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To cite this article: Celine Deneubourg, Mauricio Ramm, Luke J. Smith, Olga Baron, Kritarth Singh, Susan C. Byrne, Michael R. Duchen, Mathias Gautel, Eeva-Liisa Eskelinen, Manolis Fanto & Heinz Jungbluth (2021): The spectrum of neurodevelopmental, neuromuscular and neurodegenerative disorders due to defective autophagy, Autophagy, DOI: 10.1080/15548627.2021.1943177

To link to this article: https://doi.org/10.1080/15548627.2021.1943177

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Published online: 19 Aug 2021.

Article views: 622

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Celine Deneubourg a,b, Mauricio Ramm c,d, Luke J. Smith e, Olga Baron d, Kritarth Singh e, Susan C. Byrne e, Michael R. Duchen e, Mathias Gautel e, Eeva-Liisa Eskelinen e,f, Manolis Fanto e and Heinz Jungbluth a,c,f

a Department of Basic and Clinical Neuroscience, IoPPN, King’s College London, London, UK; b Institute of Biomedicine, University of Turku, Turku, Finland; c Randall Division of Cell and Molecular Biophysics, Muscle Signalling Section, King’s College London, London, UK; d Wolfson Centre for Age-Related Diseases, King’s College London, London, UK; e Department of Cell and Developmental Biology, University College London, London, UK; f Department of Paediatric Neurology, Neuromuscular Service, Evelina’s Children Hospital, Guy’s & St. Thomas’ Hospital NHS Foundation Trust, London, UK; g Molecular and Integrative Biosciences Research Programme, University of Helsinki, Helsinki, Finland

ABSTRACT

Primary dysfunction of autophagy due to Mendelian defects affecting core components of the autophagy machinery or closely related proteins have recently emerged as an important cause of genetic disease. This novel group of human disorders may present throughout life and comprises severe early-onset neurodevelopmental and more common adult-onset neurodegenerative disorders. Early-onset (or congenital) disorders of autophagy often share a recognizable “clinical signature,” including variable combinations of neurological, neuromuscular and multisystem manifestations. Structural CNS abnormalities, cerebellar involvement, spasticity and peripheral nerve pathology are prominent neurological features, including specific vulnerability of certain neuronal populations to autophagic disturbance. A typically biphasic disease course of late-onset neurodegeneration occurring on the background of a neurodevelopmental disorder further supports a role of autophagy in both neuronal development and maintenance. Additionally, an associated myopathy has been characterized in several conditions. The differential diagnosis comprises a wide range of other multisystem disorders, including mitochondrial, glycogen and lysosomal storage disorders, as well as ciliopathies, glycosylation and vesicular trafficking defects. The clinical overlap between the congenital disorders of autophagy and these conditions reflects the multiple roles of the proteins and/or emerging molecular connections between the pathways implicated and suggests an exciting area for future research. Therapy development for congenital disorders of autophagy is still in its infancy but may result in the identification of molecules that target autophagy more specifically than currently available compounds. The close connection with adult-onset neurodegenerative disorders highlights the relevance of research into rare early-onset neurodevelopmental conditions for much more common, age-related human diseases.

Introduction

Genetic defects affecting cellular pathways with fundamental biological functions are often associated with extensive and not infrequently lethal human multisystem disorders. These conditions are often named after the organelle/mechanisms involved and/or the most striking pathological abnormality seen on microscopy, and include ciliopathies, congenital disorders of glycosylation, cellular trafficking, mitochondrial, as well as glycogen and lysosomal storage disorders.

Congenital disorders of autophagy have been recently introduced as a group of novel human multisystem disorders [1] due to defects in primary elements of the autophagy pathway and closely associated proteins. The number of conditions included within this novel diagnostic category is rapidly increasing, suggesting disorders affecting an important mechanism of human disease that may be individually rare but not uncommon as a group. The degree of multisystem involvement may also point at multiple or ubiquitously essential roles of the proteins implicated. Besides its considerable clinical relevance, the concept of congenital disorders of autophagy may also crucially inform basic autophagy research: For example, the clinical signatures of individual disorders may highlight the common involvement of organs where the role of autophagy has not been fully explored yet, or, alternatively, suggest links with other cellular signaling pathways (for example, regulated cell death pathways [2]) and/or non-canonical roles of the autophagy proteins implicated that may be worth exploring. Moreover, although some of the individual conditions included within the group of congenital disorders of autophagy may be exceedingly rare, it is increasingly recognized that many of the proteins involved play an important role in much more common neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS), dementia and Parkinson disease (PD) [3–7].

CONTACT Heinz Jungbluth Heinz.Jungbluth@gstt.nhs.uk Children’s Neurosciences Centre, Evelina Children’s Hospital, Guy’s & St Thomas’ NHS Foundation Trust, 2nd Floor Becket House, Lambeth Palace Road, London, SE1 7EH, United Kingdom

*joint contribution

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In the following review, we will outline the key features of the currently recognized congenital disorders of autophagy, and emphasize their overlap with other multisystem disorders, in particular cellular trafficking, mitochondrial and lysosomal storage disorders. We will highlight where such overlap may reflect close links between the respective pathways involved, and/or non-canonical roles of the primary autophagy proteins implicated. The emerging links between early-onset neurodevelopmental and adult-onset neurodegenerative disorders will be highlighted as a particularly exciting area for future research. Considering the often prominent (neuro)developmental phenotypes and the predilection for certain (neuronal) tissues in the congenital disorders of autophagy, we will outline what is currently known about the role of autophagy in embryonic, in particular neuronal, development and organ maintenance. Lastly, we will summarize currently available animal models of congenital disorders of autophagy, and prospects and limitations of therapy development.

**The autophagy pathway and its intersection with other cellular pathways.**

Autophagy is a process of “self-eating” utilized by the cell to degrade material not suitable for degradation in the proteasome, for example, larger organelles such as mitochondria. Autophagy can be divided by type – macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) – and by target. These 3 different forms of autophagy all result in degradation of substrates in the lysosome, but differ in the mode of delivery: In microautophagy, the lysosomal membrane engulfs substrates directly [8]. In CMA, chaperones recognize soluble proteins bearing a specific pentapeptide motif for delivery to lysosomes, and then import them into the lysosomes via LAMP2A (lysosomal associated membrane protein 2A) [9]. Macroautophagy (hereafter autophagy) is the currently best-characterized form of autophagy, and, through the coordination of a host of specialized proteins, involves the formation of a specialized organelle, the autophagosome, and the degradation of its cargo by lysosomes. The molecular mechanisms that lead to the formation of the autophagosome and its subsequent fusion with the lysosome are well characterized (and illustrated in Figure 1). The proteins involved are encoded by 31 currently known autophagy-related (ATG) genes in mammals that were mostly discovered through genetic screens in yeast [10–12]. The autophagy pathway is highly conserved throughout evolution. The unique organelle of autophagy, the autophagosome, is formed from a phagophore. There are conflicting data regarding the origin of this structure, but the consensus is that it is derived, at least partially, from the endoplasmic reticulum (ER) [13–16].

