bolino et al., 2004; Lenk and Meisler, 2014). *MTMR13* on the other hand acts as a RAB21 GEF required for fusion of autophagosome with the lysosome. *MTMR13* GEF activity is induced upon starvation and it promotes the

trafficking of VAMP8 to the lysosome where it is needed to mediate fusion with the autophagosome (Jean et al., 2015). Autophagy has not yet been studied in the context of CMT4B causing mutations in *MTMRs* but the roles of both *MTMR2* and *MTMR13* in autophagy and their functional association with each other presents autophagy impairment as a possible common pathomechanism in mutant *MTMRs* leading to neuropathy.

VCP (Valosin Containing Protein)

Valosin containing protein is an AAA+ ATPase associated with diverse cellular activities including the ATP-dependent remodeling of proteins to unfold them or extract them from cell structures or binding partners (Erzberger and Berger, 2006). Mutations in *VCP* cause a multisystem degenerative disease consisting of inclusion body myopathy, Paget's diseases and frontotemporal dementia (IBMPFD) (Kimonis et al., 2000), familial ALS (Shaw, 2010) and can also lead to CMT2Y neuropathy with distal muscle weakness and atrophy and length-dependent sensory loss (Gonzalez et al., 2014). *VCP* also plays a role in lysosomal homeostasis and the lysosomal damage response. Lysosomal damage induced by lysomotropic reagents triggers a concomitant recruitment of *VCP* to lysosomes. *VCP* then cooperates with a set of cofactors to drive the degradation of ruptured lysosomes (Papadopoulos et al., 2016). Damaged lysosomes accumulate in cells expressing mutant *VCP* showing that its role in clearing out damaged lysosomes is compromised by neuropathy-causing mutations. *VCP* mutant knock-in mouse model shows accumulation of LC3II positive structures in myoblasts (Nalbandian et al., 2013). Furthermore, knock-down of *VCP* leads to accumulation of autophagosomes due their failure to mature into autolysosomes (Ju et al., 2009). A high percentage of the accumulated autophagic vesicles contain ubiquitin positive structures. *VCP* has been shown to be critical for the maturation of ubiquitin-containing autophagosomes into autolysosomes under basal conditions and under proteasome inhibition. This function of *VCP* in maturation of autophagosomes seems to be impaired by neuropathy-causing mutations (Lee et al., 2010).

HSPB8 (Heat Shock Protein B8)

Heat shock protein B8 belongs to the family of small heat shock proteins, ATP-independent chaperones that aid the folding of misfolded proteins by ATP-dependent chaperones (Holmgren, 2012). In addition to its function as a molecular chaperone, HSPB8 is involved in several other stress signaling functions such as removal of aggregates through CASA (Carra et al., 2008). CASA involves the recognition of substrate proteins by a complex of chaperones and co-chaperones including HSPB8 and P62 and its subsequent loading onto autophagosomes. Mutations in *HSPB8* cause CMT2L and dHMN-IIa neuropathies typically presenting with paresis of the extensor muscles of the big toe and then the feet (Irobi et al., 2004; Tang et al., 2005). Expression of mutant HSPB8 in cultured cells induces aggregate formation (Irobi et al., 2004). Transcriptional induction of WT HSPB8 in mouse models of motor neuron disease aids in the clearance of misfolded proteins and aggregates (Crippa et al., 2016). Interestingly, cells from neuropathic patients carrying HSPB8 mutations also show deficits in lysosomal delivery of

autophagosomes (Kwok et al., 2011). Taken together, these studies indicate that intact HSPB8 is necessary for aggregate clearance, possibly through CASA. Disruption of this role by mutations in *HSPB8* contribute to the neuronal pathogenicity.

IPN Genes Involved in Selective Autophagy: Mitophagy, Reticulophagy (ER-Phagy)

FAM134B (Family with Sequence Similarity 134 Member B)

Family with sequence similarity 134 member B is a transmembrane protein localized to the *cis*-golgi and predominantly expressed in the sensory and autonomic ganglia. Mutations in *FAM134B* cause hereditary sensory and autonomic neuropathy HSAN-IIB leading to impaired nociception, autonomic dysfunction, and severe mutilations (Kurth et al., 2009). *FAM134B* interacts with LC3/GABARAP through an LC3 interacting motif at its C-terminal domain. This interaction is essential for selectively directing part of the ER to autophagosomes (reticulophagy). Mutations causing sensory neuropathy disrupt the LC3 interacting motif and consequently the *FAM134B*-LC3 binding. *FAM134B* KO mice develop sensory neuropathy and degeneration of sensory neuronal axons. Deficit in reticulophagy in these mice but not general autophagy disrupts ER homeostasis leading to ER expansion and inhibition of ER turnover that ultimately leads to degeneration of sensory neurons (Khaminets et al., 2015).

