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Review

Pathogenic Single Nucleotide Polymorphisms on Autophagy-Related Genes

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Abstract: In recent years, the study of single nucleotide polymorphisms (SNPs) has gained increasing importance in biomedical research, as they can either be at the molecular origin of a determined disorder or directly affect the efficiency of a given treatment. In this regard, sequence variations in genes involved in pro-survival cellular pathways are commonly associated with pathologies, as the alteration of these routes compromises cellular homeostasis. This is the case of autophagy, an evolutionarily conserved pathway that counteracts extracellular and intracellular stressors by mediating the turnover of cytosolic components through lysosomal degradation. Accordingly, autophagy dysregulation has been extensively described in a wide range of human pathologies, including cancer, neurodegeneration, or inflammatory alterations. Thus, it is not surprising that pathogenic gene variants in genes encoding crucial effectors of the autophagosome/lysosome axis are increasingly being identified. In this review, we present a comprehensive list of clinically relevant SNPs in autophagy-related genes, highlighting the scope and relevance of autophagy alterations in human disease.

Keywords: autophagy; pathology; SNPs; variants; polymorphisms; ATGs; autophagic receptors; lysosomes

1. Introduction

Sequence variations are the basis of genetic heterogeneity, which is essential for species to improve their fitness in the environment. Among these genetic changes, alterations with a minor allele frequency of at least 1% in a given population are called polymorphisms, and variants that affect only one base of the sequence (including exchanges, deletions or insertions) are termed single nucleotide polymorphisms (SNPs). From a clinical perspective, these variants are important because they alter the activity of the affected gene products. In other words, SNPs can be the underlying origin of different types of diseases or even explain the differential effect of some treatments in determined individuals. SNPs are mainly identified and analyzed by genome-wide association studies (GWASs), unveiling alleles that determine the susceptibility of their carriers to a given condition. It is not surprising that variants that negatively impact the function of genes involved in essential processes, such as DNA repair or autophagy, have been widely associated with different pathologies.

Tightly integrated into the cellular network of the stress response, autophagy is an essential mechanism for the maintenance of cellular homeostasis [1]. This catabolic pathway, present in all nucleated cells, can be defined as any mechanism which mediates the degradation of cellular components, including entire organelles, by the action of lysosomal hydrolases (in fact, "autophagy" derives from Greek, meaning "self-eating") [2]. According to the way the cargo is transferred to the lysosome, there are three main autophagic pathways, namely microautophagy, chaperone-mediated autophagy (CMA) and macroautophagy [3]. During microautophagy, for example, substrates are

directly engulfed by lysosomal protrusions or invaginations [4], while CMA requires the activity of chaperone Hsc70 (HSPA8) and LAMP2A to selectively recognize and internalize proteins showing the KFERQ motif [5]. In contrast, macroautophagy (which is the focus of this review, and will be hereafter referred to as "autophagy") is based on the sequestration of cytoplasmic content by double-membrane vesicles, termed "autophagosomes" [6]. Once fully formed, autophagosomes eventually fuse their outer membrane with membranes of acidic lysosomes to become autolysosomes. Autolysosomes have hydrolytic activity, degrade their cargo, and recycle essential biomolecules to the cytoplasm [7]. Autophagy is active in all eukaryotic cells at basal rates, allowing the periodic renovation of cytosolic components or cytoplasmic organelles, acting as a housekeeping mechanism to preserve homeostasis. However, in response to a variety of cellular stresses, including nutrient deprivation, hypoxia, the accumulation of damaged organelles, protein aggregates or the presence of intracellular pathogens, the rate of autophagic degradation increases. This allows cells to eliminate damaged or harmful components through catabolism while supplying nutrients and energy to preserve cell viability. Given its fundamental roles in cell physiology, it was hypothesized early on that autophagy dysregulation could contribute to the pathogenesis of different diseases. Accordingly, a growing number of studies have linked autophagy alterations to a wide range of human pathologies, from immunological disorders to neurodegeneration or cancer [8] (Figure 1).

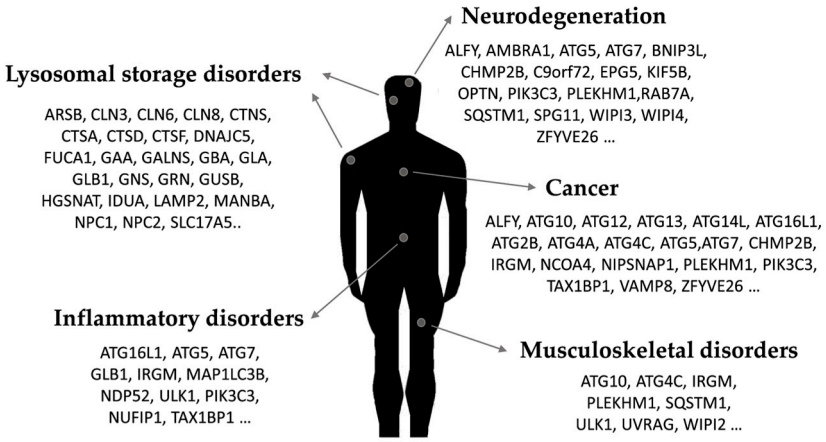

Figure 1. Representative links between autophagy-related proteins and human pathology.

In this review, we collect and go through a comprehensive list of SNPs in autophagy-related genes that have been associated with human diseases. This approach highlights the relevance of specific genes and variants in human pathology, while giving us new insights into the real scope of autophagy-related SNPs in disease. We include variants in genes whose products are part of the main autophagy core machinery and also those in genes codifying lysosomal proteins, as its disruption leads to the alteration of the autophagosome/lysosome axis.

2. Autophagy Dysregulation in Disease

As it has been previously reviewed, several human disorders show alterations in autophagy [8,9]. Pathological dysregulation of autophagy is not restricted to a specific type of disease. In fact, a wide range of disorders that may not share a common etiology and affect different tissues or organs have been connected to autophagy dysregulation [10] (Figure 1). However, how autophagy alteration contributes to the pathogenesis of specific pathologies is far from being completely understood, as important questions remain unanswered [11].

One of the clinical fields in which autophagy's role has been more extensively studied is oncology. Although it is still a long-standing subject of debate in the field, it is becoming increasingly clear that autophagy plays a dual role in this context, either favoring or fighting against the development of cancer [12]. On the one hand, the protective activity of this pathway prevents the initial malignant

transformation of cancer cells. On the other hand, once the tumor is formed, autophagy would help the cancerous cells survive. All in all, the beneficial or detrimental effect of autophagy in cancer is likely to be tumor- and stage-dependent. Unsurprisingly, pathogenic and protective SNPs have been reported in autophagy-related genes, and a growing number of studies have been profiling the autophagy-related gene prognostic signature of different types of cancer [13–24]. The pivotal role of antitumor immunity against cancer progression adds even more complexity to the autophagy–cancer relation, as autophagy is also important for immunological processes.

In fact, autophagy plays an essential role in the correct functioning of the immune system, acting at different levels [25]. It has been shown that autophagy is implicated in the development of different immune cell populations [26], in antigen presentation [27] or in adaptive immunity [28]. Additionally, autophagy contributes to the control of innate immune signaling, participating in the finely tuned balance between activated and repressed immune responses [29]. In fact, autophagy dysregulation can alter this equilibrium, leading to chronic inflammatory diseases [30]. This could explain why mutations of autophagy-related genes have been associated with several autoimmune disorders, including systemic lupus erythematosus (SLE), different types of sclerosis or rheumatoid arthritis [31]. Well-studied examples of autophagy dysregulation in uncontrolled inflammatory responses are inflammatory bowel diseases (IBDs), particularly Crohn's disease [32]. Autophagy is also an important defense barrier against infection, as it contributes to the degradation of intracellular pathogens (i.e., virus or bacteria) [33]. However, some of these infective agents have acquired molecular mechanisms to evade and use the autophagic machinery for their benefit, which aggravates infection in some cases [34].

Undoubtedly, one of the clinical contexts in which the link between deficient autophagy and pathology is more firmly-established is neurodegeneration [35]. In this regard, the inability to clear the accumulation of aggregation-prone misfolded proteins (including β-amyloid, huntingtin or α-synuclein) hampers cell viability, leading to the progressive loss of central nervous system function. This is the case of disorders such as Alzheimer's, Huntington's, or Parkinson's diseases, with some of them also showing problems in mitophagy, the selective autophagic degradation of mitochondria [36]. Development of amyotrophic lateral sclerosis (ALS) has also been associated with the accumulation of different protein aggregates or defective mitochondrial clearance, and pathogenic variants in components of the autophagic pathway have been described in patients [37]. Additional neurological disorders that have been linked to autophagy failure are spastic paraplegias, beta-propeller protein-associated neurodegeneration or Charcot–Marie–Tooth diseases, where autophagosome maturation, transport and/or its fusion with the lysosome are blocked [38].

The musculoskeletal system also requires autophagy to maintain its homeostasis, and autophagy dysregulation has also been associated with musculoskeletal pathologies. For example, different myopathies have been termed autophagic myopathies, as most of them show blocked autophagy flux and accumulation of autophagic vacuoles [39]. In bone tissue, autophagy plays an important role in controlling the balance between bone resorption and formation. Consistently, alterations in the autophagic pathway have been found in different diseases caused by the perturbation of bone physiology, such as Paget's disease, osteopetrosis or osteoporosis [40]. Moreover, chondrocytes of the cartilage are also more susceptible to cell death when autophagy is disrupted, leading to osteoarthritis [41].

Remarkably, both neurological and musculoskeletal alterations are common features observed in lysosomal storage diseases (LSDs). LSDs are rare metabolic disorders caused by alterations in genes that are required for lysosomal-mediated degradation [42]. These pathogenic variants often result in the accumulation of specific undegraded substrates in the lumen of this organelle, hindering lysosomal function [43]. The identity of the unprocessed molecule (sphingolipids, glycogen, glycosaminoglycans, etc.) is the base of the classification of LSDs. For example, mucopolysaccharidoses (MPSs) are mainly caused by mutations in specific lysosomal genes that contribute to the degradation of glycosaminoglycans (GAGs), while Danon disease and Pompe disease are characterized by the intralysosomal accumulation of glycogen. Deficiency in the catabolism of glucocerebrosides causes

Gaucher disease and failure to degrade globotriaosylceramide results in Fabry disease. Niemann–Pick type C disease is caused by the accumulation of unesterified cholesterol in several organs, while cystinosis is characterized by the accumulation of the amino acid cystine. Other important LSDs are galactosialidosis (with sialyloligosaccharide accumulation), fucosidosis (witch lysosomal aggregation of different molecules containing fucose moieties), mannosidosis (characterized by a deficiency in the degradation of mannose-rich oligosaccharides) and sialic acid storage diseases. Given the intricate connection between autophagy and lysosomal activity, it is not surprising that defects on any of them have an impact on the other one [44,45].

3. Relevant Variants on Autophagy-Related Genes

As shown in Figure 2, autophagic degradation involves different sequential stages, which operate from the regulation of autophagosome biogenesis to the last steps of autophagosome cargo degradation and recycling: (1) autophagy initiation, (2) membrane nucleation, (3) pre-autophagosomal membrane expansion, (4) autophagosome fusion with lysosomes and (5) degradation and efflux of basic components [46–48]. Each of these steps requires the coordinated temporal and spatial activation of several molecular components, namely the ULK1/2 kinase protein complex; the class III phosphatidylinositol 3-kinase (PI3KC3) protein complexes; phosphatidylinositol 3-phosphate (PI(3)P)-binding proteins and the ATG9-containing membranes; the ATG12 and ATG8 UBL conjugation systems; the selective autophagy receptors and the factors involved in autophagosome-lysosome fusion. Interestingly, pathogenic gene variants have already been described for all these different groups of effectors.

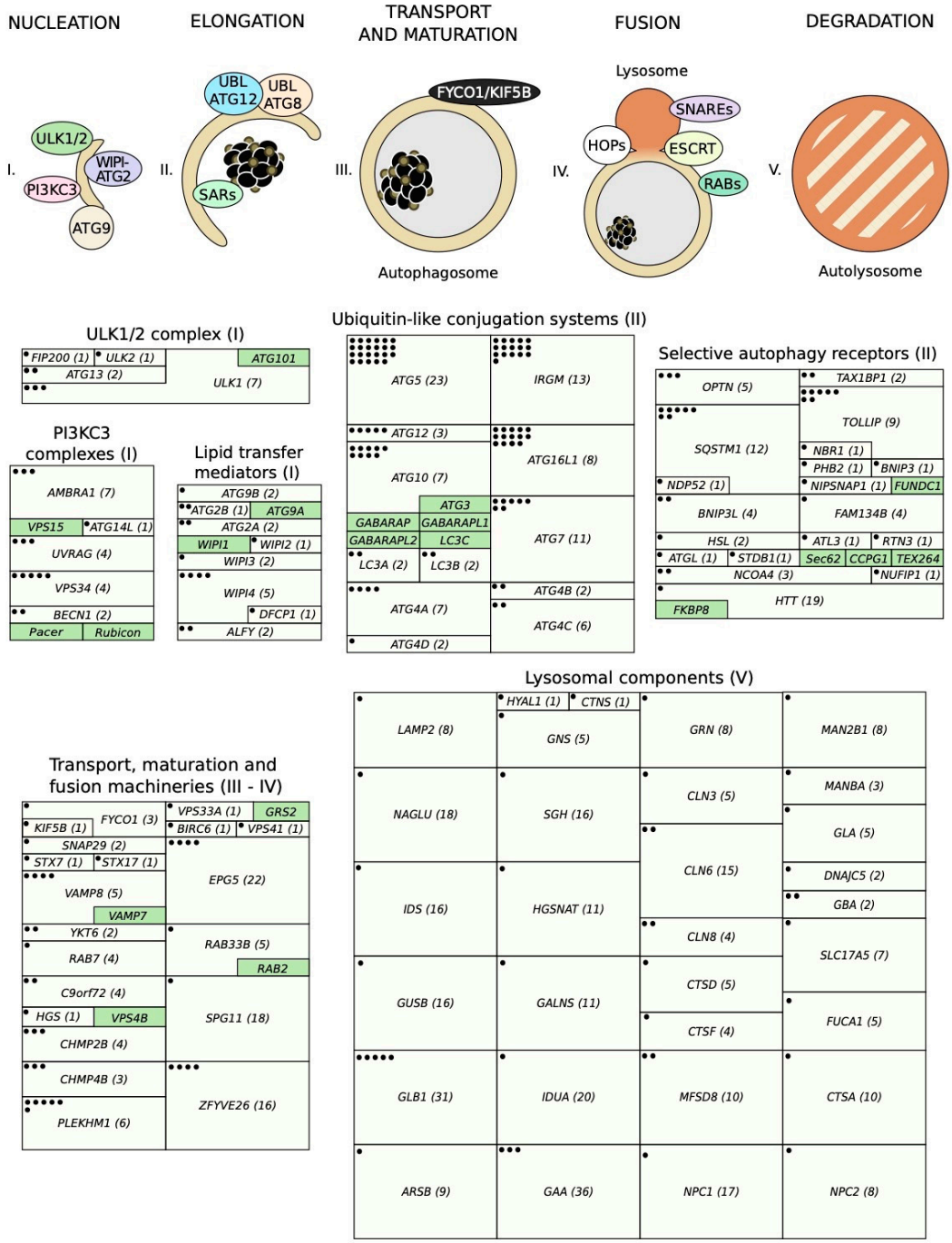

Figure 2. Schematic view of the incidence of clinically relevant single nucleotide polymorphisms (SNPs) in genes throughout the autophagosome/lysosome axis. Autophagy can be divided in different stages: (**I**) initiation and membrane nucleation, (II) membrane expansion, (**III**) autophagosome maturation and transport, (**IV**) autophagosome-lysosome fusion and (**V**) lysosomal degradation. Pathological variants have been found in genes involved in all of the steps. Boxes show the genes whose products participate in each of these stages. The size of the boxes is proportional to the number of pathological SNPs found for each of the genes depicted. The total number of pathological SNPs found in a given gene is depicted between brackets. Each different disease linked to a determined gene is represented by a dot. Green boxes contain genes without any clinically relevant SNPs identified to date. PI3KC3, class III phosphatidylinositol 3-kinase protein complexes; UBL, ubiquitin-like conjugation system; SARs, selective autophagy receptors; HOPS, homotypic fusion and protein sorting tethering complex; ESCRT, endosomal sorting complexes required for transport.

3.1. The ULK1/2 Kinase Complex

The members of the ULK (Unc-51-like kinase) family of proteins are the orthologues of the yeast Atg1, a serine/threonine protein kinase essential for autophagy initiation (Figure 3). In human cells, there are five ULK proteins (ULK1, ULK2, ULK3, ULK4 and STK36) although among them, only ULK1 and ULK2 are involved in autophagy [48]. In living cells, ULK1 or ULK2 are part of a protein complex with at least ATG13, ATG101 and FIP200 (family-interacting protein of 200kDa, also known as RB1CC1). This complex is responsible for driving autophagy initiation upon autophagy-inducing stimuli [49]. When active, the ULK1/2 complex translocates to autophagosome formation sites and regulates the recruitment and activation of the class III phosphatidylinositol 3-kinase (PI3KC3) complex, which in turn will generate phosphatidylinositol 3-phosphate (PI(3)P), a signaling molecule that recruits other downstream factors involved in autophagosome biogenesis. Moreover, the ULK1/2 protein complex carries other different autophagy-related functions, such as ATG9-vesicle recruitment or regulation of ATG4B activity, and contributes to regulate mitophagy and degradation of protein aggregates [50]. Due to its importance in autophagy initiation, this protein complex is regulated by a variety of post-translational modifications, such as acetylation, ubiquitin conjugation or phosphorylation by protein kinases. Among these, adenosine monophosphate-activated protein kinase (AMPK) and mechanistic/mammalian target of rapamycin (mTOR) are the most relevant, connecting ULK1/2 complex activity to the nutritional and energetic status of the cell [51,52].

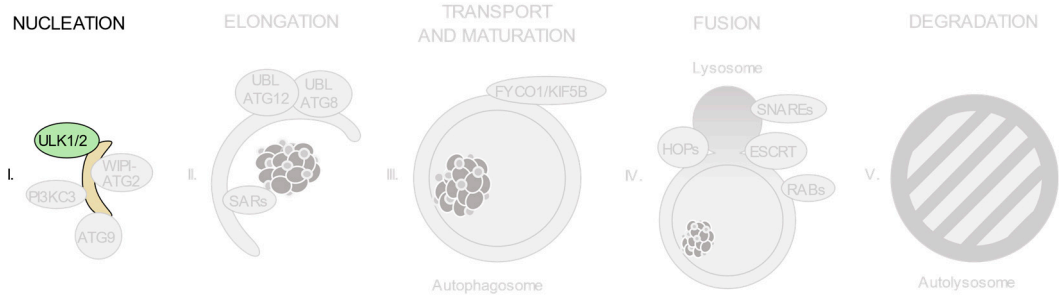

Figure 3. The ULK1/2 kinase complex participates in the nucleation of the pre-autophagosomal membrane.

Several pathogenic variants of the ULK1/2 kinase complex have been identified (Table 1 and Table S1). For example, SNPs in ULK1 have been associated with Crohn's disease susceptibility and clinical outcomes in different populations [53,54], supporting previous evidence of autophagy alterations in inflammatory bowel diseases. Additional variants of *ULK1* have shown strong associations with tuberculosis [55,56] and also with a specific type of rheumatoid arthritis termed ankylosing spondylitis [57], further linking ULK1 activity with the immune system. SNPs in *ULK2* have only been linked to asparaginase-associated pancreatitis to date [58]. Also related with the immune system is an ATG13 variant that may be associated with selective immunoglobulin A deficiency (IgAD), although it is not clear if this polymorphism affects *ATG13* or *AMBRA1* (which is another gene involved in autophagy) [59]. Additionally, altered ATG13 activity may also be involved in chemotherapy-induced cardiotoxicity in triple-negative breast cancer patients [60]. Regarding *FIP200* only one pathogenic SNP has been documented, which predicts hypertension after metastatic colorectal cancer treatment [61]. In synthesis, polymorphisms in members of the ULK1/2 kinase complex have been associated with a variety of pathologies, some of them related to immune system dysfunction. It is also remarkable that seven different pathogenic SNPs have already been identified in the *ULK1* gene (Figure 2). It is also noteworthy that different variants of this gene have been linked to a determined pathology (such as Crohn's disease or tuberculosis).

Table 1. Clinically relevant SNPs in ULK1/2 complex.

Gene	Disease	dbSNP rsID
ATG13	Selective immunoglobulin A deficiency	rs4565870
ATG13	Breast cancer	rs10838611
FIP200	Hypertension	rs1129660
ULK1	Crohn's disease	rs12303764; rs10902469; rs7488085
ULK1	Tuberculosis	rs12297124; rs7138581; rs9481
ULK1	Ankylosing spondylitis	rs9652059
ULK2	Asparaginase-associated pancreatitis	rs281366

3.2. The Class III Phosphatidylinositol 3-Kinase (PI3KC3) Complexes

After being activated at the assembling site, the ULK1/2 kinase complex acts as a scaffold for the PI3KC3 complex, whose activity is essential for the nucleation of the pre-autophagosomal membranes by generating PI(3)P, an essential signal for autophagosome formation, which will in turn recruit additional downstream factors involved in autophagosome biogenesis [49] (Figure 4). This complex is formed by Beclin 1, VPS34/PIK3C3, VPS15/p150/PIK3R4 and Barkor/ATG14L [62]. The most important event for PI3KC3 regulation is the sequestration of Beclin 1 by BCL-2, which limits its ability to bind PI3KC3 complexes, resulting in autophagy inhibition [63]. Conversely, AMBRA1 can also bind to Beclin 1 (and other autophagy-related proteins), increasing PI3KC3 complex activity and thus supporting autophagosome formation [64]. Interestingly, there is an additional version of the PI3KC3 complex (often called PI3KC3-C2) in human cells, which is also involved in autophagy regulation. PI3KC3-C2 contains UVRAG instead of ATG14 and is involved in regulating the fusion of autophagosomes to lysosomes [65]. The activity of this complex can be repressed by binding of the negative regulator Rubicon/KIAA0226, which results in the inhibition of autophagosome/lysosome fusion [66,67]. Conversely, its activity can be enhanced by binding of the protein associated with UVRAG as autophagy enhancer (Pacer), which increases autophagic degradation [68].

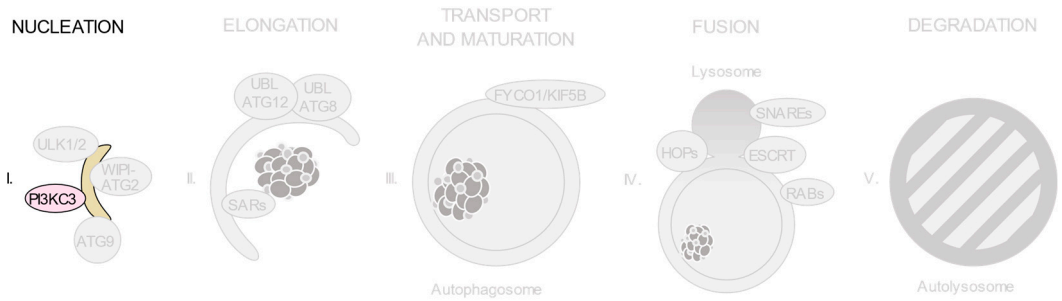

Figure 4. The phosphatidylinositol 3-kinase (PI3KC3) complexes participate in the nucleation of the pre-autophagosomal membrane.

Despite the relevance of Beclin 1 in autophagy, only two SNPs found in the *BECN1* gene have so far been associated with diabetes [69] and Machado–Joseph disease [70], a neurodegenerative disorder characterized by progressive cerebellar ataxia (Table 2 and Table S1). On the other hand, polymorphisms on *VPS34/PIK3C3* do correlate with increased cancer risk, specifically in pancreatic adenocarcinoma [71] and esophageal squamous cell carcinoma [72,73]. A third variant has been linked to gastric cardia adenocarcinoma, although it seems to be related to non-autophagical functions of VPS34 in the control of telomere length [74]. Another single nucleotide change on the promoter of *VPS34* has been associated with both systemic lupus erythematosus [75] and with bipolar disorder and schizophrenia [76]. Interestingly, several variants of *AMBRA1* have also been linked to schizophrenia [77], as well as to diverse forms of autism [78]. A polymorphism in *ATG14* has been associated with testicular germ cell tumors [79], while different *UVRAG* alleles have been linked to a less efficient treatment response in multiple sclerosis [80], susceptibility to rheumatoid arthritis [81] and non-segmental vitiligo [82].

Altogether, these findings show that genetic variants in components of the PI3KC3 complexes are linked to a variety of pathologies, including cancer, autoimmune or neurological disorders. Among all of them, *VPS34* and *UVRAG* seem to be more sensitive to nucleotide changes, with *AMBRA1* (often associated with PI3KC3 complexes) also accumulating several pathogenic polymorphisms (Figure 2).

Table 2. Clinically relevant SNPs in PI3KC3 complexes.