MTOR (mechanistic target of rapamycin kinase) is the negative master regulator of autophagy [17]. The Ser/Thr kinase MTOR forms a complex with RPTOR (regulatory associated protein of MTOR complex 1), MLST8 (MTOR associated protein, LST8 homolog), AKT1S1 (AKT1 substrate 1) and DEPTOR (DEP domain containing MTOR interacting protein), termed MTORC1 [18–22]. The MTORC1 complex is activated by interaction with the GTP-binding protein RHEB (Ras homolog, mTORC1 binding) in response to growth factors or high levels of amino acids [23–25]. Vice versa, AMP-activated protein kinase (AMPK) inactivates MTORC1 by phosphorylation of RPTOR or TSC2 (TSC complex subunit 2) [26]. Hence, MTORC1 functions as a sensor of cellular nutrient and energy levels. The inhibitory effect of MTORC1 on autophagy was first demonstrated by the phosphorylation and consequent inactivation of the ULK1 complex comprising the protein kinase ULK1 (unc-51 like autophagy activating kinase 1) and interacting proteins ATG13 and RB1CC1 (RB1 inducible coiled-coil 1) [27–29]. More recently, it was revealed that the inhibitory effect of MTORC1 is manifold and acts on various stages of the autophagy process, as it also inactivates class III phosphatidylinositol 3-kinase 3-kinase (PtdIns3K), WIP12 (WD repeat domain, phosphoinositide interacting 2), UVRAG (UV radiation resistance-associated) and RUBCNL (rubicon like autophagy enhancer), which function in the formation of the nucleation membrane, phagophore elongation and fusion of the autophagosome and lysosome [30–33]. Optimal functioning of the MTORC1 pathway is thus of utmost importance for the autophagy pathway and, not unexpectedly, both processes are therefore closely interlinked [34,35]. The MTOR pathway has been implicated in a myriad of diseases such as metabolic disorders, cancer and neurodegenerative disease, the details of which go beyond the scope of this review (for a comprehensive review on MTOR signaling in disease, see [36]).

Under starvation conditions, MTORC1 is inhibited and the active ULK1 complex triggers autophagy by activating the PtdIns3K complex comprising the phosphatidylinositol 3-kinase subunit PIK3C3 (phosphatidylinositol 3-kinase catalytic subunit type 3), adaptor protein PIK3R4 (phosphoinositide-3-kinase regulatory subunit 4), regulator BECN1/Becn1-1, assembly factor NRBF2 (nuclear receptor binding factor 2) and accessory protein ATG14. ATG14 recruits the complex to the site of phagophore formation [37]. The resulting pool of phosphatidylinositol-3-phosphate (PtdIns3P) recruits proteins that drive formation of the phagophore, which recruits lipids from a donor membrane compartment to eventually extend into a double-membrane vesicle [38], highlighting the close links between autophagy and lipid, in particular phosphoinositide metabolism. Recent research has shown that ATG9 plays a crucial role in the lipid transfer needed for this phagophore extension. ATG9 is a lipid scramblase that translocates phospholipids from the cytoplasmic leaflet to the luminal leaflet of the phagophore [39]. Multiple sites of phagophore formation and thus sources of membrane lipids have been suggested such as the ER, Golgi apparatus, endosomal vesicles and mitochondria [40,41]. It is also suggested that particular membrane contact sites between the ER and other organelles such as mitochondria are a necessary environment for phagophores to be able to appear and extend [14,41].

Recent work has shown that phosphatidylinositol-5-phosphate (PtdIns5P) can also drive phagophore formation and may be able to recruit proteins characterized as PtdIns3P-binding proteins. PtdIns3P is required for autophagy in conditions of amino acid starvation, whereas PtdIns5P is required in glucose deprivation [42], indicating
that, despite shared and consistent core elements, there may be subtle differences in the molecular autophagy machinery employed under different stimuli. WIPI proteins [43] and ZFYVE1 (zinc finger FYVE-type containing 1) [38] are PtdIns3P-binding proteins recruited to the phagophore. WIPI2 recruits another complex formed of ATG12−ATG5−ATG16L1, which acts like an E3 ligase, mediating conjugation of ubiquitin-like proteins of the ATG8 family to phosphatidylethanolamine in the phagophore membrane [44]. The best-studied mammalian ATG8-family protein is LC3B, a key autophagy adaptor whose lipidation is facilitated by other proteins acting as E1- and E2-like enzymes [45]. The E2-like enzyme ATG3 specifically targets curved membranes, potentially favoring LC3B lipidation at the highly curved rim of growing phagophores [46]. LC3B is with a few exceptions [47,48] a reliable marker of autophagic structures [49].

Beyond the proteins that drive formation of the membrane structures unique to autophagy, several specialized cargo receptors deliver substrates to the phagophore. These cargo receptors include SQSTM1 (sequestosome 1), NBR1 (NBR1 autophagy cargo receptor), CALCOCO2 (calcium binding and coiled-coil domain 2) and OPTN (optineurin) and are critical for effective clearance of autophagy substrates. Mutations in both SQSTM1 [50,51] and OPTN [52] are associated with ALS, with evidence of accumulation of both proteins in tissue samples from many types of neurodegenerative disorders [53,54]. The cargo receptors bind specifically to ubiquitinated substrates and to LC3 in the forming autophagosome. Although autophagy is often considered a largely nonselective process, it is now clear that there are many examples of selective autophagy mediated by autophagy cargo receptors [55].

Double-membraned autophagosomes, the result of phagophore expansion around its cargo and subsequent closure, can bear markers of early and late endosomes as well as lysosomes, suggesting a maturation process facilitated by multiple fusion events [56–58] and intricate links between autophagy...
and endosomal and lysosomal pathways. The final stage of autophagy is usually described as the fusion of the autophagosome and lysosome to create a hybrid organelle, the autolysosome. However, some studies suggest that autophagosomes may also deliver cargo into lysosomes via temporally and spatially limited (“kiss and run”) interactions [59], possibly depending on circumstances and/or cell types. Whatever the precise mechanisms leading to this point, autophagic substrates are then degraded by lysosomal enzymes. As a result, lysosomal storage disorders will almost invariably also result in defective autophagy [60]. As with the initiation and maturation of autophagosomes, the final steps of autophagy involve specialized machinery. Fusion of autophagosomes and lysosomes is dependent on a SNARE complex formed by the autophagosomal SNARE STX17 (syntaxin 17), Qbc SNARE SNAP29 (synaptosome associated protein 29) and the lysosomal R-SNARE VAMP8 (vesicle associated membrane protein 8) [61]. A host of other proteins are implicated in tethering autophagosomes to lysosomes, including the homotypic fusion and protein sorting (HOPS) complex [62], TECPR1 (tectonin beta-propeller repeat containing 1) [63] and EPG5 (ectopic P-granules autophagy protein 5 homolog) [64].

