Supplementary Table 1. Glossary of autophagy-related molecules and mechanisms in congenital disorders of autophagy
Aggrephagy: The selective removal of intracellular aggregates by macroautophagy.
Ambra1 (activating molecule in Beclin 1-regulated autophagy): Ambra1 binds Beclin-1 to promote autophagy initiation.
AMPK (AMP-activated protein kinase): Protein kinase that is activated by an increase in the intracellular AMP/ATP ratio. AMPK targets mTORC1, TSC1/2 and ULK1, which, overall, leads to an induction of macroautophagy.
Atg (autophagy related gene/protein): Prefix used to designate many genes/proteins involved in regulating macroautophagy.
Atg5-Atg12-Atg16L1: Protein complex that acts as an E3 ligase for LC3 - phosphatidylethanolamine conjugation, a critical process in autophagosome elongation.
Atg9: Adaptor protein that recruits membranes and lipids for expansion of the isolation membrane.
Autolysosome: Fusion product of autophagosomes (or amphisomes) and lysosomes. Autophagic cargo is degraded in autolysosomes.
Autophagic lysosome reformation: Process that describes the regeneration of lysosomes from autolysosomes. This ensures that the lysosomal pool is replenished after lysosomes have been consumed through fusion with autophagosomes.
Autophagosome: The key organelle in macroautophagy, these intracellular double-membrane vesicles sequester cytoplasmic cargo such as proteins or organelles. Autophagosomes mature and eventually fuse with lysosomes to form autolysosomes.
Autophagy: Umbrella term for intracellular pathways that deliver cytosolic cargo to lysosomes for degradation.
Beclin1-Atg14L-Vps34: Protein complex that contains Vps34, a class III phosphatidylinositol-3 kinase involved in initiating macroautophagy.
Beta-propeller protein-associated neurodegeneration (BPAN): X-linked

neurodegenerative disease caused by mutations in WDR45. Has previously been termed Static Encephalopathy of Childhood with Neurodegeneration in Adulthood (SENDA) syndrome and belongs to the spectrum of neurodegeneration with brain iron accumulation (NBIA).
Chaperone-mediated autophagy (CMA): Subtype of autophagy in mammalian cells by which proteins that contain a certain pentapeptide motif (KFERQ) are recognized, transported across the lysosomal membrane and finally degraded.
Congenital disorders of autophagy: A novel subtype of inborn errors of metabolism that comprises single-gene disorders of key autophagy genes.
Endosomes: Intracellular organelles that receive engulfed cargo from the extracellular space. So called "recycling endosomes" shuttle material back to the plasma membrane.
EPG5: Mutations in EPG5 impair the late stages of the autophagy pathway and cause Vici syndrome.
GABARAP (gamma-aminobutyric acid receptor-associated proteins): Homologs of LC3 that are involved in autophagosome formation, maturation and cargo recruitment.
HSP: Abbreviation for hereditary spastic paraplegia, a group of more than 70 different neurodegenerative diseases that share the unifying feature of distal axonal degeneration in the corticospinal tracts.
Isolation membrane: The initial membrane compartment that evolves during formation of the autophagosome. Also referred to as the "phagophore".
LAMP-1 (lysosome-associated membrane protein 1): Lamp1 is a transmembrane protein that localizes to the lysosomal membrane, making this a common marker for detecting lysosomes.
LAMP-2A (lysosome-associated membrane protein 2A): A splice variant of the Lamp2 gene, the LAMP-2A protein localizes to the lysosomal membrane where it functions as a receptor for chaperone-mediated autophagy.
LC3 (microtubule-associated protein 1 light chain 3): The most frequently used marker for autophagosomes. While LC3-I is mostly cytosolic, LC3-II,