Gene	Disease	dbSNP rsID
AMBRA1	Schizophrenia	rs11819869; rs12574668; rs61882743; rs7112229; rs7130141
AMBRA1	Autism	rs3802890
AMBRA1	Selective immunoglobulin A deficiency	rs4565870
ATG14L	Testicular germ cell tumor	rs1009647
BECN1	Machado–Joseph disease	rs60221525
BECN1	Diabetes	rs10512488
UVRAG	Multiple sclerosis treatment	rs80191572
UVRAG	Rheumatoid arthritis	rs7111334
UVRAG	Non-segmental vitiligo	rs1458836; rs7933235
VPS34	Pancreatic cancer	rs76692125
VPS34	Esophageal squamous cell carcinoma	rs52911
VPS34	Gastric cancer	rs2162440
VPS34	Schizophrenia	rs3813065
VPS34	Systemic lupus erythematosus	rs3813065

3.3. PI(3)P-Binding Proteins and the ATG9-Containing Membranes

Production of PI(3)P by the PI3KC3 complex acts as a signal for the recruitment of autophagy-related proteins able to bind this phospholipid. Among these, the most characterized are DFCP1, WIPI proteins and ALFY [83]. DFCP1 recruitment to autophagosome formation sites occurs shortly after PI(3)P generation by PI3KC3. There, it labels the omegasome, a platform for the formation of autophagosomes that originate from the ER-associated membranes. DFCP1 colocalizes with LC3 and other essential proteins for autophagosome biogenesis. However, despite DFCP1 being often used as a marker for the omegasome, its depletion has no major effect on autophagy [84]. WIPI proteins are also recruited by the presence of PI(3)P at the pre-autophagosomal membranes, where they contribute to autophagosome formation by recruiting other autophagy essential proteins for this process [85] (Figure 5). In human cells, there are four WIPI proteins (WIPI 1-4). WIPI1 and WIPI2 proteins participate in the expansion of the autophagosomal membrane, with WIPI2 being responsible for recruiting the ATG5–ATG12/ATG16 complex to nascent autophagosomes [86]. In contrast, WIPI3 and WIPI4 interact with upstream regulators, such as the ULK1/2 complex and AMPK-activated TSC complex, coupling PI(3)P generation to the activity of upstream regulatory signaling [87]. Moreover, WIPI4 plays an important role in controlling the growth and size of autophagosomes through its interaction with ATG2 proteins. In yeast, Atg2 acts as a lipid transfer protein that supplies phospholipids to autophagosomal membranes [88]. In mammals, there are two Atg2 orthologues, ATG2A and ATG2B, that can translocate lipids from other membranes to nascent autophagosomes, forming a complex with WIPI4 that acts as a membrane tether with lipid transfer activity [89]. ALFY (autophagy-FYVE-linked protein) is also a PI(3)P-binding protein, which is recruited to nascent autophagosomal membranes close to protein aggregates. Although ALFY is not essential for autophagosome biogenesis during starvation-induced autophagy, it is required for protein aggregate autophagic degradation [90]. The only transmembrane proteins directly involved in autophagosome biogenesis are those from the ATG9 family, composed by ATG9A and ATG9B. ATG9 proteins assist with lipid transport and transferring to nascent autophagosomal membranes [49,91] (Figure 5). Concurrently with PI3KC3 complex activation, the ULK1 kinase complex also mediates the recruitment of vesicles containing either ATG9A or ATG9B (depending on the tissue or cell type). These transmembrane proteins drive the aforementioned vesicles to the assembling site so they can be used as membrane sources, contributing to the elongation of

the autophagosomal membrane [83]. WIPI2 is also involved in the regulation of ATG9 traffic, as WIPI2 depletion hampers ATG9 dynamics and results in the accumulation of ATG9 pre-autophagosomal structures due to the inhibition of ATG9 retrieval to Golgi complex membranes [92].

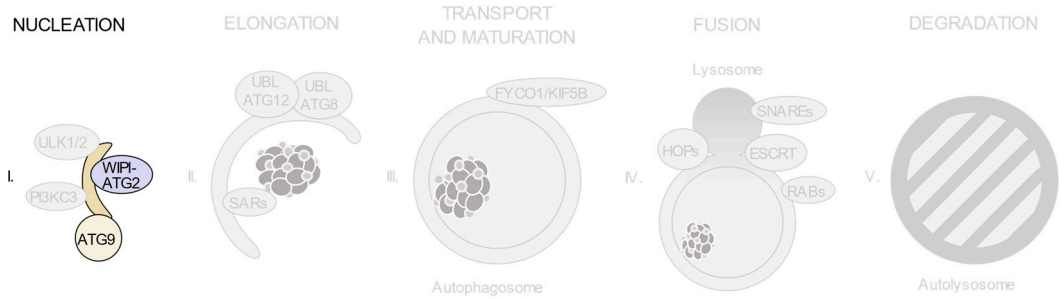

Figure 5. The phosphatidylinositol 3-phosphate (PI(3)P)-binding proteins (WIPI or ATG2 proteins) and ATG9-containing vesicles participate in the nucleation of the pre-autophagosomal membrane.

To date, only one pathogenic SNP on *DFCP1* has been found, which is linked to tuberculosis resistance [93]. In contrast, nucleotide changes on *ALFY* were identified in patients with microcephaly [94], as well as in oropharynx cancer [95]. *WIPI4* pathogenic SNPs have been shown to cause neurological disorders, such as neurodegeneration with brain iron accumulation (NBIA) and Rett syndrome [96–98], while polymorphisms on *WIPI2* and *WIPI3* have been associated with osteoporosis [99] and a neurodevelopmental syndrome [100]. Two variants of *ATG2A* have been linked with both granuloma formation in Crohn's disease and hyperuricemia [101,102]. Interestingly, the equivalent SNP in *ATG2B* increases susceptibility to neck squamous cell carcinoma in pharyngeal cancer [103] and correlates with both progression and recurrence of bladder cancer after treatment with bacillus Calmette–Guérin intravesical instillation [104]. Finally, a polymorphism associated with coronary artery disease has been identified on *ATG9B* [105] (Table 3 and Table S1). In summary, pathogenic SNPs that have been described on lipid transfer mediators are linked to pathologies of different origins. In contrast, pathogenic SNPs on genes coding for PI(3)P-binding proteins are mostly associated with neurological disorders. It is remarkable that distinct pathogenic polymorphisms related to very different diseases have been described for *WIPI4* (Figure 2).

Table 3. Clinically relevant SNPs in PI(3)P-binding proteins and ATG9 orthologues.

Gene	Disease	dbSNP rsID
ATG2A	Granuloma formation in Crohn's disease	rs17146441
ATG2A	Hyperuricemia	rs188780113
ATG2B	Non-muscle invasive bladder cancer	rs3759601
ATG2B	Head and neck squamous cell carcinoma	rs3759601
ATG9B	Coronary artery disease	rs2373929; rs7830
ALFY	Microcephaly	rs1553924800
ALFY	Malignant neoplasm of oropharynx	rs6847067
DFCP1	Tuberculosis	rs2333021
WIPI2	Osteoporosis	rs4720530
WIPI3	Neurodevelopmental disorder	rs786205510; rs1555647262
WIPI4	Rett syndrome	rs886041382; rs886041693
WIPI4	Neurodegeneration with brain iron accumulation	rs886041382
WIPI4	Early-onset epileptic encephalopathy	rs1064793294
WIPI4	β-propeller protein-associated neurodegeneration (BPAN)	rs387907330

3.4. The ATG12 and ATG8 Conjugation Systems

Two ubiquitin-like (UBL) conjugation systems are essential for autophagosome formation and autophagic cargo degradation (Figure 6). These UBL systems cooperate to drive the expansion of

the nascent autophagosomal membrane, with the final product of the first system being the responsible enzyme for the last reaction in the second one [106]. The first UBL system, the ATG12 system, mediates the activation, transfer, and covalent conjugation of ATG12 to ATG5, a process that requires the sequential activities of the E1-like enzyme ATG7 and the E2-like enzyme ATG10. Once formed, two molecules of the ATG12–ATG5 conjugate interact with an ATG16 dimer, resulting in the final ATG16 complex. This complex is recruited to nascent autophagosomes by the actions of WIPI1 and WIPI2 proteins [86]. After being recruited, ATG16 keeps the ATG5–ATG12 conjugate at the pre-autophagosomal membrane, where it acts as an E3-ligase for the ATG8 UBL system, catalyzing ATG8 covalent conjugation [107]. It is interesting that although there are two ATG16 homologues (ATG16L1-2) in human cells, only ATG16L1 seems to play a prominent role in autophagy [108,109].

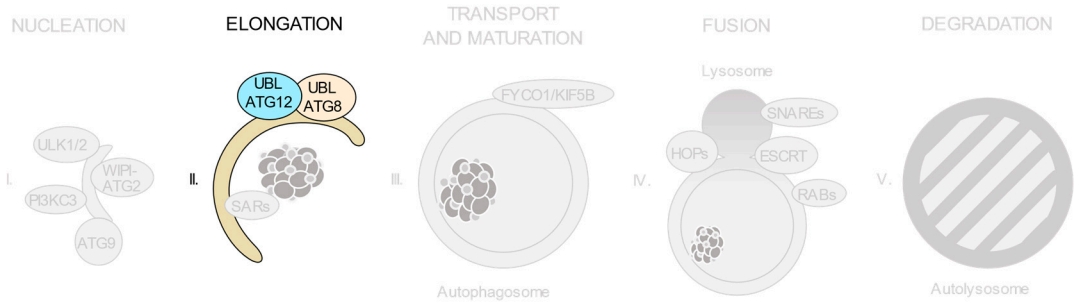

Figure 6. The ubiquitin-like (UBL) conjugation systems of ATG12 and ATG8 participate in the elongation of the pre-autophagosomal membrane.

The second UBL system, the ATG8 system, mediates the conjugation of ATG8 molecules to phosphatidyl-ethanolamine (PE) phospholipids at the pre-autophagosomal membrane (Figure 6). In humans, there are six ATG8 proteins, grouped into two subfamilies: the MAP1-LC3 subfamily (including MAP1-LC3A, MAP1-LC3B and MAP1-LC3C) and the GABARAP subfamily (including GABARAP, GABARAPL1/ATG8L and GABARAPL2/GATE-16). All these proteins can be found either free or in their lipidated (PE-conjugated) form in human cells [110]. In normal conditions, the unconjugated ATG8 forms are mostly cytosolic. In contrast, ATG8 PE-conjugated forms are mainly associated with the inner and outer membranes of the autophagosome. ATG8 conjugation first requires the activity of ATG4 proteases (ATG4A-D, also called "autophagins" in humans) [111]. ATG4s cleave and activate ATG8 proteins, leaving a glycine residue at the carboxyl terminus, which is essential for ATG8 lipidation. ATG7 (E1-like enzyme), ATG3 (E2-like enzyme) and the ATG12-ATG5–ATG16L1 multimeric complex (E3-like enzyme) are necessary for ATG8 conjugation to PE. This conjugation is, in turn, essential for the expansion of the pre-autophagosomal membrane, autophagosome maturation and degradation of autophagic cargo [106]. Once ATG8s' presence at the autophagosomal/autolysosomal membranes is no longer required, they can be deconjugated from PE by the action of ATG4s. In yeast, Atg8 deconjugation is important to keep an available pool of ready-to-use Atg8 in the cytosol and required for efficient autophagosome biogenesis and maturation [112,113].

Interestingly, most of the pathogenic polymorphisms that have been already identified on autophagy-related genes are located on the genomic sequence of members of the ATG12 conjugation system (Table 4 and Table S1). In fact, variants affecting different genes from this system are associated with the same pathology. For example, pathogenic alleles of *ATG5*, *ATG10*, *ATG12* and *ATG16L1* have been all linked to changes in susceptibility or treatment efficiency in neck squamous cell cancer [103,114–116], hepatocellular carcinoma [117] and lung adenocarcinoma [118] and others have been found to also affect development of other types of cancer, such as melanoma [119], brain metastases in patients with non-small lung cancer [120] or breast cancer [121–124]. Moreover, there is also an association between SNPs in *ATG5* and *ATG7* with clear cell renal cell carcinoma [125] and variants of *ATG5* and *ATG10* have been linked to non-small cell lung cancer [126,127]. Additional connections between changes on these genes and cancer are those of *ATG5* in multiple myeloma [128]

or non-medullary thyroid cancer [129]. Different *ATG16L1* SNPs have been linked to cell-derived thyroid carcinoma [130], colorectal cancer [131], gastric cancer [132] or prostate cancer [133]. Moreover, several polymorphisms on the ATG12 conjugation system have also been associated with other pathologies besides cancer. In fact, SNPs in *ATG5* and *ATG7* are linked to the development of neurological disorders such as cerebral palsy (both *ATG5* and *ATG7*) [134,135], Huntington's disease (*ATG7*) [136,137], and Parkinson's disease or spinocerebellar ataxia (*ATG5*) [138,139]. Additionally, nucleotide polymorphisms on *ATG5*, *ATG10* and *ATG12* have been related to pneumoconiosis in a population of coal workers [140], whereas other SNPs in *ATG7* have been associated with ischemic stroke [141].

Perhaps the most studied SNP on an autophagy-related gene is rs2241880 on *ATG16L1*, resulting in a threonine-to-alanine substitution at amino acid position 300 (T300A). Its link to inflammatory bowel disease, first described by Hampe and collaborators [142], has been extensively confirmed in different populations by an immeasurable list of studies, impossible to entirely cite in this review. Polymorphisms on other proteins with autophagy-related functions have also been associated with inflammatory bowel diseases. For example, variants of *IRGM*, an important effector that links the autophagy molecular core to innate immunity receptors [143], are well-known risk alleles in pathologies such as Crohn's disease [144]. Interestingly, two SNPs in *ATG5* correlate to a positive response to Crohn's disease therapy [145]. Moreover, variants of *ATG16L1* and other effectors of the ATG12 conjugation system have also been linked to other inflammatory disorders, autoimmune diseases or other complications related to the immune system. In this regard, polymorphisms on *ATG5*, *ATG10* and *ATG16L1* have been associated with Paget's disease of the bone [146], and SNPs in *ATG5* and *ATG7* have been extensively studied in the context of systemic lupus erythematosus [147–153]. In addition, several polymorphisms on *ATG5* may play a role in the pathogenesis of other autoimmune disorders such as Behçet's disease [154], neuromyelitis optica [155] and systemic sclerosis [156,157]. Additional inflammatory alterations linked to variants of *ATG5* are aplastic anemia [158] or asthma [159,160] as well as complications related to infections, including chronic Q fever [161], sepsis [162] or Hepatitis B [163,164]. Similarly, SNPs in *ATG16L1* are also associated with *Helicobacter pylori* infection and related gastric cancer [165–167] or skin conditions such as palmoplantar pustulosis [168] and psoriasis [169]. Finally, a variant of *ATG10* has been associated with Vogt–Koyanagi–Harada disease, which is characterized by an autoimmune response against melanin-producing cells [154].

Fewer clinically relevant variants have been identified in genes encoding members of the ATG4 and ATG8 protein families (Table 4 and Table S1), perhaps because of their marked redundancy. Different SNPs in *ATG4A* have been associated with kidney, cervical and lung cancer [125,170,171]. Meanwhile, variants of *ATG4B* may be present in patients with obesity [172] or atherosclerosis [173]. Polymorphisms on *ATG4C* have also been linked to clear cell renal cell carcinoma [125], as well as an increase in susceptibility to Kashin–Beck disease, a osteochondropathy characterized by chondrocyte death and altered autophagy in growth plate and articular cartilage [174]. Nucleotide changes on *ATG4A* and *ATG4D* genes can also lead to the formation of granulomas during Crohn's disease [101]. As for their substrates, the ATG8 proteins, only three gene variants have been associated with a pathology so far: two polymorphisms on *MAP1LC3A* that may contribute to progression of chronic Q fever [161] or coronary artery disease [175], and two SNPs that alter *MAP1LC3B* expression and correlate to myopia [176] and increased susceptibility to systemic lupus erythematosus [177]. To date, no pathogenic SNPs have been identified either in *MAP1LC3C*, *GABARAP, GABARAPL1, GABARAPL2* nor in the gene encoding the E2-like enzyme ATG3.

In summary, alterations in autophagy UBL systems have been extensively linked to disease. This is shown not only by the high number of SNPs found in genes of these systems, but also by the total number of diseases to which they are associated (Figure 2). Specifically, genes such as *ATG16L1*, *ATG5*, *ATG10* or *ATG7*, accumulate multiple SNPs linked to pathologies that include cancer, neurological disorders, or inflammatory bowel diseases.

Table 4. Clinically relevant SNPs in the ubiquitin-like conjugation systems ATG12 and ATG8.

Gene	Disease	dbSNP rsID
ATG10	Breast cancer	rs10514231; rs1864182; rs7707921
ATG10	Paget's disease of the bone	rs1864183
ATG10	Vogt–Koyanagi–Harada syndrome	rs4703863
ATG10	Lung cancer	rs10514231; rs1864182; rs1864183; rs10036653
ATG10	Melanoma	rs1864182
ATG10	Brain metastasis	rs10036653
ATG10	Head and neck squamous cell carcinoma	rs10514231; rs1864183; rs4703533
ATG10	Pneumoconiosis	rs1864182
ATG10	Hepatocellular carcinoma	rs10514231; rs1864183
ATG12	Brain metastasis	rs26532
ATG12	Pneumoconiosis	rs26538
ATG12	Lung cancer	rs26538
ATG12	Head and neck squamous cell carcinoma	rs26537
ATG12	Hepatocellular carcinoma	rs26537
ATG16L1	Crohn's disease	rs2241880
ATG16L1	Palmoplantar pustulosis	rs2241879; rs2241880; rs7587633
ATG16L1	Psoriasis vulgaris	rs10210302; rs12994971; rs13005285; rs2241879; rs2241880
ATG16L1	Cell-derived thyroid carcinoma	rs2241880
ATG16L1	Colorectal cancer	rs2241880
ATG16L1	Paget's disease of the bone	rs2241880
ATG16L1	Prostate cancer	rs78835907
ATG16L1	Gastric cancer	rs2241880
ATG16L1	Melanoma	rs2241880
ATG16L1	Brain metastasis	rs2241880
ATG16L1	Head and neck squamous cell carcinoma	rs2241880; rs4663402
ATG16L1	Lung cancer	rs2241880
ATG16L1	Hepatocellular carcinoma	rs4663402
ATG16L1	*Helicobacter pylori* infection	rs2241880
ATG4A	Cervical Cancer	rs5973822; rs4036579; rs807181; rs807182; rs807183
ATG4A	Lung cancer	rs807185
ATG4A	Granuloma formation in Crohn's disease	rs5973822
ATG4A	Clear cell renal cell carcinoma	rs7880351
ATG4B	Obesity	rs7601000
ATG4B	Atherosclerosis	rs139302128
ATG4C	Clear cell renal cell carcinoma	rs6670694; rs6683832
ATG4C	Kashin–Beck disease	rs11208030; rs4409690; rs12097658; rs6587988
ATG4D	Granuloma formation in Crohn's disease	rs7248036; rs2304165
ATG5	Systemic lupus erythematosus	rs6937876; rs3827644; rs573775; rs548234
ATG5	Asthma	rs12212740; rs11751513; rs12201458; rs2299863; rs510432
ATG5	Parkinson's disease	rs510432
ATG5	Systemic sclerosis	rs3827644; rs9373839
ATG5	Non-medullary thyroid cancer	rs2245214
ATG5	Neuromyelitis optica	rs548234; rs6937876
ATG5	Paget's disease of the bone	rs2245214
ATG5	Behçet's disease	rs573775
ATG5	Spinocerebellar ataxia	rs1131692265
ATG5	Crohn's disease	rs510432; rs9373839
ATG5	Multiple myeloma	rs9372120
ATG5	Melanoma	rs2245214; rs510432
ATG5	Sepsis	rs506027; rs510432
ATG5	Pneumoconiosis	rs510432
ATG5	Esophageal squamous cell carcinoma	rs1322178; rs3804329; rs671116
ATG5	Lung cancer	rs510432; rs688810; rs2245214
ATG5	Cerebral palsy	rs6568431

Table 4. *Cont.*

Gene	Disease	dbSNP rsID
ATG5	Breast cancer	rs473543
ATG5	Clear cell renal cell carcinoma	rs490010
ATG5	Chronic Q fever	rs2245214
ATG5	Aplastic anaemia	rs473543; rs510432; rs573775; rs803360
ATG5	HBV infection	rs510432; rs6568431; rs548234
ATG5	Hepatocellular carcinoma	rs17067724
ATG7	Systemic lupus erythematosus	rs11706903; rs2736340
ATG7	Breast cancer	rs8154
ATG7	Ischemic stroke	rs2594966; rs2594973; rs4684776
ATG7	Lung cancer	rs8154
ATG7	Clear cell renal cell carcinoma	rs2606736; rs6442260
ATG7	Cerebral palsy	rs1470612; rs2594972
ATG7	Huntington's disease	rs36117895
IRGM	Crohn's disease	rs10065172; rs1000113; rs10065172; rs11747270; rs11749391; rs180802994; rs4958843; rs4958847; rs72553867; rs7714584, rs9637876
IRGM	Systemic lupus erythematosus	rs10065172; rs13361189
IRGM	Ulcerative colitis	rs1000113; rs11747270; rs11749391; rs180802994; rs4958847
IRGM	Tuberculosis	rs10051924; rs12654043; rs4958843; rs72553867
IRGM	Celiac disease	rs10065172
IRGM	Inflammatory bowel diseases	rs10065172; rs4958847
IRGM	Ankylosing spondylitis	rs10065172; rs11749391
IRGM	Arthritis	rs11747270; rs4958847
IRGM	Chronic periodontitis	rs11747270
IRGM	Asthma	rs11747270
IRGM	Multiple sclerosis	rs11747270
IRGM	Cholangitis	rs11749391
IRGM	Psoriasis vulgaris	rs11749391
IRGM	Pathologic fistula	rs4958847
IRGM	Malignant neoplasm of stomach	rs4958847
IRGM	Non-alcoholic fatty liver disease	rs4958847
MAP1LC3A	Chronic Q fever	rs1040747
MAP1LC3A	Coronary artery disease	rs2424994
MAP1LC3B	Myopia	rs1054521
MAP1LC3B	Systemic lupus erythematosus	rs933717

3.5. Selective Autophagy Receptors

Autophagic degradation can be either bulk or selective. The last one requires the action of the so-called selective autophagy receptors (SARs), which mediate the recognition and engulfment of specific cargo in autophagosomes (Figure 7). Specifically, these adapters can simultaneously bind both to the target molecules and to the ATG8 proteins conjugated on the concave side of the autophagosomal membrane [178]. The identification and study of these SARs is likely one of the most exciting, fast-paced fields of autophagy research, as autophagy adapters show specificity to a wide variety of substrates. The most characterized mammalian SARs are those that bind ubiquitin molecules [179]. These molecules label a great variety of autophagic substrates, from protein aggregates to damaged mitochondria or intracellular pathogens. The most studied ubiquitin-binding SAR is p62/SQSTM1 [180], a multifunctional protein important for protein aggregate degradation (aggrephagy), mitophagy and the engulfment of intracellular pathogens by autophagosomes (xenophagy). Similarly, NBR1 is also involved in aggrephagy and acts synergically with p62/SQSTM1 for the degradation of ubiquitin-decorated protein aggregates [181]. OPTN is not only involved in aggrephagy [182] but also in mitophagy [183] and xenophagy [184]. Similarly, NDP52 is involved both in mitophagy [185] and

xenophagy [186], as TAX1BP1 is [183,187]. TOLLIP has also been involved in mutant huntingtin-selective degradation, although it is less studied than other ubiquitin-binding SARs [188]. Apart from this group of SARs, many other proteins, each of them localized in a specific cellular structure/organelle, interact with ATG8s and act as specific SARs for their contained subcellular structures [189]. This is the case for BNIP3, BNIP3L/NIX, FUNDC1, FKBP8, PHB2 or NIPSNAP1/2, which are specific mitophagy SARs [190–192], or that of FAM134B, Sec62, RTN3, CCPG1, ATL3 and TEX264, which are specific SARs for ER-selective autophagy [193]. Apart from these, multiple other specific autophagy receptors for other selective autophagic processes are being constantly identified. This is the case of ATGL and HSL for lipophagy [194], STBD1 for glycophagy [195], NUFIP1 for ribophagy [196], or NCOA4 for ferritin degradation [197,198]. Certainly, new specific receptors for orphan-selective autophagic processes, such as zymophagy or granulophagy will be identified in the future.

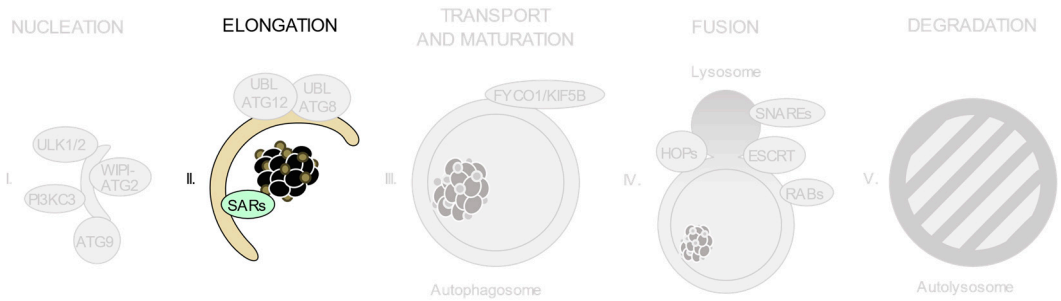

Figure 7. The autophagy receptors (SARs) participate in selective cytoplasmic cargo recognition (i.e., protein aggregates as depicted in the figure) during pre-autophagosomal membrane elongation.