Autophagosome-lysosome fusion represents the most obvious convergence of the specialized autophagy pathway and the multi-tasking endo-lysosomal system, and any disruption to lysosomal function (or indeed any other element of the complex machinery involved) may impair this crucial stage of autophagy. While both pathways differ in their starting location and cargo, with endosomes usually forming at the plasma membrane to engulf extracellular substrates and autophagosomes developing from the ER and carrying intracellular cargo, their convergence in the final step of lysosomal degradation of their respective cargos indicates their close interaction and cellular proximity. A key point of convergence between endosomal trafficking and autophagy is the endosomal sorting complexes required for transport (ESCRT). ESCRT proteins, among other roles, function sequentially in the formation of intraluminal vesicles at late endosomes to form multi-vesicular bodies. Recently ESCRT was demonstrated to function in autophagosome formation, specifically in phagophore closure [65], consistent with earlier observations that knockdown of several ESCRT proteins results in autophagosome accumulation [66].

Another group of proteins that facilitate the interactions between autophagy and the endocytic system are members of the RAB GTPase family, through their important roles in membrane trafficking, in particular the coordination of transient interactions with the outer membrane of target vesicles and the recruitment of “effector” proteins [67]. RAB7 in particular promotes processes critical for autophagosome-lysosome fusion [68], and is required to provide a pool of lysosomes for fusion with autophagosomes by interacting with the dynein-dynactin adaptor RILP (Rab interacting lysosomal protein) and thus preventing the migration of late endosomes/lysosomes to the cell periphery [69]. Especially in neuronal cells, a crucial interaction between autophagy and vesicular trafficking can be observed, as autophagosomes are usually formed in distal regions of the cells and, to allow fusion with late endosomes/lysosomes, need to be transported retrogradely along the axons to perinuclear regions [69–72]. Indirectly, impairment of the dynein-dynactin complex or microtubule obstructions can thus lead to secondary obstruction of the autophagy pathway.

Finally, after degradation of the autolyosomal content by lysosomal hydrolases, all molecules are recycled and transported to their destined cellular locations for repurposing. In addition, the autophagic lysosomal reformation (ALR) process is essential for the regeneration of a pool of functional lysosomes [73–76], and characterized by initial clathrin-mediated budding of the autolysosomal membrane, which then elongates and, through an intermediate protolysosomal stage, eventually matures into a functional lysosome. Of note, MTOR also regulates the ALR process, confirming the important interplay between MTOR and the autophagy pathway [74,75] not only at the initiation stage but at various points of the process.

The implication of these multiple and complex interactions for biologists and clinicians working on autophagy-related diseases is that autophagy must be considered not in isolation, but as part of the complex endomembrane system that is interlinked with a more complex intracellular trafficking machinery. A primary autophagy-associated disorder can thus be due to defects in any part of the autophagy pathway, including the ATG core machinery, adaptor proteins and other proteins that may not only play a role in autophagy but also in other important cellular processes.

### Congenital disorders of autophagy.

While autophagy has been implicated in a wide range of human diseases in a nonspecific way for many years, the recognition of primary Mendelian disorders with defective autophagy is only relatively recent. On clinical grounds, these disorders can be divided in often severe neurodevelopmental and neurological disorders with onset early in life (often referred to as "congenital disorders of autophagy" [1]) (Table 1), and neurodegenerative diseases presenting late in adulthood, often after a long symptom-free or subclinical interval (Table 2). However, as discussed in more detail below, the above distinction is somewhat artificial, as there is emerging evidence for a lifetime continuum of autophagy-associated disorders, both on the level of the individual patient and specific conditions.

Congenital disorders of autophagy often have a recognizable "clinical signature," characterized by 1) prominent neurological and neuromuscular phenotypes, 2) a combination of developmental and degenerative abnormalities evolving over time and 3) variable degrees of multiorgan involvement. They may affect any component associated with the autophagy machinery, and the degree of multisystem involvement in particular may also point at the multiple roles of the proteins implicated, not all necessarily primarily autophagy-related. On clinical grounds, congenital disorders of autophagy (Table 1) can be subdivided into those with prominent multisystem involvement, brain iron accumulation, hereditary spastic paraplegias and cerebellar ataxias, although there is considerable clinical overlap between those entities.
Table 1. Early-onset neurodevelopmental and neurological disorders with defects in autophagy (“Congenital disorders of autophagy”) – selection.

| Condition                        | OMIM   | Gene  | OMIM   | Protein                        | Role in autophagy/abnormality                                      |
|----------------------------------|--------|-------|--------|--------------------------------|-------------------------------------------------------------------|
| Multisystem disorders            |        |       |        |                                |                                                                   |
| Vici syndrome                    | 242840 | EP5G  | 615068 | ectopic p-granules              | Mediates autophagosome-lysosome fusion through its role as a RA77 effector [64] |
| Younis Varon syndrome            | 216340 | FIG4  | 609390 | FIG4 phosphoinositide S-phosphate | Regulates synthesis and turnover of PtdIns(3,5)P2 [267]            |
| Warburg Micro syndrome           | 600118 | RAB3GAP1 | 602536 | RAB3 ATPase activating protein catalytic subunit 1 | Role in autophagosome formation [201] |
| Neurodegeneration with Brain Iron Accumulation (NBIA) |        |       |        |                                |                                                                   |
| Beta propeller-associated neurodegeneration (BPAN) | 300894 | WDR45/ WIP4 | 300526 | WD repeat domain 45 | Phagophore/autophagosome formation [92]                           |
| Cerebellar ataxias               |        |       |        |                                |                                                                   |
| SCAR20                           | 616354 | SNX14 | 616105 | sorting nexin 14               | Role in autophagic vesicle formation through conjugation to ATG12 [256] |
| SCAR25                           | 617584 | ATG5  | 604261 | autophagy related 5            |                                                                   |
| Spastic paraplegias              |        |       |        |                                |                                                                   |
| SPG11                            | 604360 | SPG11 | 610844 | SPG11 vesicle trafficking      | Autosomal lysosome recycling via ALR [110]                         |
|                                  |        |       |        | associated, spatacsin          |                                                                   |
|                                  |        |       |        | zinc finger FYVE-type          |                                                                   |
|                                  |        |       |        | containing 26                  |                                                                   |
| SPG15                            | 270700 | ZFYVE2 | 612012 | tectonin beta-propeller repeat | Putative role in early autophagosome generation by scaffolding    |
|                                  |        |       |        | containing 2                   | at ER exit sites [106]                                            |
| SPG49                            | 615031 | TECPR2 | 615000 | tectonin beta-propeller repeat |                                                                   |