MFN2 (Mitofusin 2)

Mitofusin 2 was identified as a transmembrane mitochondrial GTPase required for mitochondrial fusion (Santel and Fuller, 2001). Mutations in *MFN2* cause CMT2A neuropathy (Züchner et al., 2004) and are one of the most frequent CMT2 causing mutations (OMIM 609260, CMT2A \approx 35% of CMT2). CMT2A presents as a severe predominantly motor neuropathy or motor accompanied with profound proprioception loss. In addition to its role in mitochondrial fusion, *MFN2* plays multiple roles including regulation of cell survival, cell proliferation, ER stress and autophagy (reviewed in Schrepfer and Scorrano, 2016). *MFN2* deletion has been shown to impair starvation-induced autophagy by disrupting the MAM (mitochondria associated membranes), a described site for autophagosome formation (Hailey et al., 2010; Hamasaki et al., 2013). *MFN2* deletion in HeLa cells has also been shown to affect cell proliferation due to autophagy impairment (Ding et al., 2015). Motor neurons derived from iPSCs obtained from CMT2A patients show increase in mitophagy and mitochondrial depletion and increased expression of *PINK1*, *PARK2* and *BNIP3*, known triggers for autophagic degradation of mitochondria (Rizzo et al., 2016). In a *MFN2* KO mouse model, sarcopenia is seen in correlation with impaired autophagy in the muscle, accumulation of damaged mitochondria, and activation of an adaptive mitophagy pathway (Sebastián et al., 2016). Taken together, *MFN2* seems to play an essential role in autophagosome formation, possibly through maintenance of mitochondrial membranes and MAMs. This role is impaired in *MFN2* deficiency

and in *MFN2* causing CMT2A mutations, leading to autophagy impairment and disruption of balance between mitophagy and general autophagy.

GDAP1 (Ganglioside Induced Differentiation Associated Protein 1)

Ganglioside induced differentiation associated protein 1 is an integral protein of the outer mitochondrial membrane formed of 2 glutathione-S-transferase domains (Huber et al., 2016). Dominant and recessive mutations in *GDAP1* cause demyelinating (CMT4A), or axonal (AR-CMT2 or CMT2K) neuropathies (Baxter et al., 2002; Senderek et al., 2003a; Sivera et al., 2010). *GDAP1* is required for the regulation of the mitochondrial network and mitochondrial integrity (Niemann et al., 2005). In a KO mouse model of *GDAP1* that recapitulates the neuropathic phenotype of CMT4A, disruption of the mitochondrial network and mitochondrial calcium homeostasis is evident in neurons and associates with accumulation of autophagic vesicles (Barneo-Muñoz et al., 2015). Mitochondrial defects can lead to abnormal increase in targeting mitochondria to autophagic degradation (mitophagy). In addition, both mitochondrial interconnectivity and calcium homeostasis are essential for the proper functioning of autophagy (Gomez-Suaga et al., 2017). It remains unclear whether the increased accumulation of autophagosomes in neurons of CMT4A mouse models is a by-product of increased mitophagy or defects in the general autophagic flux. Nonetheless, autophagic dysregulation does seem to be a feature of the pathology caused by CMT-causing *GDAP1* mutations and might explain the variety of clinical phenotypes presented by these mutations ranging from myelinating to axonal CMT and from dominant to recessive.