Several studies have described important pathogenic SNPs in the genes of selective autophagy receptors (Table 5 and Table S1). Nucleotide changes on *SQSTM1*, for example, may contribute to the origin of neurological alterations [199], as well as being implicated in the pathogenesis of amyotrophic lateral sclerosis [200,201], dementia [202], apraxia of speech [203], myopathy [204] and Paget's disease of the bone [205,206]. Additionally, *NDP52* and *NBR1* variants determine susceptibility to Crohn's disease [207] and Brooke–Spiegler syndrome [208], a rare condition where tumors form from skin structures. Meanwhile, polymorphisms on *OPTN* also show clinical relevance, as they are associated with amyotrophic lateral sclerosis [209], Paget's disease of the bone [210,211] and primary open-angle glaucoma [212]. Interestingly, SNPs in *TOLLIP* have been frequently linked to interstitial lung diseases [213] and different types of infections, including leishmaniasis [214], leprosy [215,216], malaria [217], tuberculosis [218] and septicemia [219]. Pathogenic alleles of *TAX1BP1* have been identified in unrelated alterations such as oral cavity cancer [220] and hypospadias [221]. Variants of specific mitophagy adapters have been identified in patients with depression (in the case of *BNIP3*) [222], schizophrenia or impaired cognition (BNIP3L) [223], bisphosphonate-associated osteonecrosis of the jaw (PHB2) [224], and breast cancer (NIPSNAP1) [123]. Regarding reticulophagy receptors, patients with hereditary sensory autonomic neuropathy have SNPs in either *FAM134B* [225,226] or *ATL3* [227,228], and a single nucleotide change on *RTN3* increases the susceptibility to complications after malaria [229,230]. Changes on genes encoding lipophagy receptors ATGL and HSL are unsurprisingly associated with neutral lipid storage disease with myopathy [231] and familial partial lipodystrophy [232,233]. Additional links between polymorphisms on SARs genes and pathologies are those in *STBD1* for Parkinson's disease [234,235], *NUFIP1* for asthma [236], and *NCOA4* for cancer [237,238]. Finally, a high number of pathogenic variants in the gene encoding huntingtin protein (HTT) are the cause for Huntington's disease [239]. Although it might not be considered a bona fide selective autophagy receptor, HTT can act as a scaffold for selective autophagy and interacts with ULK1, GABARAP and p62/SQSTM1 [193,240,241]. Taken together, these publications show that dysregulation of autophagy receptor function plays a role in the pathogenesis of a wide variety of diseases, with most pathogenic variants being identified in *SQSTM1*, *TOLLIP* and *HTT* (Figure 2).

Table 5. Clinically relevant SNPs in selective autophagy receptors.

Gene	Disease	dbSNP rsID
ATGL	Neutral lipid storage disease with myopathy	rs121918259
ATL3	Hereditary sensory autonomic neuropathy	rs587777108
BNIP3	Major depressive disorder	rs9419139
BNIP3L	Schizophrenia	rs1042992; rs73219805; rs73219806
BNIP3L	Cognitive decline	rs77609452
HSL	Lipodystrophy	rs766817317; rs587777699
HTT	Huntington's disease	rs1210554604; rs10015979; rs110501; rs11731237; rs2071655; rs2269499; rs2285086; rs2298969; rs2471347; rs362272; rs363066; rs363092; rs363096; rs3856973; rs6855981; rs82333; rs916171; rs118005095; rs13102260
NBR1	Brooke–Spiegler syndrome	rs202122812
NCOA4	Prostate cancer	rs10740051; rs10761581
NCOA4	Papillary thyroid carcinoma	rs782237788
NDP52	Crohn's disease	rs2303015
NIPSNAP1	Breast cancer	rs183421746
NUFIP1	Asthma	rs114280567
OPTN	Amyotrophic lateral sclerosis	rs267606928; rs267606929
OPTN	Primary open-angle glaucoma	rs28939688
OPTN	Paget's disease of the bone	rs1561570; rs2234968
PHB2	Bisphosphonate-associated osteonecrosis of the jaw	rs11064477
FAM134B	Hereditary sensory autonomic neuropathy	rs137852737; rs137852738; rs137852739; rs886037748
RTN3	Malaria	rs542998
SQSTM1	Frontotemporal dementia	rs776749939; rs772889843; rs1355424687
SQSTM1	Paget's disease of the bone	rs796051869; rs104893941
SQSTM1	Amyotrophic lateral sclerosis	rs796052214; rs796051870; rs796051870
SQSTM1	Neurodegeneration	rs886039780
SQSTM1	Parkinson's disease	rs200396166
SQSTM1	Atypical apraxia of speech	rs796052214
SQSTM1	Sporadic inclusion body myositis	rs11548633
STBD1	Parkinson's disease	rs6812193
TAX1BP1	Head and neck carcinoma	rs11540483
TAX1BP1	Hypospadias	rs10214930
TOLLIP	Leishmaniasis	rs3750920; rs5743899
TOLLIP	Leprosy	rs3793964; rs3750920
TOLLIP	Malaria	rs3750920
TOLLIP	Tuberculosis	rs3750920; rs5743867
TOLLIP	Sepsis	rs5743867
TOLLIP	Idiopathic pulmonary fibrosis	rs5743890; rs111521887; rs3750920
TOLLIP	Fibrotic idiopathic interstitial pneumonia	rs3168046; rs3750920; rs3793964; rs3829223; rs5744034

3.6. Cellular Machineries Involved in Autophagosome-Lysosome Fusion

Once fully formed, autophagosomes move along microtubules depending on the actions of the minus-end-directed motor protein dynein and a plus-end-directed motor kinesin/FYCO1 [242]. This bidirectional transport leads to autophagosome clustering around the perinuclear area, where they eventually fuse with lysosomes [243]. In fact, disruption of either dynein or KIF5B, the heavy chain of kinesin-1, impairs autophagosome/lysosome fusion, blocking autophagic degradation [244,245]. Once mature autophagosomes and lysosomes encounter, lysosomal and outer autophagosomal membranes fuse forming a new organelle called an autolysosome, in which degradation of autophagic cargo occurs [246]. This fusion requires the coordination of SNAREs, small GTPases, tethering factors, and other proteins [247]. The SNARE proteins involved in autophagosome/lysosome fusion are the Q-SNAREs STX17 and SNAP29 and the R-SNARE YKT6, all present at the autophagosomal membrane. At the lysosomal membrane, R-SNAREs such as VAMP8 or VAMP7 and Q-SNARE STX7 have been reported to interact with autophagosomal SNAREs to mediate membrane fusion. Rab GTPases also play a major role in this process, recruiting other proteins that act coordinately to enhance the efficiency and specificity of fusion [248,249]. In this context, Rab7 is likely the most important Rab protein, as it has been reported to recruit tethering factors, including EPG5, PLEKHM1, and VPS33A and VPS41 from the HOPS complex [250], which all promote the assembly of trans-SNARE complexes for fusion [251,252]. A similar role for the Rab2 protein has also been proposed in autophagy [253,254] and Rab33b has been shown to recruit the ATG16L1 complex to pre-autophagosomal membranes [255]. Moreover, ATG14L has also been shown to act in this process stabilizing the STX17–SNAP29 complex to promote autophagosome/lysosome fusion [256]. Finally, other tethering factors, such as GRS2/GRASP55 [257] or BIRC6/BRUCE [258] have been reported to play a role in this process.

To become autolysosomes, autophagosomes may either fuse directly with lysosomes or fuse their external membrane with endosomes and become an organelle called amphisome, which will eventually fuse with lysosomes [259]. This event is sometimes required for efficient autolysosome formation and disruptions in autophagosome/endosome fusion often result in autophagosome accumulation and autophagic degradation blockage [260]. Members of the ESCRT families of proteins have been shown to be required for autophagosome/endosome fusion, and thus for adequate autolysosome formation. In this regard, the ESCRT-associated AAA-ATPase VPS4B/SKD1 has been shown to be required for efficient autophagosome clearance [261]. Depletion of ESCRT-0 HRS/HGS also leads to impairment in autophagosome maturation and fusion with lysosomes [262]. Similarly, depletion of CHMP4B/SNF7-2/VPS32-2 (ESCRT-III) or the expression of a mutant form of CHMP2B causes an accumulation of autophagosomes [263]. Other proteins that have been suggested to be involved in endocytic transport and autophagy are C9orf72 [264], ZFYVE26, SPG11 [265], and Rab33B [266].

Altogether, the coordinated activity of all these proteins results in autolysosome formation, which is the last step preceding autophagosome cargo degradation (Figure 8). Table 6 shows polymorphisms on the genes encoding these effectors that are connected to diseases (with additional references collected in Table S1). Regarding the genes encoding motor proteins, SNPs in *FYCO1* and *KIF5B* have been associated with cataracts [267] and bipolar disorder [268], respectively. As for genes encoding SNARE proteins, several links with alterations have been established: *STX7* and neuronal heterotopia [269], *STX17* and alopecia [270], *YKT6* and diabetes or birth weight [271, 272], and *SNAP29* and a neurocutaneous condition termed Cednik syndrome [273]. Variants of another SNARE, *VAMP8*, are present in patients with coronary artery disease [274], cerebrovascular accident [275], tuberculosis [276] or prostate cancer [277]. An SNP in *Rab7* has been identified in patients with Charcot–Marie–Tooth disease type 2B [278–280], while SNPs in *Rab33B* are associated with Smith–McCort osteochondrodysplasia [281–283]. As for changes on genes from members of HOPS complex, a variant of *VPS33A* has been linked to a new type of mucopolysaccharidosis [284], with a specific allele of *VPS41* being implicated in major depressive disorder [285]. Additionally, SNPs in *PLEKHM1* have been involved in several diseases, including osteopetrosis [286], Parkinson's

disease [287], ovarian cancer [288,289], depression [290], and alopecia [291]. Some pathogenic variants on *EPG5* are responsible for Vici syndrome, a congenital multisystem disorder [292], while others have also been linked to Alzheimer's disease [293] or depression [294]. Only one polymorphism of *BIRC6* has been described in a disease, specifically glaucoma [295]. Variants on components of the ESCRT-III complex component are associated with a wide range of disorders. For example, SNPs in *CHMP2B* are linked to neuroblastoma [296], frontotemporal dementia [297,298] or ALS [299] and those in *CHMP4B* have been associated with cataracts [300], dysphagia [301] or diabetes mellitus [302]. Polymorphisms in *C9orf72* are also associated with frontotemporal dementia and ALS [264,303], while one SNP in *HGS* correlates with age-related macular degeneration [304]. Finally, variants of *ZFYVE26* [305] and *SPG11* [306] have been extensively analyzed in patients with spastic paraplegia, while SNPs in *ZFYVE26* have been also linked to ALS [307] and breast cancer [308]. All in all, polymorphisms on genes encoding proteins involved in autophagosome-lysosome fusion often result in the development of different diseases, with dementia, ALS and paraplegia being the most frequent ones. It is remarkable that a large number of clinically relevant SNPs have been identified in the genes encoding EPG5, SPG11 and ZFYVE26 (Figure 2).

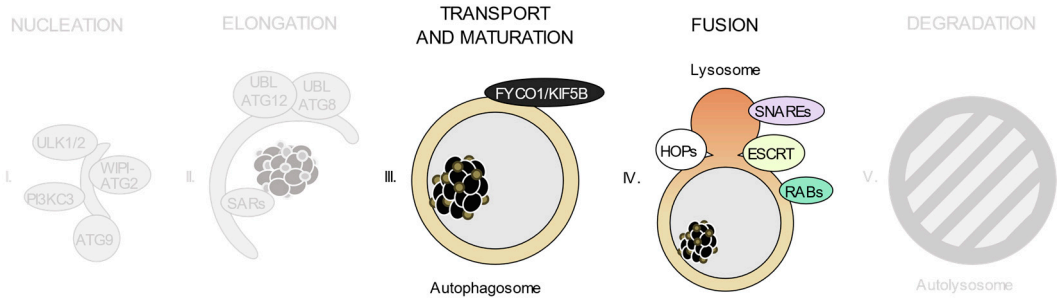

Figure 8. Different cellular machineries (including the HOPs and ESCRT complexes) and effectors (like motor proteins, as well as members of the SNARE or Rab family proteins) are involved in autophagosome transport and maturation, as well as in their fusion with lysosomes.

Table 6. Clinically relevant SNPs in cellular machineries involved in autophagosome-lysosome fusion.

Gene	Disease	dbSNP rsID
BIRC6	Glaucoma	rs2754511
C9orf72	Amyotrophic lateral sclerosis	rs3849943; rs774359; rs3849942
C9orf72	Familial frontotemporal dementia with amyotrophic lateral sclerosis	rs71492753
CHMP2B	Neuroblastoma	rs63750355; rs63750653
CHMP2B	Frontotemporal dementia	rs78268395
CHMP2B	Amyotrophic lateral sclerosis	rs281864934
CHMP4B	Bilateral cataracts	rs118203966
CHMP4B	Diabetes mellitus, non-insulin-dependent	rs7274168
CHMP4B	Dysphagia	rs2747539
EPG5	Alzheimer's disease	rs9963463; rs11082498
EPG5	Depressive disorders	rs58682566
EPG5	Vici syndrome	rs1470797555; rs1555673917; rs1568107449; rs1568112516; rs1568112543; rs1568118775; rs1568133724; rs1568133760; rs201757275; rs587776940; rs587776941; rs587776942; rs762639913; rs767638289; rs780889226; rs863225064; rs866435487; rs961245497; rs863225064

Table 6. *Cont.*

Gene	Disease	dbSNP rsID
EPG5	Cataract	rs201757275
FYCO1	Cataract	rs387906963; rs387906964; rs387906965
HGS	Age-related macular degeneration	rs8070488
KIF5B	Bipolar disorder	rs1775715
PLEKHM1	Osteopetrosis	rs786205055
PLEKHM1	Parkinson's disease	rs11012
PLEKHM1	Alopecia	rs144733372
PLEKHM1	Unipolar depression	rs144733372
PLEKHM1	Major depressive disorder	rs144733372
PLEKHM1	Ovarian cancer	rs1879586; rs2077606; rs17631303
RAB33B	Smith–McCort dysplasia	rs1085307129; rs886044716; rs1085307131; rs1085307128; rs587776958
RAB7	Charcot–Marie–Tooth disease type 2B	rs121909080; rs121909078; rs121909079; rs121909081
SNAP29	Cednik syndrome	rs387907363; rs869312906
SPG11	Spastic paraplegia	rs1085307097; rs118203963; rs140385286; rs1555447432; rs141848292; rs312262720; rs312262721; rs312262722; rs312262737; rs312262749; rs312262752; rs312262764; rs312262779; rs371334506; rs747220413; rs764647588; rs765477482; rs767798272
STX17	Alopecia	rs10760706
STX7	Neuronal heterotopia	rs864309676
VAMP8	Cerebrovascular accident	rs1010
VAMP8	Tuberculosis	rs1010
VAMP8	Coronary artery disease	rs1010
VAMP8	Prostate cancer	rs10187424; rs3731827
VPS33A	MPS-like disorder	rs767748011
VPS41	Major depressive disorder	rs10274968
YKT6	Diabetes	rs2908282
YKT6	Birth weight and subsequent risk factors	rs138715366
ZFYVE26	Spastic paraplegia	rs1049504575; rs1057518016; rs1214483973; rs1555394376; rs200832994; rs558285072; rs767164213; rs768176054; rs769329153; rs774809466; rs941230062; rs981804211
ZFYVE26	Amyotrophic lateral sclerosis	rs12891047
ZFYVE26	Breast cancer	rs200595749
ZFYVE26	Movement disorders	rs752283089; rs869312914

Once the autolysosome is formed, the inner membrane and the internal content of the original autophagosome are degraded by the action of acidic hydrolases (Figure 9). After that, the resulting new biomolecules (nucleotides, lipids, amino acids, etc.) return to the cytoplasm by the action of permeases and other transporters. Therefore, the lysosome becomes an essential player in autophagy. Disruption of lysosomal activity impacts autophagic degradation, leading to the accumulation of autophagosomes and/or autolysosomes, which physically stresses the cell while undesired cytoplasmic components accumulate without being degraded. In fact, alterations in the balance of lysosomal lipids

can hinder autophagy, either by blocking autophagosome-lysosome fusion (which is the case in multiple sulfatase deficiency (MSD) or in mucopolysaccharidosis type IIIA [309,310]), impeding autophagosomal closure (by, for example, the accumulation of sphingomyelin in Niemann–Pick type A and B [311]), impairing lysosomal proteolysis (shown in Niemann–Pick disease type C [312]) or resulting in lysosomal permeabilization (as it has been described in Niemann–Pick disease type A [313]).

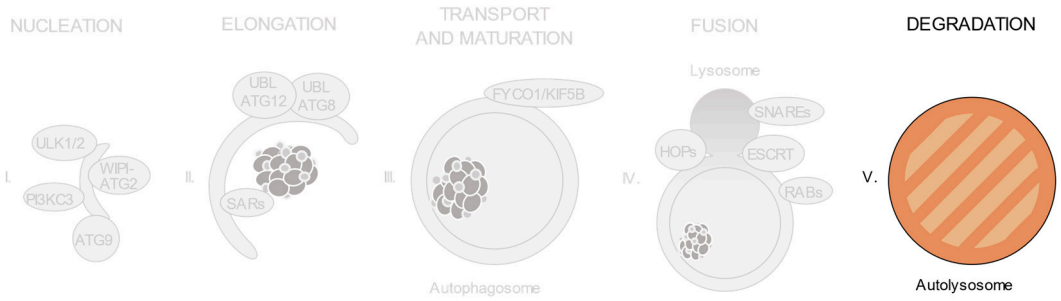

Figure 9. Lysosomal components are direct effectors of autophagosome cargo degradation.

Classic examples of human pathologies caused by alterations in lysosomal function are LSDs. These pathologies are originated by variants that alter the activity of either specific lysosomal proteins (including hydrolases, transferases, membrane proteins, activators or transporters) or non-lysosomal ones that are required for the lysosomal-mediated degradation of different molecules. Thus, glycosaminoglycans are accumulated in different types of mucopolysaccharidoses. In fact, a long list of diseases are originated by pathogenic SNPs in the genes involved in their degradation, such as *ARSB* (MPS VI or Maroteaux–Lamy syndrome) [314], *GALNS* (MPS IVA or Morchio A syndrome) [315], *GLB1* (MPS IVB or Morchio B syndrome) [316–318], *GNS* (MPS IIID or Sanfilippo syndrome type D) [319] *GUSB* (MPS VII or Sly syndrome) [320], *HGSNAT* (MPS IIIC or Sanfilippo syndrome type C) [319], *HYAL1* (MPS IX) [321], *IDS* (MPS II or Hunter syndrome) [322], *IDUA* (different subtypes of MPS I and II) [323], *NAGLU* (MPS IIIB or Sanfilippo syndrome type B) [319] or *SGSH* MPS IIIA or Sanfilippo syndrome type A) [319]. One of the most well-studied pathologies caused by lysosomal deficiency is Danon disease, which has been extensively associated with LAMP2 deficiency [324]. Another well-documented glycogen storage disorder, Pompe disease, is caused by mutations in *GAA* [325], which has also been implicated in Friedreich ataxia [326] and hypochondrogenesis [327]. Deficiency of the lysosomal hydrolase β-glucocerebrosidase (GCase), encoded by *GBA*, causes Gaucher disease [328], and a polymorphism on this gene has also been linked to Parkinson's disease [329], whereas several pathogenic SNPs in *GLA*, the gene encoding the lysosomal enzyme α-galactosidase A (a-Gal A), are associated with Fabry disease [330]. Polymorphisms in *NPC1* and *NPC2* genes results in Niemann–Pick type C disease [331], while changes in *CTNS* have been associated with cystinosis [332]. Different types of neuronal ceroid lipofuscinoses can be caused by mutations on different genes, such as *GRN*, several *CLNs*, *CTSD*, *CTSF*, *DNAJC5* or *MFSD8* [333]. Finally, pathogenic SNPs on *CTSA*, *FUCA1*, *SLC17A5*, and *MANBA* or *MAN2B1* lead to galactosialidosis [334], fucosidosis [335], sialic acid storage diseases [336] or mannosidosis [337,338], respectively. All these clinically relevant SNPs are shown in Table 7, with additional references collected in Table S1. It is remarkable that numerous SNPs on a given lysosomal gene are only associated with just one or two pathologies (*GLB1* being the single exception) (Figure 2). This contrasts with the case of the genes encoding proteins involved in autophagosome biogenesis, in which fewer variants are linked to a wider range of diseases.

Table 7. Clinically relevant SNPs in lysosomal components.

Gene	Disease	dbSNP rsID
ARSB	Mucopolysaccharidosis type VI (Maroteaux–Lamy syndrome)	rs118203938; rs118203939; rs118203940; rs431905493; rs431905495; rs431905496; rs118203942; rs118203944; rs118203943
CLN3	Neuronal ceroid lipofuscinosis type 3	rs121434286; rs267606737; rs386833720; rs786201028; rs121434286
CLN6	Neuronal ceroid lipofuscinosis type 6	rs104894483; rs104894486; rs121908079; rs121908080; rs397515352; rs774543080; rs786205065; rs786205066; rs786205067; rs104894484
CLN6	Adult neuronal ceroid lipofuscinosis	rs154774633; rs154774634; rs154774635; rs154774636
CLN8	Neuronal ceroid lipofuscinosis type 8	rs104894060; rs137852883; rs28940569
CLN8	Northern epilepsy syndrome	rs104894064
CTNS	Cystinosis	rs375952052
CTSA	Galactosialidosis	rs137854540; rs137854544; rs137854546; rs137854547; rs137854548; rs137854549; rs786200859; rs875989777; rs137854544; rs137854543
CTSD	Neuronal ceroid lipofuscinosis type 10	rs786205105; rs797045137; rs797045138; rs121912789; rs121912790
CTSF	Neuronal ceroid lipofuscinosis type 13	rs753084727; rs797045136; rs143889283; rs397514731
DNAJC5	Neuronal ceroid lipofuscinosis, Parry type,	rs587776892; rs387907043
FUCA1	Fucosidosis	rs118204450; rs80358195; rs80358196; rs80358197; rs80358198
GAA	Glycogen storage disease type II (Pompe disease)	rs1057516581; rs12450199; rs140826989; rs121907940; rs121907941; rs1393386120; rs1414146587; rs121907942; rs1344266804; rs121907943; rs121907944; rs1221948995; rs1245412108; rs121907938; rs121907945; rs121907936; rs1800309; rs121907937; rs1800307; rs147804176; rs1555600061; rs1555601773; rs1800312; rs200856561; rs1555601773; rs1800312; rs200856561; rs369531647; rs1057516277; rs886043343; rs892129065; rs28940868;rs1057516215; rs1055945806;
GAA	Friedreich ataxia	rs1245992455
GAA	Hypochondrogenesis	rs1289257741
GALNS	Mucopolysaccharidosis IVA (Morchio A syndrome)	rs1028668536; rs118204438; rs118204449; rs786205899; rs118204435; rs118204441; rs118204442; rs118204446; rs118204447; rs118204448; rs267606838
GBA	Parkinson's disease	rs75548401
GBA	Gaucher disease	rs421016
GLA	Fabry disease	rs104894828; rs104894834; rs104894845; rs28935197; rs869312142
GLB1	GM1 gangliosidosis	rs192732174; rs376663785; rs587776524; rs794727165; rs794729217; rs781658798; rs778423653; rs778700089; rs879050821; rs72555361; rs72555364; rs72555368; rs72555370; rs72555390; rs72555393; rs794729217; rs72555392; rs72555362; rs1214295886; rs1553606128; rs1553610382; rs1553610553; rs1553612189; rs1559401428; rs192732174; rs189115557;
GLB1	Mucopolysaccharidosis IVB (Morchio B syndrome)	rs72555363; rs1553606128; rs1553610382; rs1553610553; rs1553612220; rs189115557; rs192732174; rs794729217; rs794727165; rs778700089; rs778423653
GLB1	Neuraminidase 1 deficiency	rs1356418704
GLB1	Respiratory tract diseases	rs9828592

Table 7. *Cont.*

Gene	Disease	dbSNP rsID
GLB1	Asthma	rs79337446
GNS	Mucopolysaccharidosis type IIID (Sanfilippo syndrome)	rs119461974; rs119461975; rs483352898; rs483352899; rs483352900
GRN	Presenile dementia	rs373885474
GRN	Frontotemporal lobar degeneration	rs606231220; rs63749801; rs63750077; rs63751006; rs63750331; rs63751294; rs63751243
GUSB	Mucopolysaccharidosis type VII (Sly syndrome)	rs121918179; rs121918181; rs121918185; rs377519272; rs786200863; rs121918180; rs121918173; rs121918174; rs121918175; rs121918176; rs121918177; rs121918178; rs121918182; rs121918183; rs121918184; rs121918172
HGSNAT	Mucopolysaccharidosis type IIIC (Sanfilippo syndrome type C)	rs121908282; rs121908283; rs121908284; rs121908285; rs121908286; rs193066451; rs483352896; rs753355844; rs754875934; rs764206492; rs797045120
HYAL1	Mucopolysaccharidosis IX	rs104893743
IDS	Mucopolysaccharidosis type II (Hunter syndrome)	rs113993946; rs113993947; rs199422230; rs483352904; rs483352905; rs797044671; rs869025304; rs869025305; rs869025306; rs869025307; rs869025308; rs104894856; rs104894861; rs199422228; rs199422229; rs199422231
IDUA	Mucopolysaccharidosis type I (Hurler and Scheie syndrome)	rs121965025; rs121965033; rs199801029; rs387906504; rs398123258; rs762411583; rs786200915; rs869025584; rs121965021; rs121965026; rs121965027; rs121965031; rs121965023; rs121965019; rs121965021; rs121965030; rs764196171; rs121965019; rs121965033; rs121965024;
LAMP2	Danon disease	rs104894857; rs104894858; rs1060502302; rs137852527; rs727503118; rs727503119; rs727503120; rs727504742
MAN2B1	Alpha-mannosidosis	rs121434331; rs121434332; rs775200333; rs80338677; rs80338678; rs80338679; rs80338680; rs80338681
MANBA	Beta-mannosidosis	rs121434334; rs121434335; rs121434336
MFSD8	Neuronal ceroid lipofuscinosis type 7	rs11820397; rs587778809; rs724159971; rs727502801; rs118203975; rs118203976; rs140948465; rs267607235; rs749704755
MFSD8	Late-infantile neuronal ceroid lipofuscinosis	rs200319160
NAGLU	Mucopolysaccharidosis type IIIB (Sanfilippo syndrome type B)	rs104894591; rs104894592; rs104894597; rs104894598; rs118204025; rs746006696; rs886039894; rs886039895; rs118204024; rs104894590; rs104894593; rs104894594; rs104894595; rs104894597; rs104894598; rs753520553; rs796052122; rs104894601
NPC1	Niemann–Pick disease, type C	rs1055204017; rs1057518711; rs1474434210; rs753768576; rs139751448; rs143124972; rs28942104; rs756815030; rs758231839; rs886042270; rs80358257; rs80358254; rs80358259; rs150334966; rs1555634422; rs768999208; rs80358259
NPC2	Niemann–Pick disease type C	rs80358262; rs80358263; rs80358266; rs80358268; rs11694; rs80358261; rs80358264; rs104894458
SGSH	Mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A)	rs104894635; rs104894637; rs138504221; rs1057521801; rs374621913; rs770947426; rs777956287; rs778700037; rs104894638; rs104894640; rs104894642; rs104894643; rs104894636; rs104894641; rs138504221; rs104894635
SLC17A5	Sialic acid storage diseases (SASDs)	rs386833987; rs386833994; rs727504156; rs119491109; rs119491110; rs80338795; rs80338794

4. Concluding Remarks

As the number of studies on autophagy research grows, it becomes clearer how essential this catabolic pathway is for cellular homeostasis and health. What was first inferred from the characterization of animal models deficient in autophagy it is now directly described in human pathology, with an increasing record of papers showing that autophagy dysregulation drives or sustains a wide range of disorders. The extensive list of autophagy-related SNPs collected in this review further reflects the relevance of autophagy and its effectors in human pathology. In this regard, several variants present in different populations can decisively affect the origin, development or prognosis of different diseases, remarking the importance of defining autophagy-related gene signatures in these disorders. Thus, the existence of variants on autophagy-related genes allows us to better understand the role of this route in pathophysiology.