Table 2. Adult-onset neurodegenerative disorders with defects in autophagy – selection.

| Condition                        | OMIM   | Gene  | OMIM   | Protein                        | Role in autophagy/abnormality                                      |
|----------------------------------|--------|-------|--------|--------------------------------|-------------------------------------------------------------------|
| Amyotrophic lateral sclerosis (ALS) |        |       |        |                                |                                                                   |
| FTDALS1                          | 105550 | C9orf72 | 614260 | C9orf72                        | Role in autophagosome maturation [261]                             |
|                                  | 205100 | ALS2  | 606352 | Rho guanine nucleotide exchange factor ALS2 | Localizes to autophagosomes [244] and loss leads to autophagosome accumulation [245] |
| FTDALS3                          | 616437 | SQSTM1 | 601530 | sequestosome 1                  | Autophagy receptor required for aggrephagy [296]                  |
|                                  | 602433 | SETX  | 608465 | senataxin                      | Role in autophagosome maturation [282]                            |
|                                  | 602099 | SPG11 | 610844 | SPG11 vesicle trafficking      | Autosomal lysosome recycling via ALR [110]                         |
|                                  |        |       |        | associated, spatacsin          |                                                                   |
|                                  |        |       |        | zinc finger FYVE-type          |                                                                   |
|                                  |        |       |        | containing 26                  |                                                                   |
| AL51                             | 612577 | FIG4  | 609390 | FIG4 phosphoinositide S-phosphate | Regulates synthesis and turnover of PtdIns(3,5)P2 [267]            |
|                                  | 613435 | OPTN  | 602432 | optineurin                     |                                                                   |
|                                  | 613954 | VCP   | 601023 | valosin containing protein     | Role in autophagy initiation [290] and in autophagy [291]          |
|                                  | 614966 | CHMP2B | 609512 | charged multisecular body protein 2B | Part of the ESCRT-III complex [263], with a role in mitophagy-specific phagocire closure [65] |
| Parkinson disease (PD)           |        |       |        |                                |                                                                   |
| PARK2                            | 600116 | PRKN/ | 602544 | parkin RBR E3 ubiquitin protein ligase | Induces mitophagy in concert with PARK1, and within an E3 ubiquitin ligase complex [155] |
| PARK6                            | 605909 | PINK1 | 608309 | PTEN induced kinase 1          | Induces mitophagy by recruitment of PRKN [155]                    |
| PARK20                           | 615530 | SYNJ1 | 604297 | synaptotagin 1                 | Autophagosomal lysosome recycling via ALR [110]                    |

The paradigmatic disorder of defective autophagy is Vici syndrome (Figure 2), one of the most extensive human multisystem disorders reported to date and characterized by callosal agenesis, cataracts, cleft palate, cardiomyopathy, combined immunodeficiency, hypopigmentation, acquired microcephaly and failure to thrive [77–79]. Vici syndrome was initially reported in 1988 by Dionisi-Vici and colleagues in two brothers and subsequently attributed to recessive mutations in EPG5 [78,79]. EPG5 is ubiquitously expressed and has a critical role in autophagosome-lysosome fusion and, probably, other intracellular vesicular fusion events [64,80]. There may be variability of protein levels and, consequently, the clinical phenotype in particular in association with the many splice mutations identified [81]. Subtle clinical manifestations, in particular an apparently higher incidence of cataracts, vitiligo and certain cancers [82–85], have been observed in heterozygous EPG5 mutation carriers, suggesting either pathogenic haploinsufficiency or a toxic gain-of-function effect over time in cases where a truncated EPG5 protein is not subjected to intracellular decay. Although other features are less consistently associated, virtually any organ system – including thyroid, lungs, liver and kidneys – may be affected in Vici syndrome patients, in keeping with the ubiquitous expression of the EPG5 protein and its fundamental biological importance. Interestingly, on the level of specific organs, EPG5-related Vici syndrome may feature both congenital defects as well as disease acquired later in life (for example, congenital heart defects and cardiomyopathy later in life, structural central nervous system [CNS] thyroid agenesis and hypothyroidism in a normally formed thyroid), emphasizing the crucial role of normal autophagy for both organ
development and maintenance. The degree of cardiac and immune involvement are the main determinants of prognosis.

While essentially a multisystem disorder, neurological aspects are most prominent in EPG5-related Vici syndrome and comprise both neurodevelopmental and neurodegenerative aspects [86]. In addition to the structural CNS abnormalities and the acquired microcephaly already mentioned, severe developmental delay, early-onset epilepsy, sensorineural deafness and movement disorders are frequently observed [79]. Evidence for peripheral neuropathies with similarities to the neuropathy reported due to mutations in the EPG5-interactor RAB7 [87] has been reported in isolated patients. A skeletal myopathy is consistently associated with EPG5-related Vici syndrome and is evidenced by variable degrees of hypotonia and weakness, and mild creatine kinase elevations [88].

Following the genetic resolution of Vici syndrome in 2013, a number of additional early-onset neurodevelopmental and neurological disorders (Table 1 and S1) are now attributed to mutations affecting primary components of the autophagy machinery downstream of MTORC1, including other multisystem disorders such as Warburg Micro syndrome (WMS) and Younis Varon syndrome due to recessive mutations in RAB3GAP1 (RAB3 GTPase activating protein catalytic subunit 1) [89] and FIG4 (FIG4 phosphoinositide 5-phosphatase) [90], respectively, beta-propeller protein-associated neurodegeneration (BPAN) due to X-linked dominant (de novo) mutations in WDR45 (WD repeat domain 45) [91,92], cerebellar ataxia associated with autosomal-recessive mutations in SNX14 (sorting nexin 14) and in ATG5 [93], and three forms of hereditary spastic paraparesis (HSPP), SPG11 (spastic paraplegia 11), SPG15 and SPG49 caused by autosomal-recessive mutations in SPG11 (SPG11 vesicle trafficking associated, spatacsin), ZFYVE26 (zinc finger FYVE-type containing 26) and TECPR2 (tectonin beta-propeller repeat containing 2), respectively [1,94,95].

