Supplementary Note 1 | List of abbreviations.

3'SS, 3' splice site; **5'SS**, 5' splice site; **AD**, Alzheimer disease; **AMBRA1**, autophagy and beclin 1 regulator 1; **AML**, acute myeloid leukemia; **AMPK**, AMP-activated protein kinase; **APOC3**, apolipoprotein C3; **APP**, amyloid beta precursor protein; **ASO**, antisense oligonucleotide; **ATAT1**, alpha tubulin acetryltransferase 1; **ATG**, autophagy related; **ATG16L1**, autophagy related 16 like 1; **ATL3**, Atlastin GTPase 3; **BCL2L1**, BCL2 like 1; **CCD**, coiled-coil domain; **BNIP3**, BCL2 interacting protein 3; **BNIP3L**, BCL2 interacting protein 3 like; **CCPG1**, cell cycle progression 1; **ccRCC**, clear cell renal cell carcinoma; **CEBPB**, CCAAT enhancer binding protein beta; **CMA**, chaperone-mediated autophagy; **CMML**, chronic myelomonocytic leukemia; **CP**, cleavage and polyadenylation; **CQ**, chloroquine; **DS**, Down syndrome; **ER**, endoplasmic reticulum; **ESE**, exonic splicing enhancer; **ESS**, exonic splicing silencers; **FOXO1**, forkhead box O1; **GABARAP**, GABA type A receptor-associated protein; **H3K36me3**, trimethylation of lysine 36 on histone H3; **H3K4me3**, trimethylation of lysine 4 on histone H3; **HCV**, hepatitis C virus; **HDAC6**, histone deacetylase 6; **hnRNP**, heterogeneous ribonucleoprotein; **HSPA8**, heat shock protein family A (Hsp70) member 8; **HSP8A**, heat shock protein family A (Hsp70) member 8; **IFNL2**, interferon lambda 2; **LAP**, LC3-associated phagocytosis; **LAMP2,** lysosomal associated membrane protein 2; **LIR**, LC3-interacting region; **MAP1LC3/LC3**, microtubule associated protein 1 light chain 3; **MBNL**, muscleblind like splicing regulator; **MDS**, myelodysplastic syndrome; **MFN2**, mitofusin 2; **MORF4L1**, mortality factor 4 like 1; **MTOR**, mechanistic target of rapamycin kinase; **PD**, Parkinson disease; **PE**, phosphatidylethanolamine; **PINK1,** PTEN induced kinase 1; **PIK3C3**, phosphatidylinositol 3-kinase catalytic subunit type 3; **PIK3R4**, phosphoinositide-3-kinase regulatory subunit 4; **Poly(A)**, polyadenylation; **PRKN**, parkin RBR E3 ubiquitin protein ligase; **PRPF8**, pre-mRNA processing factor 8; **PSEN1**, presenilin 1; **PTBP1**, polypyrimidine tract binding protein 1; **PtdIns3K**, class III phosphatidylinositol 3-kinase; **PtdIns3P**, phosphatidylinositol-3-phosphate; **PTEN**, phosphatase and tensin homolog; **RAB33B**, RAB33B, member RAS oncogene family; **RBCC1**, RB1-inducible coiled-coil protein 1; **RBFOX2**, RNA binding fox-1 homolog 2; **RBP**, RNA-binding protein; **RETREG1**, reticulophagy regulator 1; **RELA**, RELA proto-oncogene, NF-kB subunit**RTN3,** reticulon 3; **RUBCN**, rubicon autophagy regulator; **SENDA**, static encephalopathy of childhood with neurodegeneration in adulthood; **SETD2**, SET domain containing 2, histone lysine methyltransferase; **SF1**, splicing factor 1; **SMAC**, single-membrane Atg8-family protein conjugation; **SNAP29**, synaptosome associated protein 29; **SNARE**, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; **SEC62**, SEC62 homolog, preprotein translocation factor;**SMA**, spinal muscular atrophy; **SMN1**, survival of motor neuron 1, telomeric; **SMN2**, survival of motor neuron 2, centromeric; **snRNA**, small nuclear RNA; **snRNP**, small nuclear ribonucleoprotein; **SNRPD1**, small nuclear ribonucleoprotein D1 polypeptide; **SNRPE,** small nuclear ribonucleoprotein polypeptide E; **SNRNP200**, Small Nuclear Ribonucleoprotein U5 Subunit

200; **SQSTM1/p62**, sequestosome 1; **SRSF**, serine and arginine rich splicing factor; **STX17**, syntaxin 17; **TEX264**, testis expressed 264, ER-phagy receptor; **TRIB3**, Tribbles Pseudokinase 3; **Ub**, ubiquitin; **Ubl**, ubiquitin like; **ULK1**, unc-51 like autophagy activating kinase 1; **U2AF**, U2 small nuclear RNA auxiliary factor; **VAMP8**, vesicle associated membrane protein 8; **WDFY3,** WD Repeat And FYVE Domain Containing 3; **WDR45**, WD repeat domain 45; **WIPI**, WD repeat domain, phosphoinositide-interacting; **XBP1**, X-box binding protein 1; **ZFYVE1**, zinc finger FYVE-type containing 1.