Interestingly, in some cases, the very same SNPs have been described to be associated with different disorders either with a pathogenic or a protective effect. This is the case, for example, of rs2241880, the threonine-to-alanine substitution at amino acid position 300 of ATG16L1 (T300A) that has been intensively analyzed in the context of inflammatory bowel diseases. This variant has additionally been linked to different types of cancer or to Paget's disease of the bone, and the same allele may be protective or pathogenic depending on the disorder and the population. This redundancy is also true for other genes, such as *ATG5* (rs510432, rs573775 or rs2245214) or *ATG10* (rs10514231, rs1864182 or rs1864183). Although identification of the same variant in different pathologies could be explained by the fact that already-studied SNPs are more likely to be analyzed again in the context of additional diseases, it nevertheless shows that alteration in the activity of autophagy proteins definitely contributes to the progression or repression of a given disorder. This bias could also explain why most of the autophagy-related polymorphisms that we have collected are located on genes of effectors mediating ATG12 conjugation (Table 4), as many researchers first focus on these proteins when addressing autophagy in a pathological context. Similarly, the analysis of SNPs in lysosomal genes has been favored by the direct link between mutations on these genes and lysosomal storage disorders (Table 7), entailing a fast, straightforward approach to find pathogenic variants in diseases.

Finally, and although this review is focused on SNPs, it is worth mentioning that other less-frequent pathogenic variants of autophagy-related genes have also been described in the literature. For example, the monoallelic deletion of the 17q21 region, affecting the *BECN1* gene, is associated with breast, ovarian and prostate cancer [339,340]. Two variants of *WIPI4* (c.439 + 1G > T and c.1033_1034dupAA) were identified in patients with beta-propeller protein-associated neurodegeneration [98], while a third one is specifically linked to developmental and epileptic encephalopathy in patients with the same neurological disorder [341]. Sequence variants affecting the expression levels of *ATG12* (115842507G>T, 115842394C>T and 115841817_18del) [342] and *ATG7* (11313449G>A, 11313811T>C, 1313913G>A and 11314041G>A) [343] are present in patients with sporadic Parkinson's disease. Other examples of less-common risk alleles are those of *SQSTM1* associated with frontotemporal dementia (c.1142C>T, K341V and K344E) [202,344] or muscle disorders such as sporadic inclusion body myositis (G194R) [204] and distal myopathies with rimmed vacuoles (p.G351_P388del and p.Glu389delinsAspLysTer) [345]. Although these and other minority variants have only been identified in few patients, their real allelic frequency in populations could be much higher, increasing their relevance and consolidating the clinical importance of pathogenic autophagy variants.

As a conclusion, it has to be considered that medicine is firmly progressing toward a personalized approach, given that patients respond differently to the same treatments. Although other factors are surely involved, the presence of SNPs plays a pivotal role in the specific response of a patient to a determined treatment. In this regard, autophagy-related polymorphisms are not only involved in the development of pathologies, but also may influence the effectiveness of a determined treatment. This additional clinical relevance of variants on autophagy-related genes has already been described in cancer [61,104,114,118,121], inflammatory bowel diseases [145,346,347] and others [80]. For this reason, the identification of new clinically significant SNPs is not only important in terms of disease

prevention, but also to design new therapeutic approaches aimed at modulating autophagy for clinically relevant purposes. This review should be of great help in advancing to design new therapeutic strategies.

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Abbreviations

ALFY	Autophagy-linked FYVE protein
AMBRA1	Activating molecule in BECN1-regulated autophagy protein 1
AMPK	Adenosine monophosphate-activated protein kinase
ARSB	Arylsulfatase B
ATG10	Autophagy-related protein 10
ATG101	Autophagy-related protein 101
ATG12	Autophagy-related protein 12
ATG13	Autophagy-related protein 13
ATG14	Autophagy-related protein 14
ATG16L1	Autophagy-related protein 16 like 1
ATG2A	Autophagy-related protein 2 homolog A
ATG2B	Autophagy-related protein 2 homolog B
ATG4A	Autophagy related 4A cysteine peptidase
ATG4B	Autophagy related 4B cysteine peptidase
ATG4C	Autophagy related 4C cysteine peptidase
ATG4D	Autophagy related 4D cysteine peptidase
ATG5	Autophagy-related protein 5
ATG7	Autophagy-related protein 7
ATG9A	Autophagy-related protein 9A
ATG9B	Autophagy-related protein 9B
ATGL	Adipose triglyceride lipase
ATL3	Atlastin-3
Barkor	Beclin 1-associated autophagy-related key regulator
BCL-2	Apoptosis regulator Bcl-2
BECN1	Beclin-1
BIRC6	Baculoviral IAP repeat-containing protein 6
BNIP3	BCL2/adenovirus E1B 19 kDa protein-interacting protein 3
BNIP3L	BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like
CCPG1	Cell cycle progression protein 1
CHMP2B	Charged multivesicular body protein 2b
CHMP4B	Charged multivesicular body protein 4b
CTNS	Cystinosin
CTSD	Cathepsin D
CTSF	Cathepsin F
DFCP1	Double FYVE-containing protein 1
DNAJC5	DnaJ homolog subfamily C member 5
EPG5	Ectopic P granules protein 5 homolog
FAM134B	Family With Sequence Similarity 134, Member B
FKBP8	Peptidyl-prolyl cis-trans isomerase FKBP8
FUCA1	Tissue alpha-L-fucosidase
FUNDC1	FUN14 domain-containing protein 1
FYCO1	FYVE and coiled-coil domain-containing protein 1
GAA	Lysosomal alpha-glucosidase

GABARAP	Gamma-aminobutyric acid receptor-associated protein
GABARAPL1	Gamma-aminobutyric acid receptor-associated protein-like 1
GALNS	N-acetylgalactosamine-6-sulfatase
GARARAPL2	Gamma-aminobutyric acid receptor-associated protein-like 2
GLB1	Beta-galactosidase
GNS	N-acetylglucosamine-6-sulfatase
GRASP55	Golgi reassembly-stacking protein of 55 kDa
GRN	Progranulin
GUSB	Beta-glucuronidase
HGS	Hepatocyte growth factor-regulated tyrosine kinase substrate
HGSNAT	Heparan-alpha-glucosaminide N-acetyltransferase
HOPS	Hepatocyte odd Ppotein shuttling protein
HSC70	Heat shock cognate 71 kDa protein
HSL	Hormone-sensitive lipase
HTT	Huntingtin
HYAL1	Hyaluronidase-1
IDS	Iduronate 2-sulfatase
IDUA	Alpha-L-iduronidase
KIF5B	Kinesin-1 heavy chain
LAMP2	Lysosome-associated membrane protein 2
MAN2B1	Lysosomal alpha-mannosidase
MANBA	Beta-mannosidase
MAP1-LC3A	Microtubule-associated proteins 1A/1B light chain 3A
MAP1-LC3B	Microtubule-associated proteins 1A/1B light chain 3B
MAP1-LC3C	Microtubule-associated proteins 1A/1B light chain 3C
MFSD8	Major facilitator superfamily domain-containing protein 8
mTOR	Mechanistic/mammalian target of rapamycin
NAGLU	Alpha-N-acetylglucosaminidase
NBR1	Next to BRCA1 gene 1 protein
NCOA4	Nuclear receptor coactivator 4
NDP52	Nuclear domain 10 protein 52
NPC1	NPC intracellular cholesterol transporter 1
NPC2	NPC intracellular cholesterol transporter 2
NUFIP1	Nuclear fragile X mental retardation-interacting protein 1
OPTN	Optineurin
PI3KC3	Phosphatidylinositol 3-kinase catalytic subunit type 3
PIK3R4	Phosphoinositide 3-kinase regulatory subunit 4
PLEKHM1	Pleckstrin homology domain-containing family M member 1
RB1CC1	RB1-inducible coiled-coil protein 1
RTN3	Reticulon-3
SEC62	Translocation protein SEC62
SGSH	N-sulphoglucosamine sulphohydrolase
SLC17A5	Sialin
SNAP29	Synaptosomal-associated protein 29
SQSTM1	Sequestosome-1
STK36	Serine/threonine-protein kinase 36
STX17	Syntaxin-17
TAX1BP1	Tax1-binding protein 1
TEX264	Testis-expressed protein 264
TOLLIP	Toll-interacting protein
ULK1	Unc-51 like autophagy activating kinase
UVRAG	UV radiation resistance-associated gene protein
VAMP7	Vesicle-associated membrane protein 7
VAMP8	Vesicle-associated membrane protein 8

VPS4B	Vacuolar protein sorting-associated protein 4B
WIPI1	WD repeat domain phosphoinositide-interacting protein 1
WIPI2	WD repeat domain phosphoinositide-interacting protein 2
WIPI3	WD repeat domain phosphoinositide-interacting protein 3
WIPI4	WD repeat domain phosphoinositide-interacting protein 4
YKT6	Synaptobrevin homolog YKT6

References

1. Kroemer, G.; Mariño, G.; Levine, B. Autophagy and the Integrated Stress Response. *Mol. Cell* **2010**, *40*, 280–293. [CrossRef] [PubMed]
2. Galluzzi, L.; Baehrecke, E.H.; Ballabio, A.; Boya, P.; Bravo-San Pedro, J.M.; Cecconi, F.; Choi, A.M.; Chu, C.T.; Codogno, P.; Colombo, M.I.; et al. Molecular definitions of autophagy and related processes. *Embo J.* **2017**, *36*, 1811–1836. [CrossRef] [PubMed]
3. Parzych, K.R.; Klionsky, D.J. An overview of autophagy: Morphology, mechanism, and regulation. *Antioxid. Redox Signal.* **2014**, *20*, 460–473. [CrossRef] [PubMed]
4. Mijaljica, D.; Prescott, M.; Devenish, R.J. Microautophagy in Mammalian Cells: Revisiting a 40-Year-Old Conundrum. *Autophagy* **2011**, *7*, 673–682. [CrossRef] [PubMed]
5. Kaushik, S.; Cuervo, A.M. The coming of age of chaperone-mediated autophagy. *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 365–381. [CrossRef] [PubMed]
6. Kawabata, T.; Yoshimori, T. Autophagosome Biogenesis and Human Health. *Cell Discov.* **2020**, *6*, 33. [CrossRef] [PubMed]
7. Singh, R.; Cuervo, A.M. Autophagy in the cellular energetic balance. *Cell Metab.* **2020**, *6*, 33. [CrossRef] [PubMed]
8. Levine, B.; Kroemer, G. Biological Functions of Autophagy Genes: A Disease Perspective. *Cell* **2019**, *176*, 11–42. [CrossRef]
9. Zhao, Y.G.; Zhang, H. Core autophagy genes and human diseases. *Curr. Opin. Cell Biol.* **2019**, *61*, 117–125. [CrossRef]
10. Choi, A.M.K.; Ryter, S.W.; Levine, B. Autophagy in Human Health and Disease. *N. Engl. J. Med.* **2013**, *368*, 651–662. [CrossRef]
11. Yang, Y.; Klionsky, D.J. Autophagy and disease: Unanswered questions. *Cell Death Differ.* **2020**, *27*, 858–871. [CrossRef] [PubMed]
12. Galluzzi, L.; Pietrocola, F.; Bravo-San Pedro, J.M.; Amaravadi, R.K.; Baehrecke, E.H.; Cecconi, F.; Codogno, P.; Debnath, J.; Gewirtz, D.A.; Karantza, V.; et al. Autophagy in malignant transformation and cancer progression. *Embo J.* **2015**, *34*, 856–880. [CrossRef]
13. Lai, J.; Chen, B.; Mok, H.; Zhang, G.; Ren, C.; Liao, N. Comprehensive analysis of autophagy-related prognostic genes in breast cancer. *J. Cell. Mol. Med.* **2020**, *24*, 9145–9153. [CrossRef]
14. Zhu, Y.; Wang, R.; Chen, W.; Chen, Q.; Zhou, J. Construction of a prognosis-predicting model based on autophagy-related genes for hepatocellular carcinoma (HCC) patients. *Aging* **2020**, *12*, 14582. [CrossRef]
15. Feng, H.; Zhong, L.; Yang, X.; Wan, Q.; Pei, X.; Wang, J. Development and validation of prognostic index based on autophagy-related genes in patient with head and neck squamous cell carcinoma. *Cell Death Discov.* **2020**, *6*, 1–8. [CrossRef] [PubMed]
16. Hu, D.; Jiang, L.; Luo, S.; Zhao, X.; Hu, H.; Zhao, G.; Tang, W. Development of an autophagy-related gene expression signature for prognosis prediction in prostate cancer patients. *J. Transl. Med.* **2020**, *18*, 1–12. [CrossRef]
17. Sun, Z.; Jing, C.; Xiao, C.; Li, T. An autophagy-related long non-coding RNA prognostic signature accurately predicts survival outcomes in bladder urothelial carcinoma patients. *Aging* **2020**, *12*, 15624–15637. [CrossRef] [PubMed]
18. Chen, M.; Zhang, S.; Nie, Z.; Wen, X.; Gao, Y. Identification of an Autophagy-Related Prognostic Signature for Clear Cell Renal Cell Carcinoma. *Front. Oncol.* **2020**, *10*, 873. [CrossRef] [PubMed]
19. Chen, C.; Chen, S.; Cao, H.; Wang, J.; Wen, T.; Hu, X.; Li, H. Prognostic significance of autophagy-related genes within esophageal carcinoma. *BMC Cancer* **2020**, *20*, 1–11. [CrossRef]
20. Xing, Q.; Ji, C.; Zhu, B.; Cong, R.; Wang, Y. Identification of small molecule drugs and development of a novel autophagy-related prognostic signature for kidney renal clear cell carcinoma. *Cancer Med.* **2020**, *9*, 7034–7051. [CrossRef]
21. Huo, X.; Qi, J.; Huang, K.; Bu, S.; Yao, W.; Chen, Y.; Nie, J. Identification of an autophagy-related gene signature that can improve prognosis of hepatocellular carcinoma patients. *BMC Cancer* **2020**, *20*, 771. [CrossRef] [PubMed]

22. Du, J.-X.; Chen, C.; Luo, Y.-H.; Cai, J.-L.; Cai, C.-Z.; Xu, J.; Ni, X.-J.; Zhu, W. Establishment and validation of a novel autophagy-related gene signature for patients with breast cancer. *Gene* **2020**, *762*, 144974. [CrossRef] [PubMed]
23. Wang, H.; Ma, X.; Liu, J.; Wan, Y.; Jiang, Y.; Xia, Y.; Cheng, W. Prognostic value of an autophagy-related gene expression signature for endometrial cancer patients. *Cancer Cell Int.* **2020**, *20*, 306. [CrossRef]
24. Yang, H.; Han, M.; Li, H. Construction and Validation of an Autophagy-Related Prognostic Risk Signature for Survival Predicting in Clear Cell Renal Cell Carcinoma Patients. *Front. Oncol.* **2020**, *10*, 707. [CrossRef] [PubMed]
25. Shibutani, S.T.; Saitoh, T.; Nowag, H.; Münz, C.; Yoshimori, T. Autophagy and Autophagy-Related Proteins in the Immune System. *Nat. Immunol.* **2015**, *16*, 1014–1024. [CrossRef]
26. Clarke, A.J.; Simon, A.K. Autophagy in the Renewal, Differentiation and Homeostasis of Immune Cells. *Nat. Rev. Immunol.* **2019**, *19*, 170–183. [CrossRef]
27. Münz, C. Autophagy proteins in antigen processing for presentation on MHC molecules. *Immunol. Rev.* **2016**, *272*, 17–27. [CrossRef]
28. Cui, B.; Lin, H.; Yu, J.; Yu, J.; Hu, Z. Autophagy and the Immune Response. *Adv. Exp. Med. Biol.* **2019**, *1206*, 595–634.
29. Deretic, V.; Levine, B. Autophagy Balances Inflammation in Innate Immunity. *Autophagy* **2018**, *14*, 243–251. [CrossRef]
30. Cadwell, K. Crosstalk between Autophagy and Inflammatory Signalling Pathways: Balancing Defence and Homeostasis. *Nat. Rev. Immunol.* **2016**, *16*, 661–675. [CrossRef]
31. Yin, H.; Wu, H.; Chen, Y.; Zhang, J.; Zheng, M.; Chen, G.; Li, L.; Lu, Q. The Therapeutic and Pathogenic Role of Autophagy in Autoimmune Diseases. *Front. Immunol.* **2018**, *9*, 1512. [CrossRef] [PubMed]
32. Kim, S.; Eun, H.; Jo, E.-K. Roles of Autophagy-Related Genes in the Pathogenesis of Inflammatory Bowel Disease. *Cells* **2019**, *8*, 77. [CrossRef] [PubMed]
33. Levine, B.; Mizushima, N.; Virgin, H.W. Autophagy in Immunity and Inflammation. *Nature* **2011**, *469*, 323–335. [CrossRef] [PubMed]
34. Choi, Y.; Bowman, J.W.; Jung, J.U. Autophagy during Viral infection A Double-Edged Sword. *Nat. Rev. Microbiol.* **2018**, *16*, 341–354. [CrossRef]
35. Menzies, F.M.; Fleming, A.; Caricasole, A.; Bento, C.F.; Andrews, S.P.; Ashkenazi, A.; Füllgrabe, J.; Jackson, A.; Jimenez Sanchez, M.; Karabiyik, C.; et al. Autophagy and Neurodegeneration: Pathogenic Mechanisms and Therapeutic Opportunities. *Neuron* **2017**, *93*, 1015–1034. [CrossRef]
36. Park, H.; Kang, J.H.; Lee, S. Autophagy in Neurodegenerative Diseases: A Hunter for Aggregates. *Int. J. Mol. Sci.* **2020**, *21*, 3369. [CrossRef]
37. Vicencio, E.; Beltrán, S.; Labrador, L.; Manque, P.; Nassif, M.; Woehlbier, U. Implications of Selective Autophagy Dysfunction for ALS Pathology. *Cells* **2020**, *9*, 381. [CrossRef]
38. Zhu, Y.; Runwal, G.; Obrocki, P.; Rubinsztein, D.C. Autophagy in childhood neurological disorders. *Dev. Med. Child Neurol.* **2019**, *61*, 639–645. [CrossRef]
39. Margeta, M. Autophagy Defects in Skeletal Myopathies. *Annu. Rev. Pathol. Mech. Dis.* **2020**, *15*, 261–285. [CrossRef]
40. Pierrefite-Carle, V.; Santucci-Darmanin, S.; Breuil, V.; Camuzard, O.; Carle, G.F. Autophagy in bone: Self-eating to stay in balance. *Ageing Res. Rev.* **2015**, *24*, 206–217. [CrossRef]
41. Vinatier, C.; Domínguez, E.; Guicheux, J.; Caramés, B. Role of the Inflammation-Autophagy-Senescence Integrative Network in Osteoarthritis. *Front. Physiol.* **2018**, *9*, 706. [CrossRef] [PubMed]
42. Ballabio, A.; Bonifacino, J.S. Lysosomes as dynamic regulators of cell and organismal homeostasis. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 101–118. [CrossRef] [PubMed]
43. Sun, A. Lysosomal storage disease overview. *Ann. Transl. Med.* **2018**, *6*, 476. [CrossRef] [PubMed]
44. Palhegyi, A.M.; Seranova, E.; Dimova, S.; Hoque, S.; Sarkar, S. Biomedical Implications of Autophagy in Macromolecule Storage Disorders. *Front. Cell Dev. Biol.* **2019**, *7*, 179. [CrossRef]
45. Parenti, G.; Andria, G.; Ballabio, A. Lysosomal storage diseases: From pathophysiology to therapy. *Annu. Rev. Med.* **2015**, *66*, 471–486. [CrossRef]
46. Ariosa, A.R.; Klionsky, D.J. Autophagy core machinery: Overcoming spatial barriers in neurons. *J. Mol. Med.* **2016**, *94*, 1217–1227. [CrossRef]
47. Koyama-Honda, I.; Itakura, E.; Fujiwara, T.K.; Mizushima, N. Temporal analysis of recruitment of mammalian ATG proteins to the autophagosome formation site. *Autophagy* **2013**, *9*, 1491–1499. [CrossRef]
48. Wesselborg, S.; Stork, B. Autophagy Signal Transduction by ATG Proteins: From Hierarchies to Networks. *Cell Mol Life Sci.* **2015**, *72*, 4721–4757. [CrossRef]