Clinically, among the multisystem disorders, Warburg Micro syndrome (WMS) ([96,97] for review of clinical and genetic heterogeneity) shares a number of features with Vici
syndrome, in particular severe mental retardation, corpus callosum hypoplasia, (acquired) microcephaly, congenital cata-
aracts, optic atrophy and seizures, a phenotypical overlap likely to be explained by the recently described close molecular links between EPG5 and RAB3GAP1 [98], one of the causative proteins implicated in this genetically heterogeneous condition. Interestingly, like other autophagy-related disorder-
ders, WMS typically shows a biphasic course, characterized by spastic paraparesis evolving over time following an initial presentation with profound hypotonia. Youniss Varon syn-
drome (for review [90]) is a severe neurodevelopmental dis-
order with early lethality and vacuolar changes in various tissues, including neurons and muscles, due to autosomal-
recessive mutations in FIG4. Variably associated features, in particular corpus callosum abnormalities, congenital heart defects, cardiomyopathy and hearing impairment, show some overlap with Vici syndrome. Autophagy defects have been demonstrated in FIG4-mutated Schwann cells [99]. As in other autophagy-related disorders, depending on specific gen-
type, the associated clinical spectrum is wide, ranging from severe early-onset neurodevelopmental disorders to forms of Charcot-Marie-Tooth (CMT) disease (CMT4J) [100] and ALS (ALS11) [101]. Corresponding to the human phenotype, Fig4 null mice have a multisystem disorder with neurodegenerative features [100].

WDR45-associated BPAN (previously also known as "Static Encephalopathy of Childhood with NeuroDegeneration in Adulthood", or SENDA) [102] belongs to the wider group of conditions characterized by Neurodegeneration with Brain Iron Accumulation (NBIA), predominantly affecting the basal ganglia. The condition initially presents with global developmental delay, seizures and variable additional neurological features in childhood before a relentlessly progressive course characterized by dystonia, parkinsonism and cognitive decline develop from adolescence onwards [103].

Cerebellar ataxias are also common among primary auto-
phagy disorders: In addition to global developmental delay, seizures and progressive cerebellar atrophy, children with SNX14-related ataxia (SCAR20) [104] often demonstrate additional multisystem features suggestive of a storage disor-
der. ATG5-related SCAR25 is another recessively inherited ataxia recently attributed to mutations in a core autophagy component in a single family [105].

Another common manifestation are hereditary spastic paraplegias: SPG11- and ZFYVE26-related HSPP share signs of early-onset spasticity, frequently with a consistent combi-
nation of features (referred to as "Kjellin syndrome") com-
prising intellectual impairment, pigmentary retinopathy, cerebellar dysfunction and, variably, parkinsonism. Autosomal-recessive spastic paraplegia 49 due to homozigos-
ity for a TECPR2 founder mutation in Jewish Bukharan families is a complex multisystem disorder characterized by distinct dysmorphic features, severe central apneas, progres-
sive intellectual impairment, spastic paraplegia and ataxia.

Although the genes and proteins implicated in these con-
genital disorders of autophagy are likely to have multiple functions, a connection to the autophagy pathway has been clearly established, with SPG49-associated TECPR2 and BPAN-associated WDR45 linked to the phagophore/autophagosome formation stages [91,92,106], SCAR20-associated SNX14 and EPG5 related to autophagosome-lysosome fusion [107,108] and the spastic paraplegia proteins SPG11 and ZFYVE26 [109] implicated at multiple levels, including the recycling of autolysosomes [110,111]. WDR45/WIPI4 (the mammalian homolog of C. elegans EPG-6), the protein mutated in BPAN, belongs to the family of WD40 proteins which, through their highly stable and symmetrical beta-
propeller superstructure, play a crucial role in facilitating the assembly of multiprotein complexes; with regards to autopa-
thy, they specifically interact with ATG2 and ATG9 to facilitate autophagosome formation and elongation. EPG5, the protein mutated in Vici syndrome, is an example of a RAB7 effector directly involved in autophagy. EPG5 is recruited to lysos-
omes by GTP-bound RAB7 and facilitates autophagosome-
lysosome fusion by interacting with the SNARE complex and LC3 [64]. EPG5 knockdown results in the formation of enlarged perinuclear vesicles that are positive for markers of early and late endosomes, as well as autophagy markers [64]. SNX14, the protein mutated in SCAR20, is a member of the sorting nexin family with an ability to bind membrane phosphatidylinositol residues, a quality of likely relevance to autophagosome/lysosome formation where distinct organelle phospholipid signatures ensure specificity of fusion events [107]. ZFYVE26 and SPG11, the gene products of ZFYVE26 and SPG11 implicated in two forms of hereditary spastic paraplegia, respectively, form a complex targeted to the lys-
osome and are also probably functionally closely related. A role in membrane trafficking for ZFYVE26 is suggested by its ability to bind PtdIns3P [112]. With regards to the autophagy pathway and at least partly mediated through its interactions with the BECN1-UVRAG-RUBCN (rubicon autophagy regu-
lator) complex, ZFYVE26 has been specifically implicated in autophagosome formation, autophagosome-lysosome fusion and, in concert with SPG11, the recycling of autolysosomes via the ALR pathway [111]. The role of defective TECPR2 implicated in SPG49 is not fully resolved but may involve impairment of early autophagosome generation due to reduced scaffolding at ER membrane exit sites [106].

It is likely that as yet unresolved neurodevelopmental dis-
orders with overlapping clinical features (in particular those combining multisystem involvement, cerebellar signs and spastic paraparesis) will be attributed to mutations affecting additional components of the complex autophagy machinery in future, bearing in mind, however, that some of these mutations may also be antenatally lethal.

**Neurodevelopmental features**

Congenital disorders of autophagy often show a combination of (neuro)developmental and (neuro)degenerative features evolving over time, supporting a role of autophagy in both embryonic (neuronal) development and maintenance later in life.

Autophagy genes such as EPG5 have been implicated in human and murine stem cell development [113], and obser-
vations both in congenital disorders of autophagy but also in relation to other autophagy-associated genes suggest addi-
tional roles further downstream in neuronal differentiation.
Another autophagy gene in which defects have been shown to impede neurodevelopment is WDFY3 (WD repeat and FYVE domain containing 3), a large PtIns3P-binding and scaffold protein functioning in aggrephagy, the removal of aggregated proteins by autophagy [114], and in mitophagy, the selective degradation of mitochondria by autophagy [115]. Loss of WDFY3 has been reported as a risk factor in patients with autism spectrum disorder (ASD) [116] where early brain overgrowth is a common feature [117]. Early brain overgrowth is also recapitulated in Wdfy3-mutant mice, which feature increased brain size due to altered neural progenitor proliferation [118]. Interestingly, a missense mutation in WDFY3 has been found to have the opposing effect and cause hereditary primary microcephaly [119] and reduced brain size in humans and a corresponding Drosophila model, suggesting that WDFY3 plays a general role in determining correct brain size, probably through attenuation of WNT signaling through removal of DVL3 (disheveled segment polarity protein 3) aggregates [119]. Indeed, Le Duc et al. showed that mutations in WDFY3, which putatively cause haploinsufficiency, lead to macrocephaly and nonspecific mild neurodevelopmental delay, while mutations in the PH-domain of WDFY3 lead to microcephaly in affected patients [120]. Another reported function of WDFY3 supporting a role in neuronal differentiation is its implication in the formation of axonal tracts in the brain and spinal cord of mice [121].