Supplementary Table 1 | Alteration in the alternative splicing of autophagy-related genes and impact on diseases

Autophagy-related gene	Variants	RNA splicing event(s)	Cellular function/ phenotype	Disease-associated variants	References
Initiation					
ULK1	*ULK1(1) – canonical variant*	28 exons	Autophagy induction and autophagosome biogenesis	Cancer; neurodegenerative diseases; neurodevelopment disorders; Crohn disease	[1]
	ULK1(2) – generated by splicing mutation	Skipping exon 22	Mitophagosome formation. Hypoxia-induced mitophagy	Autosomal dominant retinitis pigmentosa	[2]
	ULK1(3) – generated by splicing mutation	Skipping exon 22-23	Mitophagosome formation. Hypoxia-induced mitophagy	Autosomal dominant retinitis pigmentosa	[2]
Nucleation					
BECN1	*BECN1 Long – canonical variant*	12 exons	Autophagy induction	-	[1,3-6]
	BECN1S – generated by splicing mutation	Skipping exon 11; truncated C-terminus	Low binding affinity with class III PtdIns3K; Fail to activate autophagic response to starvation	Prostate cancer; Acute myeloid leukemia; acute lymphoblastic leukemia; B-cell acute lymphoblastic leukemia cells	[1,7,8]
	BECN1s – generated by splicing mutation	Skipping exons 10-11	Unable to initiate autophagy, but supports mitophagy	Acute myeloid leukemia	[1,7,8]

ATG14	*ATG14 Long – canonical variant*	9	Phagophore formation and autophagosome-lysosome fusion	Vici syndrome; Danon disease; cancer; neurodegenerative diseases	[9]
	ATG14 Short	Skipping exons 1-3	Inhibit autophagosome-lysosome fusion	-	[9]
WIPI1	*WIPI1α – canonical variant*	13 exons	Recruitment of ATG12–ATG5-ATG16L1 complex to nascent autophagosomes	-	[10,11]
	WIPI1β	-	Localizes to endosomal and golgi membranes	-	[12]
WIPI2	*WIPI2A – canonical variant*	13 exons	Involved in the formation of autophagosomal structures: mediates ER-phagophore contacts: recruits the ATG12–ATG5-ATG16L1 complex.	-	[10,11]
	WIPI2B	Skipping exon 12; 3' truncation end	Interacts with ATG16L1; required for innate immune response to *Salmonella* Typhimurium infection	-	[10,11,13]

	WIPI2C	-	-	-	[10,11]
	WIPI2D	Skipping exon 2; 3' truncation end	Promotes LC3 lipidation	-	[14]
	WIPI2E	-	-	-	[11]
WIPI4	*WIPI4α –canonical variant*	11 exons	PtdIns3P binding effector, autophagosome biogenesis and size control	Neurological disorders	[15,16]
	WIPI4β	Skipping exon 3-4	-	Static encephalopathy of childhood with neurodegeneration in adulthood	[15]
	WIPI4Δ	Early 3' end termination exon 11	-	Static encephalopathy of childhood with neurodegeneration in adulthood	[15]
Phagophore expansion					
ATG7	*ATG7 long – canonical variant*	19 exons	LC3/GABARAP lipidation	Neurodegeneration; hepatic diseases; cardiovascular diseases	[17-19]

	ATG7 short	Skipping exon 17	Inhibit autophagy. Unable to bind to LC3	Myelodysplastic syndrome; Acute myeloid leukemia; chronic myelomonocytic leukemia	[20,21]
	ATG7 (3)	Skipping exons 17-18	-	-	[20,21]
MAP1LC3A	*MAP1LC3A – canonical variant*	4 exons	Autophagosome biogenesis; adaptor selective cargo for autophagy	Alzheimer disease; Machado-joseph disease; cancer	[22]
	MAP1LC3A-b	Additional exon	-	-	[22]
MAP1LC3B	*MAP1LC3B - canonical variant*	4 exons	Autophagosome biogenesis; adaptor selective cargo for autophagy	Hermansky-pudlak syndrome; Parkinson disease 1, autosomal dominant; cancer	[22,23]
	MAP1LC3B-a	NAGNAG splice sites of intron 3	Inhibits interaction and binding with ATG4B	-	[22,23]
GABARAP	*GABARAP – canonical variant*	4 exons	Autophagosome biogenesis; receptor of selective cargo for autophagy	Stiff-Person syndrome; Machado-joseph disease; Parkinson disease; colorectal carcinoma	[24]