49. Nakatogawa, H. Mechanisms governing autophagosome biogenesis. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 439–458. [CrossRef]
50. Zachari, M.; Ganley, I.G. The Mammalian ULK1 Complex and Autophagy Initiation. *Esssays Biochem.* **2017**, *61*, 585–596.
51. Tamargo-Gómez, I.; Mariño, G. AMPK: Regulation of Metabolic Dynamics in the Context of Autophagy. *Int. J. Mol. Sci.* **2018**, *19*, 3812. [CrossRef] [PubMed]
52. Wang, Y.; Zhang, H. *Regulation of Autophagy by mTOR Signaling Pathway*; Springer: Berlin/Heidelberg, Germany, 2019; Volume 1206, pp. 67–83.
53. Morgan, A.R.; Lam, W.J.; Han, D.Y.; Fraser, A.G.; Ferguson, L.R. Association analysis of ULK1 with Crohn's disease in a New Zealand population. *Gastroenterol. Res. Pract.* **2012**. [CrossRef] [PubMed]
54. Henckaerts, L.; Cleynen, I.; Brinar, M.; John, J.M.; Van Steen, K.; Rutgeerts, P.; Vermeire, S. Genetic variation in the autophagy gene ULK1 and risk of Crohn's disease. *Inflamm. Bowel Dis.* **2011**, *17*, 1392–1397. [CrossRef] [PubMed]
55. Zhang, R.R.; Liang, L.; Chen, W.W.; Wen, C.; Wan, B.S.; Luo, L.L.; Zhao, Y.L.; Chen, J.; Yue, J. ULK1 polymorphisms confer susceptibility to pulmonary tuberculosis in a Chinese population. *Int. J. Tuberc. Lung Dis.* **2019**, *23*, 265–271. [CrossRef]
56. Horne, D.J.; Graustein, A.D.; Shah, J.A.; Peterson, G.; Savlov, M.; Steele, S.; Narita, M.; Hawn, T.R. Human ULK1 Variation and Susceptibility to Mycobacterium tuberculosis Infection. *J. Infect. Dis.* **2016**, *214*, 1260–1267. [CrossRef]
57. Zhang, X.; Han, R.; Wang, M.; Li, X.; Yang, X.; Xia, Q.; Liu, R.; Yuan, Y.; Hu, X.; Chen, M.; et al. Association between the autophagy-related gene ULK1 and ankylosing spondylitis susceptibility in the Chinese Han population: A case-control study. *Postgrad. Med. J.* **2017**, *93*, 752–757. [CrossRef]
58. Wolthers, B.O.; Frandsen, T.L.; Abrahamsson, J.; Albertsen, B.K.; Helt, L.R.; Heyman, M.; Jónsson, G.; Kõrgvee, L.T.; Lund, B.; Raja, R.A.; et al. Asparaginase-associated pancreatitis: A study on phenotype and genotype in the NOPHO ALL2008 protocol. *Leukemia* **2017**, *31*, 325–332. [CrossRef]
59. Bronson, P.G.; Chang, D.; Bhangale, T.; Seldin, M.F.; Ortmann, W.; Ferreira, R.C.; Urcelay, E.; Pereira, L.F.; Martin, J.; Plebani, A.; et al. Common variants at PVT1, ATG13-AMBRA1, AHI1 and CLEC16A are associated with selective IgA deficiency. *Nat. Genet.* **2016**, *48*, 1425–1429. [CrossRef]
60. Liu, B.; An, T.; Li, M.; Yi, Z.; Li, C.; Sun, X.; Guan, X.; Li, L.; Wang, Y.; Zhang, Y.; et al. The association between early-onset cardiac events caused by neoadjuvant or adjuvant chemotherapy in triple-negative breast cancer patients and some novel autophagy-related polymorphisms in their genomic DNA: A real-world study. *Cancer Commun.* **2018**, *38*, 71. [CrossRef]
61. Berger, M.D.; Yamauchi, S.; Cao, S.; Hanna, D.L.; Sunakawa, Y.; Schirripa, M.; Matsusaka, S.; Yang, D.; Groshen, S.; Zhang, W.; et al. Autophagy-related polymorphisms predict hypertension in patients with metastatic colorectal cancer treated with FOLFIRI and bevacizumab: Results from TRIBE and FIRE-3 trials. *Eur. J. Cancer* **2017**, *77*, 13–20. [CrossRef]
62. Hurley, J.H.; Young, L.N. Mechanisms of autophagy initiation. *Annu. Rev. Biochem.* **2017**, *86*, 225–244. [CrossRef] [PubMed]
63. Kang, R.; Zeh, H.J.; Lotze, M.T.; Tang, D. The Beclin 1 Network Regulates Autophagy and Apoptosis. *Cell Death Differ.* **2011**, *18*, 571–580. [CrossRef] [PubMed]
64. Cianfanelli, V.; De Zio, D.; Di Bartolomeo, S.; Nazio, F.; Strappazzon, F.; Cecconi, F. Ambra1 at a glance. *J. Cell Sci.* **2015**, *128*, 2003–2008. [CrossRef]
65. Kim, Y.M.; Jung, C.H.; Seo, M.; Kim, E.K.; Park, J.M.; Bae, S.S.; Kim, D.H. MTORC1 phosphorylates UVRAG to negatively regulate autophagosome and endosome maturation. *Mol. Cell* **2015**, *57*, 207–218. [CrossRef]
66. Zhong, Y.; Wang, Q.J.; Li, X.; Yan, Y.; Backer, J.M.; Chait, B.T.; Heintz, N.; Yue, Z. Distinct regulation of autophagic activity by Atg14L and Rubicon associated with Beclin 1-phosphatidylinositol-3-kinase complex. *Nat. Cell Biol.* **2009**, *11*, 468–476. [CrossRef] [PubMed]
67. Matsunaga, K.; Saitoh, T.; Tabata, K.; Omori, H.; Satoh, T.; Kurotori, N.; Maejima, I.; Shirahama-Noda, K.; Ichimura, T.; Isobe, T.; et al. Two Beclin 1-binding proteins, Atg14L and Rubicon, reciprocally regulate autophagy at different stages. *Nat. Cell Biol.* **2009**, *11*, 385–396. [CrossRef]
68. Cheng, X.; Ma, X.; Ding, X.; Li, L.; Jiang, X.; Shen, Z.; Chen, S.; Liu, W.; Gong, W.; Sun, Q. Pacer Mediates the Function of Class III PI3K and HOPS Complexes in Autophagosome Maturation by Engaging Stx17. *Mol. Cell* **2017**, *65*, 1029–1043.e5. [CrossRef]

69. Hamet, P.; Haloui, M.; Harvey, F.; Marois-Blanchet, F.-C.; Sylvestre, M.-P.; Tahir, M.-R.; Simon, P.H.G.; Kanzki, B.S.; Raelson, J.; Long, C.; et al. PROX1 gene CC genotype as a major determinant of early onset of type 2 diabetes in slavic study participants from Action in Diabetes and Vascular Disease. *J. Hypertens.* **2017**, *35*, S24–S32. [CrossRef]
70. Kazachkova, N.; Raposo, M.; Ramos, A.; Montiel, R.; Lima, M. Promoter Variant Alters Expression of the Autophagic BECN1 Gene: Implications for Clinical Manifestations of Machado-Joseph Disease. *Cerebellum* **2017**, *16*, 957–963. [CrossRef]
71. Zhao, L.-L.; Liu, H.-L.; Luo, S.; Walsh, K.M.; Li, W.; Wei, Q. Associations of novel variants in PIK3C3, INSR and MAP3K4 of the ATM pathway genes with pancreatic cancer risk. *Am. J. Cancer Res.* **2020**, *10*, 2128–2144.
72. Ng, D.; Hu, N.; Hu, Y.; Wang, C.; Giffen, C.; Tang, Z.-Z.; Han, X.-Y.; Yang, H.H.; Lee, M.P.; Goldstein, A.M.; et al. Replication of a genome-wide case-control study of esophageal squamous cell carcinoma. *Int. J. Cancer* **2008**, *123*, 1610–1615. [CrossRef]
73. Hu, N.; Wang, C.; Hu, Y.; Yang, H.H.; Giffen, C.; Tang, Z.Z.; Han, X.Y.; Goldstein, A.M.; Emmert-Buck, M.R.; Buetow, K.H.; et al. Genome-wide association study in esophageal cancer using GeneChip mapping 10K array. *Cancer Res.* **2005**, *65*, 2542–2546. [CrossRef] [PubMed]
74. Zhang, N.; Zheng, Y.; Liu, J.; Lei, T.; Xu, Y.; Yang, M. Genetic variations associated with telomere length confer risk of gastric cardia adenocarcinoma. *Gastric Cancer* **2019**, *22*, 1089–1099. [CrossRef]
75. Niewold, T.B.; Kariuki, S.N.; Franek, B.S.; Mikolaitis, R.A.; Utset, T.O.; Jolly, M.; Skol, A.D. Promoter variant of PIK3C3 is associated with autoimmunity against Ro and Sm epitopes in African-American lupus patients. *J. Biomed. Biotechnol.* **2010**, 2010.
76. Stopkova, P.; Saito, T.; Papolos, D.F.; Vevera, J.; Paclt, I.; Zukov, I.; Bersson, Y.B.; Margolis, B.A.; Strous, R.D.; Lachman, H.M. Identification of PIK3C3 promoter variant associated with bipolar disorder and schizophrenia. *Biol. Psychiatry* **2004**, *55*, 981–988. [CrossRef] [PubMed]
77. Rietschel, M.; Mattheisen, M.; Degenhardt, F.; Mühleisen, T.W.; Kirsch, P.; Esslinger, C.; Herms, S.; Demontis, D.; Steffens, M.; Strohmaier, J.; et al. Association between genetic variation in a region on chromosome 11 and schizophrenia in large samples from Europe. *Mol. Psychiatry* **2012**, *17*, 906–917. [CrossRef]
78. Mitjans, M.; Begemann, M.; Ju, A.; Dere, E.; Wüstefeld, L.; Hofer, S.; Hassouna, I.; Balkenhol, J.; Oliveira, B.; van der Auwera, S.; et al. Sexual dimorphism of AMBRA1-related autistic features in human and mouse. *Transl. Psychiatry* **2017**, *7*, e1247. [CrossRef]
79. Litchfield, K.; Levy, M.; Orlando, G.; Loveday, C.; Law, P.J.; Migliorini, G.; Holroyd, A.; Broderick, P.; Karlsson, R.; Haugen, T.B.; et al. Identification of 19 new risk loci and potential regulatory mechanisms influencing susceptibility to testicular germ cell tumor. *Nat. Genet.* **2017**, *49*, 1133–1140. [CrossRef]
80. Ross, C.J.; Towfic, F.; Shankar, J.; Laifenfeld, D.; Thoma, M.; Davis, M.; Weiner, B.; Kusko, R.; Zeskind, B.; Knappertz, V.; et al. A pharmacogenetic signature of high response to Copaxone in late-phase clinical-trial cohorts of multiple sclerosis. *Genome Med.* **2017**, *9*, 50. [CrossRef]
81. Kim, H.-K.; Lee, W.-Y.; Kwon, J.-T.; Sohn, D.-R.; Hong, S.-J.; Kim, H.-J. Association of ultraviolet radiation resistance-associated gene polymorphisms with rheumatoid arthritis. *Biomed. Rep.* **2014**, *2*, 117–121. [CrossRef]
82. Jeong, T.-J.; Shin, M.-K.; Uhm, Y.-K.; Kim, H.-J.; Chung, J.-H.; Lee, M.-H. Association of UVRAG polymorphisms with susceptibility to non-segmental vitiligo in a Korean sample. *Exp. Dermatol.* **2010**, *19*, e323–e325. [CrossRef]
83. Mercer, T.J.; Gubas, A.; Tooze, S.A. A Molecular Perspective of Mammalian Autophagosome Biogenesis. *Biol. Chem.* **2018**, *293*, 5386–5395. [CrossRef]
84. Axe, E.L.; Walker, S.A.; Manifava, M.; Chandra, P.; Roderick, H.L.; Habermann, A.; Griffiths, G.; Ktistakis, N.T. Autophagosome formation from membrane compartments enriched in phosphatidylinositol 3-phosphate and dynamically connected to the endoplasmic reticulum. *J. Cell Biol.* **2008**, *182*, 685–701. [CrossRef] [PubMed]
85. Proikas-Cezanne, T.; Takacs, Z.; Dönnes, P.; Kohlbacher, O. WIPI Proteins: Essential PtdIns3P Effectors at the Nascent Autophagosome. *J. Cell Sci.* **2015**, *128*, 207–217. [CrossRef]
86. Dooley, H.C.; Razi, M.; Polson, H.E.J.; Girardin, S.E.; Wilson, M.I.; Tooze, S.A. WIPI2 Links LC3 Conjugation with PI3P, Autophagosome Formation, and Pathogen Clearance by Recruiting Atg12-5-16L1. *Mol. Cell* **2014**, *55*, 238–252. [CrossRef]
87. Bakula, D.; Müller, A.J.; Zuleger, T.; Takacs, Z.; Franz-Wachtel, M.; Thost, A.K.; Brigger, D.; Tschan, M.P.; Frickey, T.; Robenek, H.; et al. WIPI3 and WIPI4 β-propellers are scaffolds for LKB1-AMPK-TSC signalling circuits in the control of autophagy. *Nat. Commun.* **2017**, *8*, 1–18. [CrossRef] [PubMed]

88. Osawa, T.; Kotani, T.; Kawaoka, T.; Hirata, E.; Suzuki, K.; Nakatogawa, H.; Ohsumi, Y.; Noda, N.N. Atg2 mediates direct lipid transfer between membranes for autophagosome formation. *Nat. Struct. Mol. Biol.* **2019**, *26*, 281–288. [CrossRef]
89. Osawa, T.; Noda, N.N. Atg2: A novel phospholipid transfer protein that mediates de novo autophagosome biogenesis. *Protein Sci. A Publ. Protein Soc.* **2019**, *28*, 1005–1012. [CrossRef]
90. Filimonenko, M.; Isakson, P.; Finley, K.D.; Anderson, M.; Jeong, H.; Melia, T.J.; Bartlett, B.J.; Myers, K.M.; Birkeland, H.C.G.; Lamark, T.; et al. The Selective Macroautophagic Degradation of Aggregated Proteins Requires the PI3P-Binding Protein Alfy. *Mol. Cell* **2010**, *38*, 265–279. [CrossRef]
91. Noda, T. Autophagy in the Context of the Cellular Membrane-Trafficking System: The Enigma of Atg9 Vesicles. *Biochem. Soc. Trans.* **2017**, *45*, 1323–1331. [CrossRef]
92. Orsi, A.; Razi, M.; Dooley, H.C.; Robinson, D.; Weston, A.E.; Collinson, L.M.; Tooze, S.A. Dynamic and transient interactions of Atg9 with autophagosomes, but not membrane integration, are required for autophagy. *Mol. Biol. Cell* **2012**, *23*, 1860–1873. [CrossRef] [PubMed]
93. Sobota, R.S.; Stein, C.M.; Kodaman, N.; Maro, I.; Wieland-Alter, W.; Igo, R.P.; Magohe, A.; Malone, L.L.; Chervenak, K.; Hall, N.B.; et al. A chromosome 5q31.1 locus associates with tuberculin skin test reactivity in HIV-positive individuals from tuberculosis hyper-endemic regions in east Africa. *PLoS Genet.* **2017**, *13*, e1006710. [CrossRef] [PubMed]
94. Kadir, R.; Harel, T.; Markus, B.; Perez, Y.; Bakhrat, A.; Cohen, I.; Volodarsky, M.; Feintsein-Linial, M.; Chervinski, E.; Zlotogora, J.; et al. ALFY-Controlled DVL3 Autophagy Regulates Wnt Signaling, Determining Human Brain Size. *PLoS Genet.* **2016**, *12*, e1005919. [CrossRef]
95. Lesseur, C.; Diergaarde, B.; Olshan, A.F.; Wünsch-Filho, V.; Ness, A.R.; Liu, G.; Lacko, M.; Eluf-Neto, J.; Franceschi, S.; Lagiou, P.; et al. Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer. *Nat. Genet.* **2016**, *48*, 1544–1550. [CrossRef]
96. Ohba, C.; Nabatame, S.; Iijima, Y.; Nishiyama, K.; Tsurusaki, Y.; Nakashima, M.; Miyake, N.; Tanaka, F.; Ozono, K.; Saitsu, H.; et al. De novo WDR45 mutation in a patient showing clinically Rett syndrome with childhood iron deposition in brain. *J. Hum. Genet.* **2014**, *59*, 292–295. [CrossRef] [PubMed]
97. Tschentscher, A.; Dekomien, G.; Ross, S.; Cremer, K.; Kukuk, G.M.; Epplen, J.T.; Hoffjan, S. Analysis of the C19orf12 and WDR45 genes in patients with neurodegeneration with brain iron accumulation. *J. Neurol. Sci.* **2015**, *349*, 105–109. [CrossRef]
98. Saitsu, H.; Nishimura, T.; Muramatsu, K.; Kodera, H.; Kumada, S.; Sugai, K.; Kasai-Yoshida, E.; Sawaura, N.; Nishida, H.; Hoshino, A.; et al. De novo mutations in the autophagy gene WDR45 cause static encephalopathy of childhood with neurodegeneration in adulthood. *Nat. Genet.* **2013**, *45*, 445–449.
99. Lee, H.-S.; Park, T. Nuclear receptor and VEGF pathways for gene-blood lead interactions, on bone mineral density, in Korean smokers. *PLoS ONE* **2018**, *13*, e0193323. [CrossRef]
100. Suleiman, J.; Allingham-Hawkins, D.; Hashem, M.; Shamseldin, H.E.; Alkuraya, F.S.; El-Hattab, A.W. WDR45B-related intellectual disability, spastic quadriplegia, epilepsy, and cerebral hypoplasia: A consistent neurodevelopmental syndrome. *Clin. Genet.* **2018**, *93*, 360–364. [CrossRef]
101. Brinar, M.; Vermeire, S.; Cleynen, I.; Lemmens, B.; Sagaert, X.; Henckaerts, L.; Van Assche, G.; Geboes, K.; Rutgeerts, P.; De Hertogh, G. Genetic variants in autophagy-related genes and granuloma formation in a cohort of surgically treated Crohn's disease patients. *J. Crohn's Colitis* **2012**, *6*, 43–50. [CrossRef]
102. Yamada, Y.; Sakuma, J.; Takeuchi, I.; Yasukochi, Y.; Kato, K.; Oguri, M.; Fujimaki, T.; Horibe, H.; Muramatsu, M.; Sawabe, M.; et al. Identification of C21orf59 and ATG2A as novel determinants of renal function-related traits in Japanese by exome-wide association studies. *Oncotarget* **2017**, *8*, 45259–45273. [CrossRef] [PubMed]
103. Fernández-Mateos, J.; Seijas-Tamayo, R.; Klain, J.C.A.; Borgonõn, M.P.; Pérez-Ruiz, E.; Mesiá, R.; Del Barco, E.; Coloma, C.S.; Dominguez, A.R.; Daroqui, J.C.; et al. Analysis of autophagy gene polymorphisms in Spanish patients with head and neck squamous cell carcinoma. *Sci. Rep.* **2017**, *7*, 1–8. [CrossRef] [PubMed]
104. Buffen, K.; Oosting, M.; Quintin, J.; Ng, A.; Kleinnijenhuis, J.; Kumar, V.; van de Vosse, E.; Wijmenga, C.; van Crevel, R.; Oosterwijk, E.; et al. Autophagy Controls BCG-Induced Trained Immunity and the Response to Intravesical BCG Therapy for Bladder Cancer. *PLoS Pathog.* **2014**, *10*, e1004485. [CrossRef] [PubMed]
105. Mehrabi Pour, M.; Nasiri, M.; Kamfiroozie, H.; Zibaeenezhad, M.J. Association of the ATG9B gene polymorphisms with coronary artery disease susceptibility: A case-control study. *J. Cardiovasc. Thorac. Res.* **2019**, *11*, 109–115. [CrossRef]
106. Mizushima, N. The ATG conjugation systems in autophagy. *Curr. Opin. Cell Biol.* **2020**, *63*, 1–10. [CrossRef]

107. Hanada, T.; Noda, N.N.; Satomi, Y.; Ichimura, Y.; Fujioka, Y.; Takao, T.; Inagaki, F.; Ohsumi, Y. The Atg12-Atg5 conjugate has a novel E3-like activity for protein lipidation in autophagy. *J. Biol. Chem.* **2007**, *282*, 37298–37302. [CrossRef]
108. Khor, B.; Conway, K.L.; Omar, A.S.; Biton, M.; Haber, A.L.; Rogel, N.; Baxt, L.A.; Begun, J.; Kuballa, P.; Gagnon, J.D.; et al. Distinct Tissue-Specific Roles for the Disease-Associated Autophagy Genes ATG16L2 and ATG16L1. *J. Immunol.* **2019**, *203*, 1820–1829. [CrossRef]
109. Ishibashi, K.; Fujita, N.; Kanno, E.; Omori, H.; Yoshimori, T.; Itoh, T.; Fukuda, M. Atg16L2, a novel isoform of mammalian Atg16L that is not essential for canonical autophagy despite forming an Atg12-5-16L2 complex. *Autophagy* **2011**, *7*, 1500–1513. [CrossRef]
110. Wesch, N.; Kirkin, V.; Rogov, V.V. Atg8-Family Proteins-Structural Features and Molecular Interactions in Autophagy and Beyond. *Cells* **2020**, *9*, 2008. [CrossRef]
111. Fernandez, A.F.; Lopez-Otin, C. The functional and pathologic relevance of autophagy proteases. *J. Clin. Investig.* **2015**, *125*, 33–41. [CrossRef]
112. Nair, U.; Yen, W.L.; Mari, M.; Cao, Y.; Xie, Z.; Baba, M.; Reggiori, F.; Klionsky, D.J. A role for Atg8-PE deconjugation in autophagosome biogenesis. *Autophagy* **2012**, *8*, 780–793. [CrossRef] [PubMed]
113. Yu, Z.Q.; Ni, T.; Hong, B.; Wang, H.Y.; Jiang, F.J.; Zou, S.; Chen, Y.; Zheng, X.L.; Klionsky, D.J.; Liang, Y.; et al. Dual roles of Atg8 - PE deconjugation by Atg4 in autophagy. *Autophagy* **2012**, *8*, 883–892. [CrossRef] [PubMed]
114. Yang, Z.; Liu, Z. Potentially functional variants of autophagy-related genes are associated with the efficacy and toxicity of radiotherapy in patients with nasopharyngeal carcinoma. *Mol. Genet. Genom. Med.* **2019**, *7*, 1–8. [CrossRef]
115. Song, X.; Yuan, Z.; Yuan, H.; Wang, L.; Ji, P.; Jin, G.; Dai, J.; Ma, H. ATG12 expression quantitative trait loci associated with head and neck squamous cell carcinoma risk in a Chinese Han population. *Mol. Carcinog.* **2018**, *57*, 1030–1037. [CrossRef] [PubMed]
116. Yang, P.W.; Hsieh, M.S.; Chang, Y.H.; Huang, P.M.; Lee, J.M. Genetic polymorphisms of ATG5 predict survival and recurrence in patients with early-stage esophageal squamous cell carcinoma. *Oncotarget* **2017**, *8*, 91494–91504. [CrossRef]
117. Shen, M.; Lin, L. Functional variants of autophagy-related genes are associated with the development of hepatocellular carcinoma. *Life Sci.* **2019**, *235*, 116675. [CrossRef]
118. Yuan, J.; Zhang, N.; Yin, L.; Zhu, H.; Zhang, L.; Zhou, L.; Yang, M. Clinical Implications of the Autophagy Core Gene Variations in Advanced Lung Adenocarcinoma Treated with Gefitinib. *Sci. Rep.* **2017**, *7*, 1–10. [CrossRef] [PubMed]
119. White, K.A.M.; Luo, L.; Thompson, T.A.; Torres, S.; Hu, C.A.A.; Thomas, N.E.; Lilyquist, J.; Anton-Culver, H.; Gruber, S.B.; From, L.; et al. Variants in autophagy-related genes and clinical characteristics in melanoma: A population-based study. *Cancer Med.* **2016**, *5*, 3336–3345. [CrossRef]
120. Li, Q.X.; Zhou, X.; Huang, T.T.; Tang, Y.; Liu, B.; Peng, P.; Sun, L.; Wang, Y.H.; Yuan, X.L. The Thr300Ala variant of ATG16L1 is associated with decreased risk of brain metastasis in patients with non-small cell lung cancer. *Autophagy* **2017**, *13*, 1053–1063. [CrossRef]
121. Li, M.; Ma, F.; Wang, J.; Li, Q.; Zhang, P.; Yuan, P.; Luo, Y.; Cai, R.; Fan, Y.; Chen, S.; et al. Genetic polymorphisms of autophagy-related gene 5 (ATG5) rs473543 predict different disease-free survivals of triple-negative breast cancer patients receiving anthracycline- and/or taxane-based adjuvant chemotherapy. *Chin. J. Cancer* **2018**, *37*, 4. [CrossRef]
122. Zhou, J.; Hang, D.; Jiang, Y.; Chen, J.; Han, J.; Zhou, W.; Jin, G.; Ma, H.; Dai, J. Evaluation of genetic variants in autophagy pathway genes as prognostic biomarkers for breast cancer. *Gene* **2017**, *627*, 549–555. [CrossRef] [PubMed]
123. Michailidou, K.; Beesley, J.; Lindstrom, S.; Canisius, S.; Dennis, J.; Lush, M.J.; Maranian, M.J.; Bolla, M.K.; Wang, Q.; Shah, M.; et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat. Genet.* **2015**, *47*, 373–380. [CrossRef] [PubMed]
124. Qin, Z.; Xue, J.; He, Y.; Ma, H.; Jin, G.; Chen, J.; Hu, Z.; Liu, X.a.; Shen, H. Potentially functional polymorphisms in ATG10 are associated with risk of breast cancer in a Chinese population. *Gene* **2013**, *527*, 491–495. [CrossRef] [PubMed]
125. Santoni, M.; Piva, F.; De Giorgi, U.; Mosca, A.; Basso, U.; Santini, D.; Buti, S.; Lolli, C.; Terrone, C.; Maruzzo, M.; et al. Autophagic gene polymorphisms in liquid biopsies and outcome of patients with metastatic clear cell renal cell carcinoma. *Anticancer Res.* **2018**, *38*, 5773–5782. [CrossRef]
126. Nikseresht, M.; Shahverdi, M.; Dehghani, M.; Abidi, H.; Mahmoudi, R.; Ghalamfarsa, G.; Manzouri, L.; Ghavami, S. Association of single nucleotide autophagy-related protein 5 gene polymorphism rs2245214 with susceptibility to non–small cell lung cancer. *J. Cell. Biochem.* **2019**, *120*, 1924–1931. [CrossRef]