Accumulating evidence suggests that autophagy has a role in various stages of neurodevelopment: In the early stages, such a role has been demonstrated by knockout of Ambr1 (autophagy and beclin 1 regulator 1) in mice, causing neural tube defects in these animals [122]. At the later stage of neurite formation, increased autophagy by cell-specific knock-out of Mtor causes suppressed proliferation in GABAergic progenitor cells, leading to reduced cortical interneurons in mice [123]. In addition, knockdown of Atg7 by siRNA causes abnormally elongated axons in primary rat cortical neurons, while autophagy induction by rapamycin has a suppressing effect on axon growth [124]. Mice with a loss of function mutation in Wdr47 (WD repeat domain 47) display increased autophagic flux. WDR47 is a negative regulator of autophagy that modulates microtubule dynamics and controls neuronal polarity [125]. In these mice, a decrease in proliferation of progenitor cells during embryonic development causes decreased neurogenesis, which results in absence of all major axonal tracts, including the anterior commissure (AC), the hippocampal commissure (HC), and the corpus callosum (CC), implying a general role of WDR47 in axonal outgrowth in vivo. Along similar lines, decreased autophagic activity due to mutations in Atg16l1 increases the size of the CC in mice [126]. An opposing effect for autophagy disruption is observed by brain-specific knockout of Atg9a in mice, where defective neurite overgrowth as well as dysgenesis of the CC and the AC are prominent features. Unexpectedly, the authors reported that primary murine neurons with a depletion of Atg7 and Atg16l1 do not display the same defects [127], suggesting that the effects observed in atg9a knockout animals may not be primarily due to autophagy interruption, but disrupted non-canonical functions of Atg9a. A similar observation has been made in epg5 knockout animals, in which non-canonical dysfunction may be an important contributor to the observed decrease in CC size [128], as demonstrated by the deceleration in endocytosis and the delay in endocytic recycling in these animals [129].

Ablation of Ulk1 and Ulk2, required for parallel fiber formation of granule cells, represents a similar scenario: Ablation of both proteins blocks neurite formation in primary murine granule cells in vitro [130] and, if specifically ablated in the CNS, causes defective axonal pathfinding and defasciculation in the CC, AC, corticothalamic axons and thalamocortical axons [131]. However, none of these defects are recapitulated in Atg7 and Rb1cc1 (RB1-inducible coiled-coil 1) mutants, suggesting a mechanism related to a disturbance of non-canonical roles rather than to the primary autophagy defect.

Interestingly, there is also some indication that the effect of autophagy on neurite and synapse formation and remodeling may be dependent on the specific neuronal subtype. Stavoe et al. [132] reported that mutations in six autophagy genes in C. elegans (atg-9, atg-13, epg-8, igg-1, atg-2 and unc-104) lead to longer nociceptors while HSN, RIA, DA9, RIB, and NSM neurons do not show a comparable phenotypic alteration. The same study reported that disruption of 18 different autophagy genes in C. elegans is not only affecting neurite formation, but also synapse formation, the subsequent step in neurodevelopment. Mutant animals exhibit impaired vesicle clustering and reduced active zone formation [132], comparable to earlier findings in Drosophila melanogaster where depletion of Atg1/unc-51 (ULK1 in mammals) leads to defects in active zone formation associated with impaired neurotransmitter release [133]. The development of neuromuscular junctions, the muscle innervating synapses, in Drosophila melanogaster is also impaired in Atg1, Atg2, Atg6, and Atg18 mutants, while overexpression of Atg1 increases the number of synaptic boutons [134]. A similar phenotype is observed in mouse models, in which motor neuron-specific ablation of Atg7 leads to 37% larger neurons, denervation of motor endplates and reduced neurotransmission [135].

Lastly, autophagy is also implicated in spine pruning, the final step of neuronal development that eliminates excess dendrites. Mice with heterozygous mutations in genes encoding MTOR inhibitors Tsc1 (TSC complex subunit 1) and Tsc2 (TSC complex subunit 2) in layer V pyramidal neurons exhibit higher numbers of spines in the cortex due to defective spine pruning as a consequence of low autophagic activity [136]. It can thus be speculated that, in the absence of critical autophagy factors, improper pruning of axons and synapses by microglia, i.e. in a non-cell-autonomous manner, causes the observed abnormalities in axon formation and neurite outgrowth mentioned above.

In conclusion, autophagy has been implicated in virtually all steps of neurodevelopment. However, its effects are not consistent and can either have a promoting or inhibiting effect on neuronal development and differentiation, depending on the developmental process and the cell type. Importantly, some studies suggest that although the ablation of autophagy genes gives rise to neurodevelopmental defects,
the observed phenotypes may be caused by non-canonical functions of these genes rather than a direct disruption of autophagic pathways.

**Neurological and neurodegenerative features**

As outlined in more detail above, congenital disorders of autophagy often show a characteristic evolution of neurological features over time, with neurological symptoms such as spasticity, ataxia, dystonia and epilepsy often evolving on the background of a preexisting neurodevelopmental disorder. In addition, an increasing number of adult-onset neurodegenerative disorders have recently been attributed to primary defects in the autophagy pathway (Table 2 and S1), supporting a role of autophagy not only in normal neuronal development and differentiation but also in maintenance of the nervous system.