AUTOPHAGY MODULATION AS A THERAPEUTIC TARGET IN HEREDITARY NEUROPATHIES

So far, finding a treatment for hereditary neuropathies remains a challenge. An important step toward a successful therapy, from both an economic and a pharmaceutical perspective, is finding a common pathomechanism that can be targeted in different neuropathic genotypes. By bridging different neuropathic phenotypes and different causal genes, autophagy impairment emerges as a good candidate for modulation by therapeutic measures. Autophagy modulation as a therapy approach has been used in several more common neurodegenerative disease models. Inducing autophagy has been shown to reduce the severity of the Huntington's disease phenotype and improve clearance of Htt aggregates in mouse and neuronal cell models (Rose et al., 2010). In Alzheimer's disease, accumulation of autophagosomes contributes to the pathology (Ohta et al., 2010). Inhibition of autophagy has been reported as a mode of action in drugs that decrease amyloid- β accumulation in Alzheimer's patients (Lipinski et al., 2010). Accumulation of autophagosomes has also been attributed to defects in beclin-1 expression, hence autophagy enhancing treatments such as resveratrol and lithium can improve the pathology

of Alzheimer's disease (Vingtdeux et al., 2010; Rahvar et al., 2011). In addition, expression of beclin-1 in neuronal cells of transgenic mice improves their Parkinson's disease phenotype by enhancing lysosomal activation (Spencer et al., 2009). Similarly, the mTOR-independent autophagy inducer trehalose improves the clearance of α -synuclein, huntingtin (Sarkar et al., 2007) and SOD1 aggregates (Castillo et al., 2013a). Furthermore, autophagy modulating compounds are already in use to treat different neurodegenerative diseases and cancers, and are currently at different phases of clinical trials (reviewed in Towers and Thorburn, 2016). Despite its promise, autophagy modulation as a treatment for hereditary neuropathies still presents many challenges. The model of treating mutants that increase autophagic activation with inhibitors of autophagy and those that inhibit autophagy with activators is oversimplified. Many autophagy modulating drugs can have off-target effects. For example, mTORC1 inhibitors can affect cell metabolism and lipid synthesis in an autophagy-independent manner (Li et al., 2014). Therefore, targeting the specific autophagy step affected by a hereditary neuropathy causing-mutation is a better and more elegant approach to enhance the autophagic status without hindering other vital cellular processes. Certain step-specific approaches already exist and include direct stimulation of autophagy by targeting beclin1 with the alkaloid isorhynchophylline (Lu et al., 2012). Targeting the lysosomal fusion and degradation is also possible using pharmacological activators of lysosomal enzymes such as amprolium (McNeill et al., 2014) or acidic nanoparticles that increase the acidity of the lysosomes (Baltazar et al., 2012). Non-pharmacological enhancement of autophagy such as caloric restriction or exercise presents another way of overcoming the pharmacological modulation of other cellular pathways. Physical exercise has already been described as a rehabilitating measure in CMT patients (Roberts-Clarke et al., 2016; Vita et al., 2016). Whether improvement of autophagy is a mediator of the positive impact of exercise remains to be investigated, but exercise has been shown to enhance autophagy in the brain (He et al., 2012) and skeletal muscles (Ferraro et al., 2014). Another caveat of autophagy directed therapy is the difficulty of tracing autophagy *in vivo*. In other words, there is a need for biomarkers that can be used to make sure that the intended therapy is improving the autophagic status in patients in order to alleviate their symptoms. Such markers are as of yet unavailable, but recent advances using mouse models allows following up a treatment's effect on autophagy in mouse tissues

(Castillo et al., 2013b). This strategy, combined to behavioral and electrophysiological testing in a neuropathic mouse model can permit the direct correlation between a drug's effect on autophagy and its ultimate modulation of the neuropathic status laying out a strong case for such a drug to enter clinical trials.

CONCLUSION

The genetic heterogeneity of IPNs and the fact that they are rare disorders, highlights the need for finding common cellular and molecular pathomechanisms among the different disease-linked genes. This review complements recent work in attempting to find shared molecular mechanisms underlying IPNs (Bucci et al., 2012; Prior et al., 2017). The relevance of autophagy as a target pathway stems from the fact that it has been implicated in other disease conditions, mainly neurodegeneration, where autophagy targeting drugs have already entered clinical trials. In addition, autophagic impairment presents a unique overlap among neuropathies affecting both sensory and motor nerves on one hand, and the myelin sheath and the neuronal axon on the other. While more research is required to get a clearer view of the involvement of autophagy in neuropathic mechanisms, current evidence points out to the emergence of autophagy as a frequently affected pathway in IPN conditions.

AUTHOR CONTRIBUTIONS

MH wrote the manuscript and designed table and figures. VT supervised and recommended the content of the manuscript, corrected, and submitted.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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