127. Xie, K.; Liang, C.; Li, Q.; Yan, C.; Wang, C.; Gu, Y.; Zhu, M.; Du, F.; Wang, H.; Dai, J.; et al. Role of ATG10 expression quantitative trait loci in non-small cell lung cancer survival. *Int. J. Cancer* **2016**, *139*, 1564–1573. [CrossRef]
128. Mitchell, J.S.; Li, N.; Weinhold, N.; Försti, A.; Ali, M.; Van Duin, M.; Thorleifsson, G.; Johnson, D.C.; Chen, B.; Halvarsson, B.M.; et al. Genome-wide association study identifies multiple susceptibility loci for multiple myeloma. *Nat. Commun.* **2016**, *7*, 22. [CrossRef]
129. Plantinga, T.S.; van de Vosse, E.; Huijbers, A.; Netea, M.G.; Joosten, L.A.B.; Smit, J.W.A.; Netea-Maier, R.T. Role of Genetic Variants of Autophagy Genes in Susceptibility for Non-Medullary Thyroid Cancer and Patients Outcome. *PLoS ONE* **2014**, *9*, e94086. [CrossRef]
130. Huijbers, A.; Plantinga, T.S.; Joosten, L.A.B.; Aben, K.K.H.; Gudmundsson, J.; den Heijer, M.; Kiemeney, L.A.L.M.; Netea, M.G.; Hermus, A.R.M.M.; Netea-Maier, R.T. The effect of the ATG16L1 Thr300Ala Polymorphism on Susceptibility and Outcome of Patients with Epithelial Cell-Derived Thyroid Carcinoma. *Endocr. Relat. Cancer* **2012**, *19*, L15–L18. [CrossRef]
131. Grimm, W.A.; Messer, J.S.; Murphy, S.F.; Nero, T.; Lodolce, J.P.; Weber, C.R.; Logsdon, M.F.; Bartulis, S.; Sylvester, B.E.; Springer, A.; et al. The Thr300Ala variant in ATG16L1 is associated with improved survival in human colorectal cancer and enhanced production of type I interferon. *Gut* **2016**, *65*, 456–464. [CrossRef]
132. Burada, F.; Ciurea, M.E.; Nicoli, R.; Streata, I.; Vilcea, I.D.; Rogoveanu, I.; Ioana, M. ATG16L1 T300A Polymorphism is Correlated with Gastric Cancer Susceptibility. *Pathol. Oncol. Res.* **2016**, *22*, 317–322. [CrossRef] [PubMed]
133. Huang, C.Y.; Huang, S.P.; Lin, V.C.; Yu, C.C.; Chang, T.Y.; Lu, T.L.; Chiang, H.C.; Bao, B.Y. Genetic variants of the autophagy pathway as prognostic indicators for prostate cancer. *Sci. Rep.* **2015**, *5*, 14045. [CrossRef] [PubMed]
134. Xia, L.; Xu, J.; Song, J.; Xu, Y.; Zhang, B.; Gao, C.; Zhu, D.; Zhou, C.; Bi, D.; Wang, Y.; et al. Autophagy-Related Gene 7 Polymorphisms and Cerebral Palsy in Chinese Infants. *Front. Cell. Neurosci.* **2019**, *13*, 494. [CrossRef] [PubMed]
135. Xu, J.; Xia, L.; Shang, Q.; Du, J.; Zhu, D.; Wang, Y.; Bi, D.; Song, J.; Ma, C.; Gao, C.; et al. A Variant of the Autophagy-Related 5 Gene Is Associated with Child Cerebral Palsy. *Cell. Neurosci.* **2017**, *11*, 407. [CrossRef]
136. Metzger, S.; Saukko, M.; Van Che, H.; Tong, L.; Puder, Y.; Riess, O.; Nguyen, H.P. Age at onset in Huntington's disease is modified by the autophagy pathway: Implication of the V471A polymorphism in Atg7. *Hum. Genet.* **2010**, *128*, 453–459. [CrossRef]
137. Metzger, S.; Walter, C.; Riess, O.; Roos, R.A.C.; Nielsen, J.E.; Craufurd, D.; Nguyen, H.P. The V471A Polymorphism in Autophagy-Related Gene ATG7 Modifies Age at Onset Specifically in Italian Huntington Disease Patients. *PLoS ONE* **2013**, *8*, e68951. [CrossRef]
138. Kim, M.; Sandford, E.; Gatica, D.; Qiu, Y.; Liu, X.; Zheng, Y.; Schulman, B.A.; Xu, J.; Semple, I.; Ro, S.H.; et al. Mutation in ATG5 reduces autophagy and leads to ataxia with developmental delay. *eLife* **2016**, *5*, e12245. [CrossRef]
139. Chen, D.; Zhu, C.; Wang, X.; Feng, X.; Pang, S.; Huang, W.; Hawley, R.G.; Yan, B. A novel and functional variant within the ATG5 gene promoter in sporadic Parkinson's disease. *Neurosci. Lett.* **2013**, *538*, 49–53. [CrossRef]
140. Yuan, J.; Han, R.; Esther, A.; Wu, Q.; Yang, J.; Yan, W.; Ji, X.; Liu, Y.; Li, Y.; Yao, W.; et al. Polymorphisms in autophagy related genes and the coal workers' pneumoconiosis in a Chinese population. *Gene* **2017**, *632*, 36–42. [CrossRef]
141. Lee, T.H.; Ko, T.M.; Chen, C.H.; Chang, Y.J.; Lu, L.S.; Chang, C.H.; Huang, K.L.; Chang, T.Y.; Lee, J.D.; Chang, K.C.; et al. A genome-wide association study links small-vessel ischemic stroke to autophagy. *Sci. Rep.* **2017**, *7*, 1–7. [CrossRef]
142. Hampe, J.; Franke, A.; Rosenstiel, P.; Till, A.; Teuber, M.; Huse, K.; Albrecht, M.; Mayr, G.; De La Vega, F.M.; Briggs, J.; et al. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. *Nat. Genet.* **2007**, *39*, 207–211. [CrossRef] [PubMed]
143. Chauhan, S.; Mandell, M.A.; Deretic, V. IRGM governs the core autophagy machinery to conduct antimicrobial defense. *Mol. Cell* **2015**, *58*, 507–521. [CrossRef] [PubMed]
144. Bekpen, C.; Xavier, R.J.; Eichler, E.E. Human IRGM gene "to be or not to be". *Semin. Immunopathol.* **2010**, *32*, 437–444. [CrossRef] [PubMed]
145. Dezelak, M.; Repnik, K.; Koder, S.; Ferkolj, I.; Potočnik, U. A Prospective Pharmacogenomic Study of Crohn's Disease Patients during Routine Therapy with Anti-TNF-α Drug Adalimumab: Contribution of ATG5, NFKB1, and CRP Genes to Pharmacodynamic Variability. *Omics A J. Integr. Biol.* **2016**, *20*, 296–309. [CrossRef] [PubMed]
146. Usategui-Martín, R.; García-Aparicio, J.; Corral-Gudino, L.; Calero-Paniagua, I.; Del Pino-Montes, J.; González Sarmiento, R. Polymorphisms in Autophagy Genes Are Associated with Paget Disease of Bone. *PLoS ONE* **2015**, *10*, e0128984. [CrossRef] [PubMed]

147. Kamel, A.M.; Badary, M.S.; Mohamed, W.A.; Ahmed, G.H.; El-Feky, M.A. Evaluation of autophagy-related genes in Egyptian systemic lupus erythematosus patients. *Int. J. Rheum. Dis.* **2020**, *5*, 1–7. [CrossRef]
148. Ciccacci, C.; Perricone, C.; Alessandri, C.; Latini, A.; Politi, C.; Delunardo, F.; Pierdominici, M.; Conti, F.; Novelli, G.; Ortona, E.; et al. Evaluation of ATG5 polymorphisms in Italian patients with systemic lupus erythematosus: Contribution to disease susceptibility and clinical phenotypes. *Lupus* **2018**, *27*, 1464–1469. [CrossRef]
149. Dang, J.; Li, J.; Xin, Q.; Shan, S.; Bian, X.; Yuan, Q.; Liu, N.; Ma, X.; Li, Y.; Liu, Q. Gene–gene interaction of ATG5, ATG7, BLK and BANK1 in systemic lupus erythematosus. *Int. J. Rheum. Dis.* **2016**, *19*, 1284–1293. [CrossRef]
150. López, P.; Alonso-Pérez, E.; Rodríguez-Carrio, J.; Suárez, A. Influence of Atg5 Mutation in SLE Depends on Functional IL-10 Genotype. *PLoS ONE* **2013**, *8*, e78756. [CrossRef]
151. Alonso-Perez, E.; Suarez-Gestal, M.; Calaza, M.; Ordi-Ros, J.; Balada, E.; Bijl, M.; Papasteriades, C.; Carreira, P.; Skopouli, F.N.; Witte, T.; et al. Further Evidence of Subphenotype Association with Systemic Lupus Erythematosus Susceptibility Loci: A European Cases Only Study. *PLoS ONE* **2012**, *7*, e45356. [CrossRef]
152. Zhou, X.J.; Lu, X.L.; Lv, J.C.; Yang, H.Z.; Qin, L.X.; Zhao, M.H.; Su, Y.; Li, Z.G.; Zhang, H. Genetic association of PRDM1-ATG5 intergenic region and autophagy with systemic lupus erythematosus in a Chinese population. *Ann. Rheum. Dis.* **2011**, *70*, 1330–1337. [CrossRef] [PubMed]
153. Harley, J.B.; Alarcón-Riquelme, M.E.; Criswell, L.A.; Jacob, C.O.; Kimberly, R.P.; Moser, K.L.; Tsao, B.P.; Vyse, T.J.; Langefeld, C.D.; Nath, S.K.; et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. *Nat. Genet.* **2008**, *40*, 204–210. [CrossRef] [PubMed]
154. Zheng, M.; Yu, H.; Zhang, L.; Li, H.; Liu, Y.; Kijlstra, A.; Yang, P. Association of ATG5 gene polymorphisms with behçet's disease and ATG10 gene polymorphisms with VKH syndrome in a chinese han population. *Investig. Ophthalmol. Vis. Sci.* **2015**, *56*, 8280–8287. [CrossRef] [PubMed]
155. Cai, P.P.; Wang, H.X.; Zhuang, J.C.; Liu, Q.B.; Zhao, G.X.; Li, Z.X.; Wu, Z.Y. Variants of autophagy-related gene 5 are associated with neuromyelitis optica in the Southern Han Chinese population. *Autoimmunity* **2014**, *47*, 563–566. [CrossRef] [PubMed]
156. Mayes, M.D.; Bossini-Castillo, L.; Gorlova, O.; Martin, J.E.; Zhou, X.; Chen, W.V.; Assassi, S.; Ying, J.; Tan, F.K.; Arnett, F.C.; et al. Immunochip analysis identifies multiple susceptibility loci for systemic sclerosis. *Am. J. Hum. Genet.* **2014**, *94*, 47–61. [CrossRef]
157. Martin, J.E.; Assassi, S.; Diaz-Gallo, L.M.; Broen, J.C.; Simeon, C.P.; Castellvi, I.; Vicente-Rabaneda, E.; Fonollosa, V.; Ortego-Centeno, N.; González-Gay, M.A.; et al. A systemic sclerosis and systemic lupus erythematosus pan-meta-GWAS reveals new shared susceptibility loci. *Hum. Mol. Genet.* **2013**, *22*, 4021–4029. [CrossRef]
158. You, Y.; Huo, J.; Huang, J.; Wang, M.; Shao, Y.; Ge, M.; Li, X.; Huang, Z.; Zhang, J.; Nie, N.; et al. Contribution of autophagy-related gene 5 variants to acquired aplastic anemia in Han-Chinese population. *J. Cell. Biochem.* **2019**, *120*, 11409–11417. [CrossRef]
159. Martin, L.J.; Gupta, J.; Jyothula, S.S.S.K.; Butsch Kovacic, M.; Biagini Myers, J.M.; Patterson, T.L.; Ericksen, M.B.; He, H.; Gibson, A.M.; Baye, T.M.; et al. Functional Variant in the Autophagy-Related 5 Gene Promotor is Associated with Childhood Asthma. *PLoS ONE* **2012**, *7*, e33454. [CrossRef]
160. Poon, A.H.; Chouiali, F.; Tse, S.M.; Litonjua, A.A.; Hussain, S.N.A.; Baglole, C.J.; Eidelman, D.H.; Olivenstein, R.; Martin, J.G.; Weiss, S.T.; et al. Genetic and histologic evidence for autophagy in asthma pathogenesis. *J. Allergy Clin. Immunol.* **2012**, *129*, 569–571. [CrossRef]
161. Jansen, A.F.M.; Schoffelen, T.; Bleeker-Rovers, C.P.; Wever, P.C.; Jaeger, M.; Oosting, M.; Adriaans, A.; Joosten, L.A.B.; Netea, M.G.; van Deuren, M.; et al. Genetic variations in innate immunity genes affect response to Coxiella burnetii and are associated with susceptibility to chronic Q fever. *Clin. Microbiol. Infect.* **2019**, *25*, e11–e631. [CrossRef]
162. Shao, Y.; Chen, F.; Chen, Y.; Zhang, W.; Lin, Y.; Cai, Y.; Yin, Z.; Tao, S.; Liao, Q.; Zhao, J.; et al. Association between genetic polymorphisms in the autophagy-related 5 gene promoter and the risk of sepsis. *Sci. Rep.* **2017**, *7*, 1–14. [CrossRef] [PubMed]
163. Li, N.; Fan, X.; Wang, X.; Zhang, X.; Zhang, K.; Han, Q.; Lv, Y.; Liu, Z. Genetic association of polymorphisms at the intergenic region between PRDM1 and ATG5 with hepatitis B virus infection in Han Chinese patients. *J. Med Virol.* **2020**, *92*, 1198–1205. [CrossRef] [PubMed]
164. Li, N.; Fan, X.; Wang, X.; Deng, H.; Zhang, K.; Zhang, X.; Han, Q.; Lv, Y.; Liu, Z. Autophagy-Related 5 Gene rs510432 Polymorphism Is Associated with Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Virus Infection. *Immunol. Investig.* **2019**, *48*, 378–391. [CrossRef]

165. Tanaka, S.; Nagashima, H.; Uotani, T.; Graham, D.Y.; Yamaoka, Y. Autophagy-related genes in Helicobacter pylori infection. *Helicobacter* **2017**, *22*, 1–10. [CrossRef]
166. Castaño-Rodríguez, N.; Kaakoush, N.O.; Goh, K.L.; Fock, K.M.; Mitchell, H.M. Autophagy in Helicobacter pylori Infection and Related Gastric Cancer. *Helicobacter* **2015**, *20*, 353–369. [CrossRef] [PubMed]
167. Raju, D.; Hussey, S.; Ang, M.; Terebiznik, M.R.; Sibony, M.; Galindo-Mata, E.; Gupta, V.; Blanke, S.R.; Delgado, A.; Romero-Gallo, J.; et al. Vacuolating cytotoxin and variants in Atg16L1 that disrupt autophagy promote helicobacter pylori infection in humans. *Gastroenterology* **2012**, *142*, 1160–1171. [CrossRef] [PubMed]
168. Douroudis, K.; Kingo, K.; Traks, T.; Rätsep, R.; Silm, H.; Vasar, E.; Kõks, S. ATG16L1 gene polymorphisms are associated with palmoplantar pustulosis. *Hum. Immunol.* **2011**, *72*, 613–615. [CrossRef] [PubMed]
169. Douroudis, K.; Kingo, K.; Traks, T.; Reimann, E.; Raud, K.; Rätsep, R.; Mössner, R.; Silm, H.; Vasar, E.; Kõks, S. Polymorphisms in the ATG16L1 Gene are Associated with Psoriasis Vulgaris. *Acta Derm. Venereol.* **2012**, *92*, 85–87. [CrossRef]
170. Mao, J.J.; Wu, L.X.; Wang, W.; Ye, Y.Y.; Yang, J.; Chen, H.; Yang, Q.F.; Zhang, X.Y.; Wang, B.; Chen, W.X. Nucleotide variation in ATG4A and susceptibility to cervical cancer in southwestern chinese women. *Oncol. Lett.* **2018**, *15*, 2992–3000. [CrossRef]
171. He, Q.; Lu, Y.; Hu, S.; Huang, Q.; Li, S.; Huang, Y.; Hu, Q.; Wu, L.; Chen, W. An intron SNP rs807185 in ATG4A decreases the risk of lung cancer in a southwest Chinese population. *Eur. J. Cancer Prev.* **2016**, *25*, 255–258. [CrossRef]
172. Turcot, V.; Lu, Y.; Highland, H.M.; Schurmann, C.; Justice, A.E.; Fine, R.S.; Bradfield, J.P.; Esko, T.; Giri, A.; Graff, M.; et al. Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity. *Nat. Genet.* **2018**, *50*, 26–41. [CrossRef]
173. Franceschini, N.; Giambartolomei, C.; de Vries, P.S.; Finan, C.; Bis, J.C.; Huntley, R.P.; Lovering, R.C.; Tajuddin, S.M.; Winkler, T.W.; Graff, M.; et al. GWAS and colocalization analyses implicate carotid intima-media thickness and carotid plaque loci in cardiovascular outcomes. *Nat. Commun.* **2018**, *9*, 1–14. [CrossRef] [PubMed]
174. Wu, C.; Wen, Y.; Guo, X.; Yang, T.; Shen, H.; Chen, X.; Tian, Q.; Tan, L.; Deng, H.W.; Zhang, F. Genetic association, mRNA and protein expression analysis identify ATG4C as a susceptibility gene for Kashin–Beck disease. *Osteoarthr. Cartil.* **2017**, *25*, 281–286. [CrossRef] [PubMed]
175. Portilla-Fernandez, E.; Ghanbari, M.; van Meurs, J.B.J.; Danser, A.H.J.; Franco, O.H.; Muka, T.; Roks, A.; Dehghan, A. Dissecting the association of autophagy-related genes with cardiovascular diseases and intermediate vascular traits: A population-based approach. *PLoS ONE* **2019**, *14*, e0214137. [CrossRef]
176. Hysi, P.G.; Choquet, H.; Khawaja, A.P.; Wojciechowski, R.; Tedja, M.S.; Yin, J.; Simcoe, M.J.; Patasova, K.; Mahroo, O.A.; Thai, K.K.; et al. Meta-analysis of 542,934 subjects of European ancestry identifies new genes and mechanisms predisposing to refractive error and myopia. *Nat. Genet.* **2020**, *52*, 401–407. [CrossRef]
177. Qi, Y.Y.; Zhou, X.J.; Nath, S.K.; Sun, C.; Wang, Y.N.; Hou, P.; Mu, R.; Li, C.; Guo, J.P.; Li, Z.G.; et al. A Rare Variant (rs933717) at FBXO31-MAP1LC3B in Chinese Is Associated With Systemic Lupus Erythematosus. *Arthritis Rheumatol.* **2018**, *70*, 287–297. [CrossRef] [PubMed]
178. Johansen, T.; Lamark, T. Selective Autophagy: ATG8 Family Proteins, LIR Motifs and Cargo Receptors. *J. Mol. Biol.* **2020**, *432*, 80–103. [CrossRef]
179. Khaminets, A.; Behl, C.; Dikic, I. Ubiquitin-Dependent and Independent Signals In Selective Autophagy. *Trends Cell Biol.* **2016**, *26*, 6–16. [CrossRef]
180. Katsuragi, Y.; Ichimura, Y.; Komatsu, M. P62/SQSTM1 Functions as a Signaling Hub and an Autophagy Adaptor. *FEBS J.* **2015**, *82*, 4672–4678. [CrossRef]
181. Kirkin, V.; McEwan, D.G.; Novak, I.; Dikic, I. *A Role for Ubiquitin in Selective Autophagy*; Elsevier: Amsterdam, The Netherlands, 2009; Volume 34, pp. 259–269.
182. Korac, J.; Schaeffer, V.; Kovacevic, I.; Clement, A.M.; Jungblut, B.; Behl, C.; Terzic, J.; Dikic, I. Ubiquitin-independent function of optineurin in autophagic clearance of protein aggregates. *J. Cell Sci.* **2013**, *126*, 580–592. [CrossRef]
183. Lazarou, M.; Sliter, D.A.; Kane, L.A.; Sarraf, S.A.; Wang, C.; Burman, J.L.; Sideris, D.P.; Fogel, A.I.; Youle, R.J. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature* **2015**, *524*, 309–314. [CrossRef]
184. Wild, P.; Farhan, H.; McEwan, D.G.; Wagner, S.; Rogov, V.V.; Brady, N.R.; Richter, B.; Korac, J.; Waidmann, O.; Choudhary, C.; et al. Phosphorylation of the autophagy receptor optineurin restricts Salmonella growth. *Science* **2011**, *333*, 228–233. [CrossRef] [PubMed]

185. Vargas, J.N.S.; Wang, C.; Bunker, E.; Hao, L.; Maric, D.; Schiavo, G.; Randow, F.; Youle, R.J. Spatiotemporal Control of ULK1 Activation by NDP52 and TBK1 during Selective Autophagy. *Mol. Cell* **2019**, *74*, 347–362.e6. [CrossRef]
186. Ravenhill, B.J.; Boyle, K.B.; von Muhlinen, N.; Ellison, C.J.; Masson, G.R.; Otten, E.G.; Foeglein, A.; Williams, R.; Randow, F. The Cargo Receptor NDP52 Initiates Selective Autophagy by Recruiting the ULK Complex to Cytosol-Invading Bacteria. *Mol. Cell* **2019**, *74*, 320–329.e6. [CrossRef] [PubMed]
187. Tumbarello, D.A.; Manna, P.T.; Allen, M.; Bycroft, M.; Arden, S.D.; Kendrick-Jones, J.; Buss, F. The Autophagy Receptor TAX1BP1 and the Molecular Motor Myosin VI Are Required for Clearance of Salmonella Typhimurium by Autophagy. *PLoS Pathog.* **2015**, *11*, e1005174. [CrossRef] [PubMed]
188. Lu, K.; Psakhye, I.; Jentsch, S. Autophagic clearance of PolyQ proteins mediated by ubiquitin-Atg8 adaptors of the conserved CUET protein family. *Cell* **2014**, *158*, 549–563. [CrossRef] [PubMed]
189. Gatica, D.; Lahiri, V.; Klionsky, D.J. Cargo recognition and degradation by selective autophagy. *Nat. Cell Biol.* **2018**, *20*, 233–242. [CrossRef]
190. Yoo, S.M.; Jung, Y.K. A Molecular Approach to Mitophagy and Mitochondrial Dynamics. *Mol. Cells* **2018**, *41*, 18–26.
191. Wei, Y.; Chiang, W.C.; Sumpter, R.; Mishra, P.; Levine, B. Prohibitin 2 Is an Inner Mitochondrial Membrane Mitophagy Receptor. *Cell* **2017**, *168*, 224–238.e10. [CrossRef]
192. Princely Abudu, Y.; Pankiv, S.; Mathai, B.J.; Håkon Lystad, A.; Bindesbøll, C.; Brenne, H.B.; Yoke Wui Ng, M.; Thiede, B.; Yamamoto, A.; Mutugi Nthiga, T.; et al. NIPSNAP1 and NIPSNAP2 Act as "Eat Me" Signals for Mitophagy. *Dev. Cell* **2019**, *49*, 509–525.e12. [CrossRef]
193. Kirkin, V.; Rogov, V.V. A Diversity of Selective Autophagy Receptors Determines the Specificity of the Autophagy Pathway. *Mol. Cell* **2019**, *76*, 268–285. [CrossRef] [PubMed]
194. Martinez-Lopez, N.; Garcia-Macia, M.; Sahu, S.; Athonvarangkul, D.; Liebling, E.; Merlo, P.; Cecconi, F.; Schwartz, G.J.; Singh, R. Autophagy in the CNS and Periphery Coordinate Lipophagy and Lipolysis in the Brown Adipose Tissue and Liver. *Cell Metab.* **2016**, *23*, 113–127. [CrossRef] [PubMed]
195. Jiang, S.; Wells, C.D.; Roach, P.J. Starch-binding domain-containing protein 1 (Stbd1) and glycogen metabolism: Identification of the Atg8 family interacting motif (AIM) in Stbd1 required for interaction with GABARAPL1. *Biochem. Biophys. Res. Commun.* **2011**, *413*, 420–425. [CrossRef] [PubMed]
196. Wyant, G.A.; Abu-Remaileh, M.; Frenkel, E.M.; Laqtom, N.N.; Dharamdasani, V.; Lewis, C.A.; Chan, S.H.; Heinze, I.; Ori, A.; Sabatini, D.M. Nufip1 is a ribosome receptor for starvation-induced ribophagy. *Science* **2018**, *360*, 751–758. [CrossRef] [PubMed]
197. Dowdle, W.E.; Nyfeler, B.; Nagel, J.; Elling, R.A.; Liu, S.; Triantafellow, E.; Menon, S.; Wang, Z.; Honda, A.; Pardee, G.; et al. Selective VPS34 inhibitor blocks autophagy and uncovers a role for NCOA4 in ferritin degradation and iron homeostasis in vivo. *Nat. Cell Biol.* **2014**, *16*, 1069–1079. [CrossRef]
198. Mancias, J.D.; Wang, X.; Gygi, S.P.; Harper, J.W.; Kimmelman, A.C. Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. *Nature* **2014**, *508*, 105–109. [CrossRef]
199. Haack, T.B.; Ignatius, E.; Calvo-Garrido, J.; Iuso, A.; Isohanni, P.; Maffezzini, C.; Lönnqvist, T.; Suomalainen, A.; Gorza, M.; Kremer, L.S.; et al. Absence of the Autophagy Adaptor SQSTM1/p62 Causes Childhood-Onset Neurodegeneration with Ataxia, Dystonia, and Gaze Palsy. *Am. J. Hum. Genet.* **2016**, *99*, 735–743. [CrossRef]
200. Teyssou, E.; Takeda, T.; Lebon, V.; Boillée, S.; Doukouré, B.; Bataillon, G.; Sazdovitch, V.; Cazeneuve, C.; Meininger, V.; Leguern, E.; et al. Mutations in SQSTM1 encoding p62 in amyotrophic lateral sclerosis: Genetics and neuropathology. *Acta Neuropathol.* **2013**, *125*, 511–522. [CrossRef]
201. Fecto, F.; Yan, J.; Vemula, S.P.; Liu, E.; Yang, Y.; Chen, W.; Zheng, J.G.; Shi, Y.; Siddique, N.; Arrat, H.; et al. SQSTM1 mutations in familial and sporadic amyotrophic lateral sclerosis. *Arch. Neurol.* **2011**, *68*, 1440–1446. [CrossRef]
202. Le Ber, I.; Camuzat, A.; Guerreiro, R.; Bouya-Ahmed, K.; Bras, J.; Nicolas, G.; Gabelle, A.; Didic, M.; De Septenville, A.; Millecamps, S.; et al. SQSTM1 Mutations in french patients with frontotemporal dementia or frontotemporal dementia with amyotrophic lateral sclerosis. *JAMA Neurol.* **2013**, *70*, 1403–1410.
203. Boutoleau-Bretonnière, C.; Camuzat, A.; Le Ber, I.; Bouya-Ahmed, K.; Guerreiro, R.; Deruet, A.L.; Evrard, C.; Bras, J.; Lamy, E.; Auffray-Calvier, E.; et al. A phenotype of atypical apraxia of speech in a family carrying SQSTM1 mutation. *J. Alzheimer's Dis.* **2015**, *43*, 625–630. [CrossRef]
204. Gang, Q.; Bettencourt, C.; Machado, P.M.; Brady, S.; Holton, J.L.; Pittman, A.M.; Hughes, D.; Healy, E.; Parton, M.; Hilton-Jones, D.; et al. Rare variants in SQSTM1 and VCP genes and risk of sporadic inclusion body myositis. *Neurobiol. Aging* **2016**, *47*, e1–e218. [CrossRef] [PubMed]