which is conjugated to phsophatidylethanolamine, is present on autophagosomal membranes where it is involved in autophagosome formation and cargo recruitment.
Lipophagy: The selective removal of lipid droplets by macroautophagy.
Lysosomes: Acidic organelles that contain hydrolytic enzymes and enable cargo degradation.
Macroautophagy: A subtype of autophagy that involves the *de novo* formation of double-membrane vesicles, called autophagosomes.
Microautophagy: A subtype of autophagy that involves the direct uptake of cargo through protrusion and invagination of the lysosomal membrane.
Mitophagy: The selective removal of damaged mitochondria by macroautophagy.
mTORC1 (mammalian target of rapamycin complex 1): A rapamycin-sensitive protein complex that includes mTOR, Raptor, mLST8, PRAS40 and DEPTOR. mTORC1 regulated many downstream pathways and cell functions including macroautophagy.
NBR1 (neighbor of BRCA1 gene 1): An adaptor protein that binds ubiquitin-coated cargo and LC3. Structurally similar to p62, NBR1 is also a substrate of macroautophagy.
NDP52 (nuclear dot protein 52 kDa): An adaptor protein that binds ubiquitin-coated cargo and LC3.
Optineurin: Adaptor protein that binds ubiquitin-coated cargo and LC3. Recent evidence indicates that optineurin is particularly important to mitophagy.
p62/SQSTM1: Adaptor protein that binds ubiquitin-coated cargo and LC3. p62 is a substrate of macroautophagy and accumulates in cells with impaired macroautophagy.
Pexophagy: The selective removal of peroxisomes by macroautophagy.
Ribophagy: The selective removal of ribosomes by macroautophagy.
Rubicon (RUN domain protein as Beclin 1-interacting and cysteine-rich containing): Part of the Rubicon-UVRAG-Beclin-Vps34-Vps15 multiprotein

complex that inhibits macroautophagy.
SNX14 (sorting nexin 14): Mutations in SNX14 likely impair the late stages of the macroautophagy pathway and cause SNX14-associated cerebellar ataxia and intellectual disability syndrome.
Spastizin: The protein encoded by ZYFE26 (SPG15).
Spatacsin: The protein encoded by SPG11.
SPG: Spastic paraplegia gene.
SPG11: A subtype of hereditary spastic paraplegia that is caused by mutations in the SPG11 gene, which impair the late stages of the autophagy pathway.
SPG15: A subtype of hereditary spastic paraplegia that is caused by mutations in the ZFYVE26 gene, which impair multiple stages of the autophagy pathway.
SPG49: A subtype of hereditary spastic paraplegia that is caused by mutations in the TECPR2 gene, which likely impair the middle stages of the autophagy pathway.
TECPR2 (tectonin beta-propeller repeat containing 2): Mutations in TECPR2 likely impair the middle stages of the autophagy pathway and cause the SPG49 subtype of hereditary spastic paraplegia.
TFEB (transcription factor eb): Transcription factor that positively regulates the expression of a network of genes (CLEAR: Coordinated Lysosomal Expression and Regulation network) involved in macroautophagy and lysosomal biogenesis.
TSC (tuberous sclerosis complex): Autosomal-recessive multisystem disease caused by mutations in TSC1 or TSC2.
TSC1/2 (tuberous sclerosis complex 1/2): TSC1 and TSC2 form a stable heterodimeric protein complex that acts as a GTPase activating protein for Rheb, thus inhibiting mTORC1. Mutations in the TSC1 or TSC2 genes cause Tuberous Sclerosis Complex.
Ubiquitin: A small protein that is conjugated to lysine residues of cargo for proteasomal or autophagic degradation.
ULK family (Unc51-like kinase): Serine/threonine-protein kinases involved in autophagy initiation.

UVRAG (UV irradiation resistance-associated gene): Protein that regulates autophagy in multiple ways through interactions with Beclin-1, Bif-1 and rubicon.
WDR45 (WD repeat domain 45): Mutations in WDR45 impair the early stages of the autophagy pathway and cause beta-propeller protein-associated neurodegeneration (BPAN).
ZFYVE26 (zinc finger, FYVE domain containing 26): Mutations in ZFYVE26 impair multiple stages in the autophagy pathway and cause hereditary spastic paraplegia (SPG15).