	GABARAP-a	Different 3' end points	Inhibits interaction and binding with ATG4	-	[24]
GABARAPL1	*GABARAPL1*	4 exons	Autophagosome biogenesis; receptor of selective cargo for autophagy	Vici syndrome; Alzheimer disease; cancer	[24]
	GABARAPL1-a	Different 3' end points	Inhibits interaction and binding with ATG4	-	[24]
Autophagosome completion					
ATG10	*ATG10 long (ATG10L) – canonical variant*	8 exons	Formation of the ATG12–ATG5 complex	Cancer; infection; inflammation	[25-27]
	ATG10 short (ATG10S)	Early termination 3'; Skipping exon 4	Autophagy induction in HCV infection; transcription factor	Hepatitis C virus infection	[25,28,29]
ATG12	*ATG12 long (ATG12L)*	4 exons	Autophagosome biogenesis; proviral factor; required for HCV translation.	Clear cell renal cell carcinoma; neurodegenerative diseases	[30]
	ATG12 short (ATG12S)	Alternative exon 2	Decrease autophagy flux	SETD2-deficient clear cell renal cell carcinoma	[30]

ATG5	*ATG5 long*	11 exons	Autophagosome formation, LC3 lipidation and mitochondria quality.	Neurodegenerative diseases; cardiovascular diseases; pathogen infection; immune diseases	[17]
	ATG5 Short	Skipping exon 6 or exons 3 and 6	Unable to form ATG12–ATG5 complex	Prostate DU145 cancer cells	[31,32]
	ATG5 short – splice site mutation	Skipping exon 2	Unable to form ATG12–ATG5 complex	Cervical squamous cell carcinoma	[33]
	ATG5 short (1) – splice site mutation	Skipping exon 3, 6 or 7	Unable to form ATG12–ATG5 complex	Hepatocellular carcinoma	[33]
	ATG5 short (2) – splice site mutation	Skipping exon 4 and 7	Unable to form ATG12–ATG5 complex	Uterine corpus endometrial carcinoma	[33]
ATG16L1	*ATG16L1α*	Skipping exons 8-9	Unable to lipidate LC3	Crohn disease; gastric cancer; brain metastasis in lung cancer	[34-38]
	ATG16L1β – canonical variant	Skipping exon 9	ATG12–ATG5 conjugation and LC3 lipidation	Crohn disease; gastric cancer; brain metastasis in lung cancer	[36,39,17,40]
	ATG16L1γ	All 20 exons	-	-	[36]

ATG16L2	*ATG16L2 Long - canonical variant*	18 exons	May play a role in regulating epithelial homeostasis in an ATG16L1-dependent manner	Crohn disease; systemic lupus erythematosus	17,33,40-42
	ATG16L2 short	Skipping exon 8	-	-	42
Autophagosome-lysosome function					
LAMP2	*LAMP2A – canonical variant*	9 exons	Involved in CMA	Danon disease; hypertrophic cardiomyopathy; neurological diseases; cancer	17,43
	LAMP2B	9 exons	Involved in macroautophagy. Interacts with ATG14 and VAMP8 to promote fusion	Danon disease; hypertrophic cardiomyopathy; renal cell carcinoma	17,43,44
	LAMP2C	9 exons	Interact with RBPs and histone 1. Involved in RNautophagy and DNautophagy; negative regulator of CMA	Danon disease; hypertrophic cardiomyopathy	17,43,45,46
Mitophagy					
PINK1	*PINK1FL – canonical variant*	8 exons	Located at the mitochondria, involved in mitochondria clearance	Parkinson disease; Alzheimer disease	47,48
	PINK1-cyto	-	Located at the cytosol. Sequester ubiquitinated proteins into aggresomes	Parkinson disease; Alzheimer disease	47,48

	PINK1A – splice site mutation in exon 7	Skipping exon 7	-	-	[49,50]
PRKN	*PRKN H1 – Canonical variant*	12 exons	Mitophagy	Parkinson disease; Alzheimer disease; cancer	[51,52]
	PRKN H2	-	-	-	[52]
	PRKN H20	-	-	-	[52]
Reticulophagy					
RETREG1/ FAM134B	*FAM134B – canonical variant*	*9 exons*	Located in ER sheets, mediates ER remodeling by direct binding with LC3. Located in brain, spleen and testis.	Neurological diseases; viral replication; inflammation; cancer	[53,54]
	RETREG1/FAM134B-2	*6 exons*	Regulate selective reticulophagy of secretory proteins. Located in peripheral tissues.	-	[54]
RTN3	*RTN3L – canonical variant*	*9 exons*	Interact with MAP1LC3. Promote ER fragmentation and degradation.	Alzheimer disease; astrocytoma	[55,56]
	RTN3s	-	Unable to facilitate ER degradation. Induces neurite dystrophy	Alzheimer disease	[55]

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