205. Rea, S.L.; Walsh, J.P.; Ward, L.; Yip, K.; Ward, B.K.; Kent, G.N.; Steer, J.H.; Xu, J.; Ratajczak, T. A novel mutation (K378X) in the Sequestosome 1 gene associated with increased NF-κB signaling and Paget's disease of bone with a severe phenotype. *J. Bone Miner. Res.* **2006**, *21*, 1136–1145. [CrossRef]
206. Hocking, L.J.; Lucas, G.J.A.; Daroszewska, A.; Mangion, J.; Olavesen, M.; Cundy, T.; Nicholson, G.C.; Ward, L.; Bennett, S.T.; Wuyts, W.; et al. Domain-specific mutations in sequestosome 1 (SQSTM1) cause familial and sporadic Paget's diease. *Hum. Mol. Genet.* **2002**, *11*, 2735–2739. [CrossRef] [PubMed]
207. Ellinghaus, D.; Zhang, H.; Zeissig, S.; Lipinski, S.; Till, A.; Jiang, T.; Stade, B.; Bromberg, Y.; Ellinghaus, E.; Keller, A.; et al. Association between variants of PRDM1 and NDP52 and crohn's disease, based on exome sequencing and functional studies. *Gastroenterology* **2013**, *145*, 339–347. [CrossRef]
208. Pap, É.M.; Farkas, K.; Széll, M.; Németh, G.; Rajan, N.; Nagy, N. Identification of putative phenotype-modifying genetic factors associated with phenotypic diversity in Brooke-Spiegler syndrome. *Exp. Dermatol.* **2020**.
209. Maruyama, H.; Morino, H.; Ito, H.; Izumi, Y.; Kato, H.; Watanabe, Y.; Kinoshita, Y.; Kamada, M.; Nodera, H.; Suzuki, H.; et al. Mutations of optineurin in amyotrophic lateral sclerosis. *Nature* **2010**, *465*, 223–226. [CrossRef]
210. Silva, I.A.L.; Conceição, N.; Gagnon, É.; Caiado, H.; Brown, J.P.; Gianfrancesco, F.; Michou, L.; Cancela, M.L. Effect of genetic variants of OPTN in the pathophysiology of Paget's disease of bone. *Biochim. Et Biophys. Acta Mol. Basis Dis.* **2018**, *1864*, 143–151. [CrossRef]
211. Albagha, O.M.E.; Visconti, M.R.; Alonso, N.; Langston, A.L.; Cundy, T.; Dargie, R.; Dunlop, M.G.; Fraser, W.D.; Hooper, M.J.; Isaia, G.; et al. Genome-wide association study identifies variants at CSF1, OPTN and TNFRSF11A as genetic risk factors for Paget's disease of bone. *Nat. Genet.* **2010**, *42*, 520–524. [CrossRef]
212. Rezaie, T.; Child, A.; Hitchings, R.; Brice, G.; Miller, L.; Coca-Prados, M.; Héon, E.; Krupin, T.; Ritch, R.; Kreutzer, D.; et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Sci. N.Y.* **2002**, *295*, 1077–1079. [CrossRef] [PubMed]
213. Newton, C.A.; Oldham, J.M.; Ley, B.; Anand, V.; Adegunsoye, A.; Liu, G.; Batra, K.; Torrealba, J.; Kozlitina, J.; Glazer, C.; et al. Telomere length and genetic variant associations with interstitial lung disease progression and survival. *Eur. Respir. J.* **2019**, *53*, 1–4. [CrossRef] [PubMed]
214. Araujo, F.J.d.; Silva, L.D.O.d.; Mesquita, T.G.; Pinheiro, S.K.; Vital, W.d.S.; Chrusciak-Talhari, A.; Guerra, J.A.d.O.; Talhari, S.; Ramasawmy, R. Polymorphisms in the TOLLIP Gene Influence Susceptibility to Cutaneous Leishmaniasis Caused by Leishmania guyanensis in the Amazonas State of Brazil. *PLoS Negl. Trop. Dis.* **2015**, *9*, e0003875. [CrossRef]
215. Montoya-Buelna, M.; Fafutis-Morris, M.; Tovar-Cuevas, A.J.; Alvarado-Navarro, A.; Valle, Y.; Padilla-Gutierrez, J.R.; Muñoz-Valle, J.F.; Figuera-Villanueva, L.E. Role of toll-interacting protein gene polymorphisms in leprosy Mexican patients. *Biomed Res. Int.* **2013**, *2013*. [CrossRef] [PubMed]
216. Shah, J.A.; Berrington, W.R.; Vary, J.C.; Wells, R.D.; Peterson, G.J.; Kunwar, C.B.; Khadge, S.; Hagge, D.A.; Hawn, T.R. Genetic variation in toll-interacting protein is associated with leprosy susceptibility and cutaneous expression of interleukin 1 receptor antagonist. *J. Infect. Dis.* **2016**, *213*, 1189–1197. [CrossRef]
217. Brasil, L.W.; Barbosa, L.R.A.; De Araujo, F.J.; Da Costa, A.G.; Da Silva, L.D.O.; Pinheiro, S.K.; De Almeida, A.C.G.; Kuhn, A.; Vitor-Silva, S.; De Melo, G.C.; et al. TOLLIP gene variant is associated with Plasmodium vivax malaria in the Brazilian Amazon. *Malar. J.* **2017**, *16*, 116. [CrossRef]
218. Wu, S.; Huang, W.; Wang, D.; Wang, Y.; Wang, M.; Zhang, M.; He, J.Q. Evaluation of TLR2, TLR4, and TOLLIP polymorphisms for their role in tuberculosis susceptibility. *Apmis* **2018**, *126*, 501–508. [CrossRef]
219. Song, Z.; Yin, J.; Yao, C.; Sun, Z.; Shao, M.; Zhang, Y.; Tao, Z.; Huang, P.; Tong, C. Variants in the Toll-interacting protein gene are associated with susceptibility to sepsis in the Chinese Han population. *Crit. Care* **2011**, *15*, R12. [CrossRef]
220. Ruiz, M.T.; Balachi, J.F.; Fernandes, R.A.; Galbiatti, A.L.S.; Manigua, J.V.; Pavarino-Bertelli, É.C.; Goloni-Bertollo, E.M. Analysis of the TAX1BP1 gene in head and neck cancer patients. *Braz. J. Otorhinolaryngol.* **2010**, *76*, 193–198. [CrossRef]
221. Geller, F.; Feenstra, B.; Carstensen, L.; Pers, T.H.; Van Rooij, I.A.L.M.; Körberg, I.B.; Choudhry, S.; Karjalainen, J.M.; Schnack, T.H.; Hollegaard, M.V.; et al. Genome-wide association analyses identify variants in developmental genes associated with hypospadias. *Nat. Genet.* **2014**, *46*, 957–963. [CrossRef]
222. Lin, E.; Kuo, P.-H.; Liu, Y.-L.; Yu, Y.W.Y.; Yang, A.C.; Tsai, S.-J. A Deep Learning Approach for Predicting Antidepressant Response in Major Depression Using Clinical and Genetic Biomarkers. *Front. Psychiatry* **2018**, *9*, 290. [CrossRef]

223. Ikeda, M.; Takahashi, A.; Kamatani, Y.; Momozawa, Y.; Saito, T.; Kondo, K.; Shimasaki, A.; Kawase, K.; Sakusabe, T.; Iwayama, Y.; et al. Genome-wide association study detected novel susceptibility genes for schizophrenia and shared trans-populations/diseases genetic effect. *Schizophr. Bull.* **2019**, *45*, 824–834. [CrossRef] [PubMed]
224. Nicoletti, P.; Cartsos, V.M.; Palaska, P.K.; Shen, Y.; Floratos, A.; Zavras, A.I. Genomewide Pharmacogenetics of Bisphosphonate-Induced Osteonecrosis of the Jaw: The Role of RBMS3. *Oncologist* **2012**, *17*, 279–287. [CrossRef]
225. Ilgaz Aydinlar, E.; Rolfs, A.; Serteser, M.; Parman, Y. Mutation in FAM134B causing hereditary sensory neuropathy with spasticity in a Turkish family. *Muscle Nerve* **2014**, *49*, 774–775. [CrossRef] [PubMed]
226. Murphy, S.M.; Davidson, G.L.; Brandner, S.; Houlden, H.; Reilly, M.M. Mutation in FAM134B causing severe hereditary sensory neuropathy. *J. Neurol. Neurosurg. Psychiatry* **2012**, *83*, 119–120. [CrossRef]
227. Fischer, D.; Schabhüttl, M.; Wieland, T.; Windhager, R.; Strom, T.M.; Auer-Grumbach, M. A Novel Missense Mutation Confirms ATL3 as a Gene for Hereditary Sensory Neuropathy Type 1. *Brain* **2014**, *137*, 286. [CrossRef] [PubMed]
228. Kornak, U.; Mademan, I.; Schinke, M.; Voigt, M.; Krawitz, P.; Hecht, J.; Barvencik, F.; Schinke, T.; Gießelmann, S.; Beil, F.T.; et al. Sensory neuropathy with bone destruction due to a mutation in the membrane-shaping atlastin GTPase 3. *Brain* **2014**, *137*, 683–692. [CrossRef] [PubMed]
229. Manjurano, A.; Clark, T.G.; Nadjm, B.; Mtove, G.; Wangai, H.; Sepulveda, N.; Campino, S.G.; Maxwell, C.; Olomi, R.; Rockett, K.R.; et al. Candidate Human Genetic Polymorphisms and Severe Malaria in a Tanzanian Population. *PLoS ONE* **2012**, *7*, e47463. [CrossRef] [PubMed]
230. Apinjoh, T.O.; Anchang-Kimbi, J.K.; Njua-Yafi, C.; Ngwai, A.N.; Mugri, R.N.; Clark, T.G.; Rockett, K.A.; Kwiatkowski, D.P.; Achidi, E.A. Association of candidate gene polymorphisms and TGF-beta/IL-10 levels with malaria in three regions of Cameroon: A case-control study. *Malar. J.* **2014**, *13*, 236. [CrossRef]
231. Tavian, D.; Missaglia, S.; Redaelli, C.; Pennisi, E.M.; Invernici, G.; Wessalowski, R.; Maiwald, R.; Arca, M.; Coleman, R.A. Contribution of novel ATGL missense mutations to the clinical phenotype of NLSD-M: A strikingly low amount of lipase activity may preserve cardiac function. *Hum. Mol. Genet.* **2012**, *21*, 5318–5328. [CrossRef]
232. Zolotov, S.; Xing, C.; Mahamid, R.; Shalata, A.; Sheikh-Ahmad, M.; Garg, A. Homozygous LIPE mutation in siblings with multiple symmetric lipomatosis, partial lipodystrophy, and myopathy. *Am. J. Med Genet. Part A* **2017**, *173*, 190–194. [CrossRef]
233. Farhan, S.M.K.; Robinson, J.F.; McIntyre, A.D.; Marrosu, M.G.; Ticca, A.F.; Loddo, S.; Carboni, N.; Brancati, F.; Hegele, R.A. A Novel LIPE Nonsense Mutation Found Using Exome Sequencing in Siblings With Late-Onset Familial PartialLipodystrophy. *Can. J. Cardiol.* **2014**, *30*, 1649–1654. [CrossRef] [PubMed]
234. Jansen, I.E.; Gibbs, J.R.; Nalls, M.A.; Price, T.R.; Lubbe, S.; van Rooij, J.; Uitterlinden, A.G.; Kraaij, R.; Williams, N.M.; Brice, A.; et al. Establishing the role of rare coding variants in known Parkinson's disease risk loci. *Neurobiol. Aging* **2017**, *59*, e11–e220. [CrossRef] [PubMed]
235. International Parkinson's Disease Genomics, C.; Wellcome Trust Case Control, C. A two-stage meta-analysis identifies several new loci for Parkinson's disease. *PLoS Genet.* **2011**, *7*, e1002142.
236. Yucesoy, B.; Kaufman, K.M.; Lummus, Z.L.; Weirauch, M.T.; Zhang, G.; Cartier, A.; Boulet, L.P.; Sastre, J.; Quirce, S.; Tarlo, S.M.; et al. Genome-wide association study identifies novel loci associated with diisocyanate-induced occupational asthma. *Toxicol. Sci.* **2015**, *146*, 192–201. [CrossRef]
237. Wang, Y.; Ray, A.M.; Johnson, E.K.; Zuhlke, K.A.; Cooney, K.A.; Lange, E.M. Evidence for an association between prostate cancer and chromosome 8q24 and 10q11 genetic variants in African American men: The flint men's health study. *Prostate* **2011**, *71*, 225–231. [CrossRef]
238. Sheu, S.Y.; Schwertheim, S.; Worm, K.; Grabellus, F.; Schmid, K.W. Diffuse sclerosing variant of papillary thyroid carcinoma: Lack of BRAF mutation but occurrence of RET/PTC rearrangements. *Mod. Pathol.* **2007**, *20*, 779–787. [CrossRef]
239. Lee, J.M.; Gillis, T.; Mysore, J.S.; Ramos, E.M.; Myers, R.H.; Hayden, M.R.; Morrison, P.J.; Nance, M.; Ross, C.A.; Margolis, R.L.; et al. Common SNP-based haplotype analysis of the 4p16.3 Huntington disease gene region. *Am. J. Hum. Genet.* **2012**, *90*, 434–444. [CrossRef]
240. Martinez-Vicente, M.; Talloczy, Z.; Wong, E.; Tang, G.; Koga, H.; Kaushik, S.; de Vries, R.; Arias, E.; Harris, S.; Sulzer, D.; et al. Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. *Nat. Neurosci.* **2010**, *13*, 567–576. [CrossRef]
241. Rui, Y.N.; Xu, Z.; Patel, B.; Chen, Z.; Chen, D.; Tito, A.; David, G.; Sun, Y.; Stimming, E.F.; Bellen, H.J.; et al. Huntingtin functions as a scaffold for selective macroautophagy. *Nat. Cell Biol.* **2015**, *17*, 262–275. [CrossRef]
242. Kast, D.J.; Dominguez, R. The Cytoskeleton–Autophagy Connection. *Curr Biol.* **2017**, *27*, 318–326. [CrossRef]

243. Jahreiss, L.; Menzies, F.M.; Rubinsztein, D.C. The itinerary of autophagosomes: From peripheral formation to kiss-and-run fusion with lysosomes. *Traffic* **2008**, *9*, 574–587. [CrossRef] [PubMed]
244. Cardoso, C.M.P.; Groth-Pedersen, L.; Høyer-Hansen, M.; Kirkegaard, T.; Corcelle, E.; Andersen, J.S.; Jäättelä, M.; Nylandsted, J. Depletion of Kinesin 5B Affects Lysosomal Distribution and Stability and Induces Peri-Nuclear Accumulation of Autophagosomes in Cancer Cells. *PLoS ONE* **2009**, *4*, e4424. [CrossRef]
245. Kimura, S.; Noda, T.; Yoshimori, T. Dynein-dependent movement of autophagosomes mediates efficient encounters with lysosomes. *Cell Struct. Funct.* **2008**, *33*, 109–122. [CrossRef] [PubMed]
246. Lőrincz, P.; Juhász, G. Autophagosome-Lysosome Fusion. *J Mol Biol.* **2020**, *432*, 2462–2482. [CrossRef]
247. Zhao, Y.G.; Zhang, H. Autophagosome Maturation: An Epic Journey from the ER to Lysosomes. *J Cell Biol.* **2019**, *218*, 757–770. [CrossRef] [PubMed]
248. Takáts, S.; Boda, A.; Csizmadia, T.; Juhász, G. Small GTPases controlling autophagy-related membrane traffic in yeast and metazoans. *Small Gtpases* **2018**, *9*, 465–471. [CrossRef] [PubMed]
249. Szatmári, Z.; Sass, M. The Autophagic Roles of Rab Small GTPases and Their Upstream Regulators. *Autophagy* **2014**, *10*, 1154–1166. [CrossRef]
250. Bröcker, C.; Kuhlee, A.; Gatsogiannis, C.; Kleine Balderhaar, H.J.; Hönscher, C.; Engelbrecht-Vandré, S.; Ungermann, C.; Raunser, S. Molecular architecture of the multisubunit homotypic fusion and vacuole protein sorting (HOPS) tethering complex. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 1991–1996. [CrossRef] [PubMed]
251. Wang, Z.; Miao, G.; Xue, X.; Guo, X.; Yuan, C.; Wang, Z.; Zhang, G.; Chen, Y.; Feng, D.; Hu, J.; et al. The Vici Syndrome Protein EPG5 Is a Rab7 Effector that Determines the Fusion Specificity of Autophagosomes with Late Endosomes/Lysosomes. *Mol. Cell* **2016**, *63*, 781–795. [CrossRef]
252. McEwan, D.G.; Popovic, D.; Gubas, A.; Terawaki, S.; Suzuki, H.; Stadel, D.; Coxon, F.P.; MirandadeStegmann, D.; Bhogaraju, S.; Maddi, K.; et al. PLEKHM1 regulates autophagosome-lysosome fusion through HOPS complex and LC3/GABARAP proteins. *Mol. Cell* **2015**, *57*, 39–54. [CrossRef]
253. Ding, X.; Jiang, X.; Tian, R.; Zhao, P.; Li, L.; Wang, X.; Chen, S.; Zhu, Y.; Mei, M.; Bao, S.; et al. RAB2 regulates the formation of autophagosome and autolysosome in mammalian cells. *Autophagy* **2019**, *15*, 1774–1786. [CrossRef] [PubMed]
254. Lörincz, P.; Tóth, S.; Benkö, P.; Lakatos, Z.; Boda, A.; Glatz, G.; Zobel, M.; Bisi, S.; Hegedüs, K.; Takáts, S.; et al. Rab2 promotes autophagic and endocytic lysosomal degradation. *J. Cell Biol.* **2017**, *216*, 1937–1947. [CrossRef] [PubMed]
255. Pantoom, S.; Konstantinidis, G.; Voss, S.; Han, H.; Hofnagel, O.; Li, Z.; Wu, Y.W. RAB33B recruits the ATG16L1 complex to the phagophore via a noncanonical RAB binding protein. *Autophagy* **2020**, 1–15. [CrossRef] [PubMed]
256. Diao, J.; Liu, R.; Rong, Y.; Zhao, M.; Zhang, J.; Lai, Y.; Zhou, Q.; Wilz, L.M.; Li, J.; Vivona, S.; et al. ATG14 promotes membrane tethering and fusion of autophagosomes to endolysosomes. *Nature* **2015**, *520*, 563–566. [CrossRef]
257. Zhang, X.; Wang, L.; Lak, B.; Li, J.; Jokitalo, E.; Wang, Y. GRASP55 Senses Glucose Deprivation through O-GlcNAcylation to Promote Autophagosome-Lysosome Fusion. *Dev. Cell* **2018**, *45*, 245–261.e6. [CrossRef]
258. Ebner, P.; Poetsch, I.; Deszcz, L.; Hoffmann, T.; Zuber, J.; Ikeda, F. The IAP family member BRUCE regulates autophagosome–lysosome fusion. *Nat. Commun.* **2018**, *9*, 1–15. [CrossRef]
259. Nakamura, S.; Yoshimori, T. New Insights into Autophagosome-Lysosome Fusion. *J Cell Sci.* **2017**, *130*, 209–1216. [CrossRef]
260. Lefebvre, C.; Legouis, R.; Culetto, E. ESCRT and autophagies: Endosomal functions and beyond. *Semin. Cell Dev. Biol.* **2018**, *74*, 21–28. [CrossRef]
261. Nara, A.; Mizushima, N.; Yamamoto, A.; Kabeya, Y.; Ohsumi, Y.; Yoshimori, T. SKD1 AAA ATPase-dependent endosomal transport is involved in autolysosome formation. *Cell Struct. Funct.* **2002**, *27*, 29–37. [CrossRef]
262. Tamai, K.; Tanaka, N.; Nara, A.; Yamamoto, A.; Nakagawa, I.; Yoshimori, T.; Ueno, Y.; Shimosegawa, T.; Sugamura, K. Role of Hrs in maturation of autophagosomes in mammalian cells. *Biochem. Biophys. Res. Commun.* **2007**, *360*, 721–727. [CrossRef]
263. Lee, J.A.; Beigneux, A.; Ahmad, S.T.; Young, S.G.; Gao, F.B. ESCRT-III Dysfunction Causes Autophagosome Accumulation and Neurodegeneration. *Curr. Biol.* **2007**, *17*, 1561–1567. [CrossRef] [PubMed]
264. Farg, M.A.; Sundaramoorthy, V.; Sultana, J.M.; Yang, S.; Atkinson, R.A.K.; Levina, V.; Halloran, M.A.; Gleeson, P.A.; Blair, I.P.; Soo, K.Y.; et al. C9ORF72, implicated in amytrophic lateral sclerosis and frontotemporal dementia, regulates endosomal trafficking. *Hum. Mol. Genet.* **2014**, *23*, 3579–3595. [CrossRef] [PubMed]

265. Vantaggiato, C.; Panzeri, E.; Castelli, M.; Citterio, A.; Arnoldi, A.; Santorelli, F.M.; Liguori, R.; Scarlato, M.; Musumeci, O.; Toscano, A.; et al. ZFYVE26/SPASTIZIN and SPG11/SPATACSIN mutations in hereditary spastic paraplegia types AR-SPG15 and AR-SPG11 have different effects on autophagy and endocytosis. *Autophagy* **2019**, *15*, 34–57. [CrossRef]
266. Morgan, N.E.; Cutrona, M.B.; Simpson, J.C. Multitasking Rab Proteins in Autophagy and Membrane Trafficking: A Focus on Rab33b. *Int J Mol Sci.* **2019**, *20*, 3916. [CrossRef]
267. Chen, J.; Ma, Z.; Jiao, X.; Fariss, R.; Kantorow, W.L.; Kantorow, M.; Pras, E.; Frydman, M.; Pras, E.; Riazuddin, S.; et al. Mutations in FYCO1 cause autosomal-recessive congenital cataracts. *Am. J. Hum. Genet.* **2011**, *88*, 827–838. [CrossRef] [PubMed]
268. Goes, F.S.; Hamshere, M.L.; Seifuddin, F.; Pirooznia, M.; Belmonte-Mahon, P.; Breuer, R.; Schulze, T.; Nöthen, M.; Cichon, S.; Rietschel, M.; et al. Genome-wide association of mood-incongruent psychotic bipolar disorder. *Transl. Psychiatry* **2012**, *2*, e180. [CrossRef] [PubMed]
269. Zillhardt, J.L.; Poirier, K.; Broix, L.; Lebrun, N.; Elmorjani, A.; Martinovic, J.; Saillour, Y.; Muraca, G.; Nectoux, J.; Bessieres, B.; et al. Mosaic parental germline mutations causing recurrent forms of malformations of cortical development. *Eur. J. Hum. Genet.* **2016**, *24*, 611–614. [CrossRef]
270. Petukhova, L.; Duvic, M.; Hordinsky, M.; Norris, D.; Price, V.; Shimomura, Y.; Kim, H.; Singh, P.; Lee, A.; Chen, W.V.; et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature* **2010**, *466*, 113–117. [CrossRef]
271. Xue, A.; Wu, Y.; Zhu, Z.; Zhang, F.; Kemper, K.E.; Zheng, Z.; Yengo, L.; Lloyd-Jones, L.R.; Sidorenko, J.; Wu, Y.; et al. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. *Nat. Commun.* **2018**, *9*, 1–14. [CrossRef]
272. Horikoshi, M.; Beaumont, R.N.; Day, F.R.; Warrington, N.M.; Kooijman, M.N.; Fernandez-Tajes, J.; Feenstra, B.; Van Zuydam, N.R.; Gaulton, K.J.; Grarup, N.; et al. Genome-wide associations for birth weight and correlations with adult disease. *Nature* **2016**, *538*, 248–252. [CrossRef]
273. Fuchs-Telem, D.; Stewart, H.; Rapaport, D.; Nousbeck, J.; Gat, A.; Gini, M.; Lugassy, Y.; Emmert, S.; Eckl, K.; Hennies, H.C.C.; et al. CEDNIK syndrome results from loss-of-function mutations in SNAP29. *Br. J. Dermatol.* **2011**, *164*, 610–616. [CrossRef] [PubMed]
274. Bare, L.A.; Morrison, A.C.; Rowland, C.M.; Shiffman, D.; Luke, M.M.; Iakoubova, O.A.; Kane, J.P.; Malloy, M.J.; Ellis, S.G.; Pankow, J.S.; et al. Five common gene variants identify elevated genetic risk for coronary heart disease. *Genet. Med.* **2007**, *9*, 682–689. [CrossRef] [PubMed]
275. Luke, M.M.; Lalouschek, W.; Rowland, C.M.; Catanese, J.J.; Bolonick, J.I.; Bui, N.D.; Greisenegger, S.; Endler, G.; Devlin, J.J.; Mannhalter, C. Polymorphisms Associated with Both Noncardioembolic Stroke and Coronary Heart Disease: Vienna Stroke Registry. *Cerebrovasc. Dis.* **2009**, *28*, 499–504. [CrossRef]
276. Cheng, S.; Sun, C.; Lao, W.; Kang, H. Association of VAMP8 rs1010 Polymorphism with Host Susceptibility to Pulmonary Tuberculosis in a Chinese Han Population. *Genet. Test. Mol. Biomark.* **2019**, *23*, 299–303. [CrossRef]
277. Hoffmann, T.J.; Van Den Eeden, S.K.; Sakoda, L.C.; Jorgenson, E.; Habel, L.A.; Graff, R.E.; Passarelli, M.N.; Cario, C.L.; Emami, N.C.; Chao, C.R.; et al. A large multiethnic genome-wide association study of prostate cancer identifies novel risk variants and substantial ethnic differences. *Cancer Discov.* **2015**, *5*, 878–891. [CrossRef] [PubMed]
278. Houlden, H.; King, R.H.M.; Muddle, J.R.; Warner, T.T.; Reilly, M.M.; Orrell, R.W.; Ginsberg, L. A novel RAB7 mutation associated with ulcero-mutilating neuropathy. *Ann. Neurol.* **2004**, *56*, 586–590. [CrossRef]
279. Meggouh, F.; Bienfait, H.M.E.; Weterman, M.A.J.; De Visser, M.; Baas, F. Charcot-Marie-tooth disease due to a de novo mutation of the RAB7 gene. *Neurology* **2006**, *67*, 1476–1478. [CrossRef]
280. Verhoeven, K.; De Jonghe, P.; Coen, K.; Verpoorten, N.; Auer-Grumbach, M.; Kwon, J.M.; FitzPatrick, D.; Schmedding, E.; De Vriendt, E.; Jacobs, A.; et al. Mutations in the small GTP-ase late endosomal protein RAB7 cause Charcot-Marie-Tooth type 2B neuropathy. *Am. J. Hum. Genet.* **2003**, *72*, 722–727. [CrossRef]
281. Alshammari, M.J.; Al-Otaibi, L.; Alkuraya, F.S. Mutation in RAB33B, which encodes a regulator of retrograde Golgi transport, defines a second Dyggve-Melchior-Clausen locus. *J. Med Genet.* **2012**, *49*, 455–461. [CrossRef]
282. Dupuis, N.; Lebon, S.; Kumar, M.; Drunat, S.; Graul-Neumann, L.M.; Gressens, P.; El Ghouzzi, V. A Novel RAB33B Mutation in Smith-McCort Dysplasia. *Hum. Mutat.* **2013**, *34*, 283–286. [CrossRef]
283. Salian, S.; Cho, T.J.; Phadke, S.R.; Gowrishankar, K.; Bhavani, G.S.L.; Shukla, A.; Jagadeesh, S.; Kim, O.H.; Nishimura, G.; Girisha, K.M. Additional three patients with Smith-McCort dysplasia due to novel RAB33B mutations. *Am. J. Med Genet. Part A* **2017**, *173*, 588–595. [CrossRef]