In general terms, the large size and the high energy demands of neuronal cells represent a special challenge for homeostasis. Neurons as highly specialized cells are maintained mostly throughout the whole lifespan of an organism, and therefore rely heavily on housekeeping mechanisms that safeguard the integrity of organelles and proteostatic processes. More specifically, evidence for the crucial role of autophagy in physiological neuronal maintenance was originally derived from conditional knockout of the key autophagy genes Atg5 and Atg7 in the mouse brain [137,138], resulting in axonal swellings and ultimately degeneration of cerebellar Purkinje cells and hippocampal pyramidal neurons. Along similar lines, neuron-specific knockout of Bnip1 leads to accumulation of ubiquitin-positive aggregates and degeneration of Purkinje cells in mice [139], whereas heterozygous deletion of Beclin1 shows loss of synapses and dendrites of the hippocampus [139,140]. Since then, much attention has been invested in further elucidating the role of autophagy in neurons and glial cells, in relation to their specific function and their very distinct polarized morphology: Synapse development and maintenance, generation and turnover of autophagosomes, their subsequent transport along the microtubules inside the long dendritic and axonal projections and concurring consumption rely on precise spatial and temporal regulation and coordination [141], resulting in complex compartmentalization of neuronal autophagic mechanisms [142]. Other peculiar features of the nervous system adding further levels of complexity are the transcellular exchange of debris from neurons to glial cells [143], and, as a metabolically highly demanding tissue, its heavy reliance on mitochondrial integrity and function. Research concerning aging-related neurodegenerative conditions has therefore focused on the selective autophagic digestion of dysfunctional mitochondria (or mitophagy) as well as removal of aggregation-prone proteins (or aggrephagy) [141].

A peculiar feature of the congenital disorders of autophagy is their predilection for certain parts of the nervous system, in particular the cerebellum, long white matter tracts and peripheral neurons. Why exactly certain neuronal subtypes such as cerebellar Purkinje cells are predominantly affected in these conditions has yet to be clarified, but it is conceivable that their complex architecture and high metabolic activity could be the reason for their selective vulnerability. In addition, autophagy plays a crucial role in the homeostasis of axons, as supported by the axonal pathology observed in autophagy-deficient mouse models, and by the prominent involvement of brain white matter tracts and peripheral nerves, structures consisting mainly of axonal projections, in humans with congenital disorders of autophagy. Autophagosomes in particular constitutively form in the distal end of axons and are transported retrogradely to the cell soma for degradation [144,145], and any defect disturbing this essential mechanism is likely to result in neuronal pathology. The latter hypothesis is supported by the observation that mutations affecting proteins primarily involved in axonal (including autophagosomal) transport cause similar phenotypes as primary autophagy disorders, probably due to secondary effects on correct autophagosomal positioning [146,147].

In addition to these basic considerations and in a more clinical context, autophagy has been associated with adult-onset neurodegenerative disorders in several ways (for review [148]), nonspecifically through its complex interactions with the potentially toxic protein aggregates implicated in these conditions, and, specifically, through primary genetic mutations directly or indirectly affecting components of the autophagy machinery (summarized in Table S1): Autophagy plays a role, for example, in the removal of SNCA (synuclein alpha) in PD [149,150], misfolded proteins in ALS [52,151], mutant HTT (huntingtin; mHTT) in Huntington disease (HD) [114,152] and intracellular MAP2/Tau tangles in Alzheimer disease (AD) [153,154], but at the same time these targets of autophagic digestions may impair normal autophagic flux and functioning through their inherent toxicity. While rare, primary genetic causes in particular of PD also indicate a role of defective autophagy, for example autosomal-recessive mutations in PINK1 and PARK2, encoding two proteins that act in concert to designate damaged mitochondria for mitophagic digestion and thus play an important role in mitochondrial quality control [155]. Mutations in LRRK2 have been associated with dominant forms of PD and have been demonstrated to affect the proper functioning of CMA [156], but LRRK2’s precise role in autophagy currently still awaits resolution [157]. Of note, heterozygosity for mutations in the lysosomal enzyme GBA (glucosylceramidase beta), the gene recessively mutated in Gaucher disease (GD), is the most common genetic risk factor for PD and associated with autophagic impairment, emphasizing the intimate crosstalk between autophagic and lysosomal pathways [158,159].

The role of autophagy in ALS is illustrated through a small proportion of familial ALS cases due to pathogenic variants in the autophagy receptors SQSTM1 [160], OPTN [161], and UBQLN2 (ubiquilin 2) [162], all of which facilitate cargo recruitment into phagophores through their interactions with LC3. Homozygous mutations in SQSTM1 lead to a congenital absence of the autophagy receptor and cause a childhood-onset neurodegenerative condition with a phenotype comprising ataxia/cerebellar syndrome, parkinsonism, and cognitive decline [163]. Different forms of ALS (and/or of frontotemporal dementia [FTD] with overlapping clinical features) have also been linked to heterozygous dominant mutations in VCP encoding valosin-containing
protein (FTDALS6) [164] (also implicated in inclusion myopathy with Paget disease of the bone and FTD [165]), CHMP2B encoding charged multivesicular body protein 2B (FTDALS7) [166], and GRN encoding progranulin [167]. Although the roles of these proteins are clearly multiple, VCP and CHMP2B both function in autophagy, while progranulin is important for both autophagosome and lysosome function [168]. Interestingly and corresponding to what has been observed with SQSTM1, while heterozygous mutations in GRN lead to frontotemporal degeneration later in life, homozygous GRN mutations cause a neurodevelopmental disorder with features similar to a lysosomal storage disorder or a neuronal ceroid lipofuscinosis (NCL11) [169].

Although not a primary component of the autophagy machinery and likely to be associated with multiple roles, C9orf72, the gene most commonly associated with ALS, has also been linked to autophagy [170,171]. ALS-associated hexanucleotide repeat expansions in the C9orf72 gene are translated into dipeptide repeat (DPR) proteins, which are prone to aggregate and ultimately lead to neurodegeneration. Interestingly, EPG5 has been shown to be a modifier of this DPR toxicity, emphasizing again the role of autophagy in neurodegenerative diseases [172].

It is clear from SQSTM1 and GBA that the age of onset and phenotype severity are related to the genetic burden, with homozygous mutations causing rare childhood-onset neurodegenerative syndromes while heterozygous mutations are associated with more common late-onset neurodegenerative disorders such as ALS and PD. Simply put, the mutation dosage may very well determine the phenotype due to the time it takes for aggregates to accumulate. This also suggests that the key to effective therapeutic intervention in classical late-onset neurodegenerative disorders may lie in earlier treatment. In addition, family studies in rare early-onset autophagy disorders may play a valuable role in the identification of additional genetic risk factors for neurodegenerative disorders, or vice versa.