284. Kondo, H.; Maksimova, N.; Otomo, T.; Kato, H.; Imai, A.; Asano, Y.; Kobayashi, K.; Nojima, S.; Nakaya, A.; Hamada, Y.; et al. Mutation in VPS33A affects metabolism of glycosaminoglycans: A new type of mucopolysaccharidosis with severe systemic symptoms. *Hum. Mol. Genet.* **2017**, *26*, 173–183. [PubMed]
285. Nagel, M.; Jansen, P.R.; Stringer, S.; Watanabe, K.; De Leeuw, C.A.; Bryois, J.; Savage, J.E.; Hammerschlag, A.R.; Skene, N.G.; Muñoz-Manchado, A.B.; et al. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nat. Genet.* **2018**, *50*, 920–927. [CrossRef]
286. Van Wesenbeeck, L.; Odgren, P.R.; Coxon, F.P.; Frattini, A.; Moens, P.; Perdu, B.; MacKay, C.A.; Van Hul, E.; Timmermans, J.P.; Vanhoenacker, F.; et al. Involvement of PLEKHM1 in osteoclastic vesicular transport and osteopetrosis in incisors absent rats and humans. *J. Clin. Investig.* **2007**, *117*, 919–930. [CrossRef]
287. Edwards, T.L.; Scott, W.K.; Almonte, C.; Burt, A.; Powell, E.H.; Beecham, G.W.; Wang, L.; Züchner, S.; Konidari, I.; Wang, G.; et al. Genome-Wide association study confirms SNPs in SNCA and the MAPT region as common risk factors for parkinson disease. *Ann. Hum. Genet.* **2010**, *74*, 97–109. [CrossRef]
288. Couch, F.J.; Wang, X.; McGuffog, L.; Lee, A.; Olswold, C.; Kuchenbaecker, K.B.; Soucy, P.; Fredericksen, Z.; Barrowdale, D.; Dennis, J.; et al. Genome-Wide Association Study in BRCA1 Mutation Carriers Identifies Novel Loci Associated with Breast and Ovarian Cancer Risk. *PLoS Genet.* **2013**, *9*, e1003212. [CrossRef] [PubMed]
289. Phelan, C.M.; Kuchenbaecker, K.B.; Tyrer, J.P.; Kar, S.P.; Lawrenson, K.; Winham, S.J.; Dennis, J.; Pirie, A.; Riggan, M.J.; Chornokur, G.; et al. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. *Nat. Genet.* **2017**, *49*, 680–691. [CrossRef]
290. Amare, A.T.; Schubert, K.O.; Tekola-Ayele, F.; Hsu, Y.H.; Sangkuhl, K.; Jenkins, G.; Whaley, R.M.; Barman, P.; Batzler, A.; Altman, R.B.; et al. Association of the polygenic scores for personality traits and response to selective serotonin reuptake inhibitors in patients with major depressive disorder. *Front. Psychiatry* **2018**, *9*, 16. [CrossRef]
291. Hagenaars, S.P.; Hill, W.D.; Harris, S.E.; Ritchie, S.J.; Davies, G.; Liewald, D.C.; Gale, C.R.; Porteous, D.J.; Deary, I.J.; Marioni, R.E. Genetic prediction of male pattern baldness. *PLoS Genet.* **2017**, *13*, e1006594. [CrossRef]
292. Piano Mortari, E.; Folgiero, V.; Marcellini, V.; Romania, P.; Bellacchio, E.; D'Alicandro, V.; Bocci, C.; Carrozzo, R.; Martinelli, D.; Petrini, S.; et al. The Vici syndrome protein EPG5 regulates intracellular nucleic acid trafficking linking autophagy to innate and adaptive immunity. *Autophagy* **2018**, *14*, 22–37. [CrossRef]
293. Wang, K.S.; Liu, X.; Xie, C.; Liu, Y.; Xu, C. Non-parametric Survival Analysis of EPG5 Gene with Age at Onset of Alzheimer's Disease. *J. Mol. Neurosci.* **2016**, *60*, 436–444. [CrossRef]
294. Mekli, K.; Phillips, D.F.; Arpawong, T.E.; Vanhoutte, B.; Tampubolon, G.; Nazroo, J.Y.; Lee, J.; Prescott, C.A.; Stevens, A.; Pendleton, N. Genome-wide scan of depressive symptomatology in two representative cohorts in the United States and the United Kingdom. *J. Psychiatr. Res.* **2018**, *100*, 63–70. [CrossRef] [PubMed]
295. Ayub, H.; Micheal, S.; Akhtar, F.; Khan, M.I.; Bashir, S.; Waheed, N.K.; Ali, M.; Schoenmaker-Koller, F.E.; Shafique, S.; Qamar, R.; et al. Association of a Polymorphism in the BIRC6 Gene with Pseudoexfoliative Glaucoma. *PLoS ONE* **2014**, *9*, e105023. [CrossRef] [PubMed]
296. van der Zee, J.; Urwin, H.; Engelborghs, S.; Bruyland, M.; Vandenberghe, R.; Dermaut, B.; De Pooter, T.; Peeters, K.; Santens, P.; De Deyn, P.P.; et al. CHMP2B C-truncating mutations in frontotemporal lobar degeneration are associated with an aberrant endosomal phenotype in vitro. *Hum. Mol. Genet.* **2008**, *17*, 313–322. [CrossRef] [PubMed]
297. Ferrari, R.; Kapogiannis, D.; Huey, E.D.; Grafman, J.; Hardy, J.; Momeni, P. Novel missense mutation in charged multivesicular body protein 2B in a patient with frontotemporal dementia. *Alzheimer Dis. Assoc. Disord.* **2010**, *24*, 397–401. [CrossRef] [PubMed]
298. Skibinski, G.; Parkinson, N.J.; Brown, J.M.; Chakrabarti, L.; Lloyd, S.L.; Hummerich, H.; Nielsen, J.E.; Hodges, J.R.; Spillantini, M.G.; Thusgaard, T.; et al. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. *Nat. Genet.* **2005**, *37*, 806–808. [CrossRef]
299. Cox, L.E.; Ferraiuolo, L.; Goodall, E.F.; Heath, P.R.; Higginbottom, A.; Mortiboys, H.; Hollinger, H.C.; Hartley, J.A.; Brockington, A.; Burness, C.E.; et al. Mutations in CHMP2B in Lower Motor Neuron Predominant Amyotrophic Lateral Sclerosis (ALS). *PLoS ONE* **2010**, *5*, e9872. [CrossRef]
300. Shiels, A.; Bennett, T.M.; Knopf, H.L.S.; Yamada, K.; Yoshiura, K.I.; Niikawa, N.; Shim, S.; Hanson, P.I. CHMP4B, a novel gene for autosomal dominant cataracts linked to chromosome 20q. *Am. J. Hum. Genet.* **2007**, *81*, 596–606. [CrossRef]
301. Raginis-Zborowska, A.; Mekli, K.; Payton, A.; Ollier, W.; Hamdy, S.; Pendleton, N. Genetic determinants of swallowing impairments among community dwelling older population. *Exp. Gerontol.* **2015**, *69*, 196–201. [CrossRef]

302. Kichaev, G.; Bhatia, G.; Loh, P.R.; Gazal, S.; Burch, K.; Freund, M.K.; Schoech, A.; Pasaniuc, B.; Price, A.L. Leveraging Polygenic Functional Enrichment to Improve GWAS Power. *Am. J. Hum. Genet.* **2019**, *104*, 65–75. [CrossRef]
303. Shamim, U.; Ambawat, S.; Singh, J.; Thomas, A.; Pradeep-Chandra-Reddy, C.; Suroliya, V.; Uppilli, B.; Parveen, S.; Sharma, P.; Chanchal, S.; et al. C9orf72 hexanucleotide repeat expansion in Indian patients with ALS: A common founder and its geographical predilection. *Neurobiol. Aging* **2020**, *88*, e1–e156. [CrossRef]
304. Logue, M.W.; Schu, M.; Vardarajan, B.N.; Farrell, J.; Lunetta, K.L.; Jun, G.; Baldwin, C.T.; DeAngelis, M.M.; Farrer, L.A. A search for age-related macular degeneration risk variants in Alzheimer disease genes and pathways. *Neurobiol. Aging* **2014**, *35*, e7–e1510. [CrossRef] [PubMed]
305. Morais, S.; Raymond, L.; Mairey, M.; Coutinho, P.; Brandão, E.; Ribeiro, P.; Loureiro, J.L.; Sequeiros, J.; Brice, A.; Alonso, I.; et al. Massive sequencing of 70 genes reveals a myriad of missing genes or mechanisms to be uncovered in hereditary spastic paraplegias. *Eur. J. Hum. Genet.* **2017**, *25*, 1217–1228. [CrossRef] [PubMed]
306. Bowling, K.M.; Thompson, M.L.; Amaral, M.D.; Finnila, C.R.; Hiatt, S.M.; Engel, K.L.; Cochran, J.N.; Brothers, K.B.; East, K.M.; Gray, D.E.; et al. Genomic diagnosis for children with intellectual disability and/or developmental delay. *Genome Med.* **2017**, *9*, 1–11. [CrossRef]
307. Xie, T.; Deng, L.; Mei, P.; Zhou, Y.; Wang, B.; Zhang, J.; Lin, J.; Wei, Y.; Zhang, X.; Xu, R. A genome-wide association study combining pathway analysis for typical sporadic amyotrophic lateral sclerosis in Chinese Han populations. *Neurobiol. Aging* **2014**, *35*, e9–e1778. [CrossRef] [PubMed]
308. Sagona, A.P.; Nezis, I.P.; Bache, K.G.; Haglund, K.; Bakken, A.C.; Skotheim, R.I.; Stenmark, H. A tumor-associated mutation of FYVE-CENT prevents its interaction with Beclin 1 and interferes with cytokinesis. *PLoS ONE* **2011**, *6*, 1–10. [CrossRef] [PubMed]
309. Settembre, C.; Fraldi, A.; Jahreiss, L.; Spampanato, C.; Venturi, C.; Medina, D.; de Pablo, R.; Tacchetti, C.; Rubinsztein, D.C.; Ballabio, A. A block of autophagy in lysosomal storage disorders. *Hum Mol Genet* **2008**, *17*, 119–129. [CrossRef]
310. Fraldi, A.; Annunziata, F.; Lombardi, A.; Kaiser, H.J.; Medina, D.L.; Spampanato, C.; Fedele, A.O.; Polishchuk, R.; Sorrentino, N.C.; Simons, K.; et al. Lysosomal fusion and SNARE function are impaired by cholesterol accumulation in lysosomal storage disorders. *Embo J* **2010**, *29*, 3607–3620. [CrossRef]
311. Corcelle-Termeau, E.; Vindelov, S.D.; Hamalisto, S.; Mograbi, B.; Keldsbo, A.; Brasen, J.H.; Favaro, E.; Adam, D.; Szyniarowski, P.; Hofman, P.; et al. Excess sphingomyelin disturbs ATG9A trafficking and autophagosome closure. *Autophagy* **2016**, *12*, 833–849. [CrossRef]
312. Elrick, M.J.; Yu, T.; Chung, C.; Lieberman, A.P. Impaired proteolysis underlies autophagic dysfunction in Niemann-Pick type C disease. *Hum Mol Genet* **2012**, *21*, 4876–4887. [CrossRef]
313. Gabande-Rodriguez, E.; Boya, P.; Labrador, V.; Dotti, C.G.; Ledesma, M.D. High sphingomyelin levels induce lysosomal damage and autophagy dysfunction in Niemann Pick disease type A. *Cell Death Differ* **2014**, *21*, 864–875. [CrossRef]
314. Tomanin, R.; Karageorgos, L.; Zanetti, A.; Al-Sayed, M.; Bailey, M.; Miller, N.; Sakuraba, H.; Hopwood, J.J. Mucopolysaccharidosis type VI (MPS VI) and molecular analysis: Review and classification of published variants in the ARSB gene. *Hum. Mutat.* **2018**, *39*, 1788–1802. [CrossRef]
315. Morrone, A.; Caciotti, A.; Atwood, R.; Davidson, K.; Du, C.; Francis-Lyon, P.; Harmatz, P.; Mealiffe, M.; Mooney, S.; Oron, T.R.; et al. Morquio a syndrome-associated mutations: A review of alterations in the GALNS gene and a new locus-specific database. *Hum. Mutat.* **2014**, *35*, 1271–1279. [CrossRef]
316. Brunetti-Pierri, N.; Scaglia, F. GM1 gangliosidosis: Review of clinical, molecular, and therapeutic aspects. *Mol. Genet. Metab.* **2008**, *94*, 391–396. [CrossRef] [PubMed]
317. Zhu, Z.; Zhu, X.; Liu, C.L.; Shi, H.; Shen, S.; Yang, Y.; Hasegawa, K.; Camargo, C.A., Jr.; Liang, L. Shared genetics of asthma and mental health disorders: A large-scale genome-wide cross-trait analysis. *Eur. Respir. J.* **2019**, *54*, 1901507. [CrossRef]
318. Callahan, J.W. Molecular basis of GM1 gangliosidosis and Morquio disease, type B. Structure-function studies of lysosomal β-galactosidase and the non-lysosomal β-galactosidase-like protein. *Biochim. Et Biophys. Acta Mol. Basis Dis.* **1999**, *1455*, 85–103. [CrossRef]
319. Jakobkiewicz-Banecka, J.; Gabig-Ciminska, M.; Kloska, A.; Malinowska, M.; Piotrowska, E.; Banecka-Majkutewicz, Z.; Banecki, B.; Wegrzyn, A.; Wegrzyn, G. Glycosaminoglycans and mucopolysaccharidosis type III. *Front Biosci.* **2016**, *1*, 1393–1409.
320. Tomatsu, S.; Montano, A.M.; Dung, V.C.; Grubb, J.H.; Sly, W.S. Mutations and polymorphisms in GUSB gene in mucopolysaccharidosis VII (sly syndrome). *Hum. Mutat.* **2009**, *30*, 511–519. [CrossRef] [PubMed]

321. Triggs-Raine, B. Biology of hyaluronan: Insights from genetic disorders of hyaluronan metabolism. *World J. Biol. Chem.* **2015**, *6*, 110. [CrossRef]
322. Froissart, R.; Da Silva, I.M.; Maire, I. Mucopolysaccharidosis type II: An update on mutation spectrum. *Acta Paediatr. Int. J. Paediatr.* **2007**, *96*, 71–77. [CrossRef] [PubMed]
323. Poletto, E.; Pasqualim, G.; Giugliani, R.; Matte, U.; Baldo, G. Worldwide distribution of common IDUA pathogenic variants. *Clin. Genet.* **2018**, *94*, 95–102. [CrossRef] [PubMed]
324. Rowland, T.J.; Sweet, M.E.; Mestroni, L.; Taylor, M.R.G. Danon disease dysregulation of autophagy in a multisystem disorder with cardiomyopathy. *J. Cell Sci.* **2016**, *129*, 2135–2143. [CrossRef]
325. Peruzzo, P.; Pavan, E.; Dardis, A. Molecular genetics of Pompe disease: A comprehensive overview. *Ann. Transl. Med.* **2019**, *7*, 278. [CrossRef] [PubMed]
326. Potter, N.T.; Miller, C.A.; Anderson, I.J. Mutation detection in an equivocal case of Friedreich's ataxia. *Pediatric Neurol.* **2000**, *22*, 413–415. [CrossRef]
327. Bogaert, R.; Tiller, G.E.; Weis, M.A.; Gruber, H.E.; Rimoin, D.L.; Cohn, D.H.; Eyre, D.R. An amino acid substitution (Gly853 → Glu) in the collagen α1(II) chain produces hypochondrogenesis. *J. Biol. Chem.* **1992**, *267*, 22522–22526.
328. Kinghorn, K.J.; Asghari, A.M.; Castillo-Quan, J.I. The emerging role of autophagic-lysosomal dysfunction in Gaucher disease and Parkinson's disease. *Neural Regen. Res.* **2017**, *12*, 380–384. [CrossRef] [PubMed]
329. Benitez, B.A.; Davis, A.A.; Jin, S.C.; Ibanez, L.; Ortega-Cubero, S.; Pastor, P.; Choi, J.; Cooper, B.; Perlmutter, J.S.; Cruchaga, C. Resequencing analysis of five Mendelian genes and the top genes from genome-wide association studies in Parkinson's Disease. *Mol. Neurodegener.* **2016**, *11*, 1–12. [CrossRef]
330. Ortiz, A.; Germain, D.P.; Desnick, R.J.; Politei, J.; Mauer, M.; Burlina, A.; Eng, C.; Hopkin, R.J.; Laney, D.; Linhart, A.; et al. Fabry disease revisited: Management and treatment recommendations for adult patients. *Mol. Genet. Metab.* **2018**, *123*, 416–427. [CrossRef]
331. Bräuer, A.U.; Kuhla, A.; Holzmann, C.; Wree, A.; Witt, M. Current challenges in understanding the cellular and molecular mechanisms in niemann-pick disease type C1. *Int. J. Mol. Sci.* **2019**, *20*, 4392. [CrossRef]
332. Wilmer, M.J.; Schoeber, J.P.; Van Den Heuvel, L.P.; Levtchenko, E.N. Cystinosis: Practical tools for diagnosis and treatment. *Pediatric Nephrol.* **2011**, *26*, 205–215. [CrossRef]
333. Mole, S.E.; Cotman, S.L. Genetics of the neuronal ceroid lipofuscinoses (Batten disease). *Biochim. Et Biophys. Acta Mol. Basis Dis.* **2015**, *1852*, 2237–2241. [CrossRef] [PubMed]
334. Caciotti, A.; Catarzi, S.; Tonin, R.; Lugli, L.; Perez, C.R.; Michelakakis, H.; Mavridou, I.; Donati, M.A.; Guerrini, R.; d'Azzo, A.; et al. Galactosialidosis: Review and analysis of CTSA gene mutations. *Orphanet J. Rare Dis.* **2013**, *8*, 114. [CrossRef] [PubMed]
335. Wali, G.; Wali, G.M.; Sue, C.M.; Kumar, K.R. A Novel Homozygous Mutation in the FUCA1 Gene Highlighting Fucosidosis as a Cause of Dystonia: Case Report and Literature Review. *Neuropediatrics* **2019**, *50*, 248–252. [CrossRef] [PubMed]
336. Aula, N.; Salomäki, P.; Timonen, R.; Verheijen, F.; Mancini, G.; Månsson, J.E.; Aula, P.; Peltonen, L. The spectrum of SLC17A5-gene mutations resulting in free sialic acid-storage diseases indicates some genotype-phenotype correlation. *Am. J. Hum. Genet.* **2000**, *67*, 832–840. [CrossRef] [PubMed]
337. Malm, D.; Nilssen, Ø. Alpha-mannosidosis. *Orphanet J. Rare Dis.* **2008**, *3*, 1–10. [CrossRef]
338. Molho-Pessach, V.; Bargal, R.; Abramowitz, Y.; Doviner, V.; Ingber, A.; Raas-Rothschild, A.; Ne'eman, Z.; Zeigler, M.; Zlotogorski, A. Angiokeratoma corporis diffusum in human β-mannosidosis: Report of a new case and a novel mutation. *J. Am. Acad. Dermatol.* **2007**, *57*, 407–412. [CrossRef]
339. Saito, H.; Inazawa, J.; Saito, S.; Kasumi, F.; Koi, S.; Sagae, S.; Kudo, R.; Saito, J.; Noda, K.; Nakamura, Y. Detailed Deletion Mapping of Chromosome 17q in Ovarian and Breast Cancers: 2-cM Region on 17q21.3 Often and Commonly Deleted in Tumors. *Cancer Res.* **1993**, *53*, 3382–3385.
340. Gao, X.; Zacharek, A.; Salkowski, A.; Grignon, D.J.; Sakr, W.; Porter, A.T.; Honn, K.V. Loss of heterozygosity of the BRCA1 and other loci on chromosome 17q in human prostate cancer. *Cancer Res.* **1995**, *55*, 1002–1005.
341. Carvill, G.L.; Liu, A.; Mandelstam, S.; Schneider, A.; Lacroix, A.; Zemel, M.; McMahon, J.M.; Bello-Espinosa, L.; Mackay, M.; Wallace, G.; et al. Severe infantile onset developmental and epileptic encephalopathy caused by mutations in autophagy gene *WDR45*. *Epilepsia* **2018**, *59*, e5–e13. [CrossRef]
342. Li, Y.; Huang, J.; Pang, S.; Wang, H.; Zhang, A.; Hawley, R.G.; Yan, B. Novel and functional ATG12 gene variants in sporadic Parkinson's disease. *Neurosci. Lett.* **2017**, *643*, 22–26. [CrossRef]
343. Chen, D.; Pang, S.; Feng, X.; Huang, W.; Hawley, R.G.; Yan, B. Genetic analysis of the ATG7 gene promoter in sporadic Parkinson's disease. *Neurosci. Lett.* **2013**, *534*, 193–198. [CrossRef] [PubMed]

344. Elisa, R.; Rainero, I.; Chiò, A.; Rogaeva, E.; Galimberti, D.; Fenoglio, P.; Grinberg, Y.; Isaia, G.; Calvo, A.; Gentile, S.; et al. SQSTM1 mutations in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Neurology* **2012**, *79*, 1556–1562.
345. Bucelli, R.C.; Arhzaouy, K.; Pestronk, A.; Pittman, S.K.; Rojas, L.; Sue, C.M.; Evilä, A.; Hackman, P.; Udd, B.; Harms, M.B.; et al. SQSTM1 splice site mutation in distal myopathy with rimmed vacuoles. *Neurology* **2015**, *85*, 665–674. [CrossRef] [PubMed]
346. Nuij, V.J.A.A.; Peppelenbosch, M.P.; Woude, C.J.; Fuhler, G.M. Genetic polymorphism in ATG16L1 gene is associated with adalimumab use in inflammatory bowel disease. *J. Transl. Med.* **2017**, *15*, 248. [CrossRef] [PubMed]
347. Koder, S.; Repnik, K.; Ferkolj, I.; Pernat, C.; Skok, P.; Weersma, R.K.; Potočnik, U. Genetic polymorphism in ATG16L1 gene influences the response to adalimumab in Crohn's disease patients. *Pharmacogenomics* **2015**, *16*, 191–204. [CrossRef] [PubMed]