**Neuromuscular features**

EPG5-related Vici syndrome, the paradigmatic disorder of defective autophagy, shows a consistently associated myopathy, on the histopathological level characterized by increased fiber size variability, increased (central) nucleation, fiber type disproportion with predominance of type 1 fibers, vaculization, increased glycogen storage and variable mitochondrial abnormalities, including respiratory chain enzyme abnormalities [79,88,173]. The EPG5-associated myopathy shows considerable histopathological overlap with primary vacuolar myopathies, centronuclear myopathy (CNM), X-linked myotubular myopathy (XLMTM), and glycogen storage disorders (GSDs), and it is not unexpected that also in these disorders both primary and secondary defects of autophagy have now been critically implicated (Table 3): Danon Disease and X-linked myopathy with excess autophagy (MEAX), the most common vacuolar myopathies, are due to X-linked mutations in LAMP2 [174] and VMA21 (vacuolar ATPase assembly factor VMA21) [175], two genes encoding a lysosomal membrane component and a subunit of the lysosomal vacuolar-type H+-ATPase important for lysosomal acidification, respectively. While in both conditions, the primary defect thus likely originates in the lysosome, histopathological features of marked autophagic buildup and variable degrees of exocytosis are identical to what has been observed in EPG5-related Vici syndrome. “Retrograde” abnormalities of autophagosome formation and autophagosome-lysosome fusion have also been observed in Pompe Disease [176], a GSD secondary to deficiency of lysosomal GAA (alpha glucosidase), emphasizing the close connection between lysosomal and autophagic abnormalities. The marked similarities between the EPG5-related myopathy and CNM/XLMTM are particularly intriguing, considering that many of the major genes implicated in these conditions – MTM1 (myotubularin 1), DN2M (dynamin 2) and BIN1 (bridging integrator 1) – play an important role in intracellular membrane trafficking and have been linked with defective autophagy in human cells and animal models [147,177,178]. In addition, MTM1 plays a specific role in the regulation of PtdIns3P levels [179], an important substrate at the phagophore initiation stages (see above).

In contrast to EPG5-related Vici syndrome, a skeletal myopathy has not been reported in any of the other congenital disorders of autophagy yet. This may reflect a genuine absence or, more likely considering the prominent expression of genes such as WDR45 in skeletal muscle, an overlooked aspect due to the overwhelming severity of neurological and other multisystem features. Of note, all genes/proteins implicated in the

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**Table 3. Neuromuscular disorders with defects in autophagy – selection.**

| Condition | OMIM | Gene | OMIM | Protein |
|-----------|------|------|------|---------|
| **Vacuolar myopathies** | | | | |
| Danon disease | 300257 | LAMP2 | 309060 | lysosomal associated membrane protein 2 |
| X-linked myopathy with excessive autophagy (XMEA) | 310440 | VMA21 | 300913 | vacuolar ATPase assembly factor |
| **Glycogen storage disorders (GSD)** | | | | |
| Glycogen storage disease (GSD) type 2 | 232300 | GAA | 606800 | alpha glucosidase |
| **Centronuclear myopathies** | | | | |
| X-linked myotubular myopathy (XLMTM) | 310400 | MTM1 | 300415 | myotubularin 1 |
| Centronuclear myopathy (CNM) | 160150 | DN2M | 602378 | dynamin 2 |

**Role in autophagy/abnormality**

- “Retrograde” autophagic abnormalities secondary to impaired autolysosomal fusion [174]
- “Retrograde” autophagic abnormalities secondary to abnormal lysosomal acidification [175]
- “Retrograde” abnormalities of autophagosome formation and autophagosome-lysosome fusion secondary to abnormal lysosomal glycogen storage [176]
- Regulator of PtdIns3P pool; disconnection between fasting and autophagy initiation [178]; failure of ATG machinery to dissociate from PAS site [295]; Autophagic buildup and delayed autophagosome maturation in DN2M mouse models [147]
congenital disorders of autophagy are also expressed in skeletal muscle, although for TECPR2 so far this has only been demonstrated at the gene/RNA level and not yet at the protein level.

**Differential diagnosis and overlap with other early-onset neurological multisystem disorders**

Congenital disorders of autophagy show a wide range of clinical and histopathological features, and other multisystem disorders with neurological involvement, as well as acquired or inherited primary neurological or neuromuscular disorders, ought to be considered in the differential diagnosis (Table 4). The overlap with other neurological multisystem disorders may reflect close links between the autophagy pathway and the organelles implicated in the respective multisystem disorder, or, alternatively, a genuine dual role of the protein implicated in the respective congenital disorder of autophagy. Examples for clinical similarities based on the close links of the autophagy pathway with other pathways are lysosomal storage and mitochondrial disorders, which often have similar clinical features, reflective of the lysosome as the endpoint of autophagy, and of autophagy (in its specialized form of mitophagy) as an important mitochondrial quality control mechanism.

Although the primary defects in congenital disorders of autophagy do not reside directly in the lysosome, they may mimic some of the clinical features of lysosomal storage disorders (for review [180,181]), for example the coarse facial appearance seen in SNX14-related cerebellar ataxia and, occasionally, EPG5-related Vici syndrome. The latter group of patients may also develop thalamic changes on brain MRI similar to those seen in disorders of primary lysosomal origin [79]. In addition to the intracellular accumulation of undigested macromolecules in lysosomes, a hallmark feature of lysosomal storage disorders, secondary deficits in upstream autophagy pathway have been frequently documented [60,182]. Impaired autophagic flux and accumulation of autophagosomes in EPG5-related Vici syndrome closely resembles the histopathological findings in lysosomal storage disorders such as GM1 gangliosidosis, Niemann-Pick disease type C1 (NPC1), and the neuronal ceroid lipofuscinoses (NCLs) [182,183]. Along similar lines, patients with bi-allelic SNX14 mutations share both clinical and pathological features of lysosomal storage (such as enlarged lysosomes) and autophagic (such as reduced autophagic flux) disorders, suggesting that deficits in both autophagy and lysosomal function may contribute to certain features of the clinical phenotype in SNX14-related ataxia such as prominent cerebellar involvement and Purkinje cell loss [107].

In addition to lysosomal storage disorders, many clinical aspects of congenital disorders of autophagy also resemble mitochondrial disorders. Progressive impairment of the mitochondrial form and function is the hallmark feature of mono- genetic mitochondrial disorders, a heterogeneous group of nearly 50 diseases caused by mutations in 228 protein-encoding nuclear DNA genes and 13 mitochondrial DNA (mtDNA) genes [184,185]. The mitochondrial morphology and/or respiratory chain defects caused by these mutations primarily affect energy production, leading to neuropathological and neuromuscular manifestations of mitochondrial disorders, which preferentially affect the striated muscles and nervous system [186,187]. Abnormal mitochondrial ultrastructure as well as altered respiratory chain enzyme function with predominant skeletal myopathy diagnosed in patients suggest secondary mitochondrial dysfunction as an important mechanism in EPG5-related Vici syndrome, and may lead to the differential diagnosis of one of the mitochondrial disorders [187,188]. Since mitochondrial homeostasis critically depends on downstream pathways that mediate selective removal of damaged mitochondria by autophagy and lysosomal degradation, secondary mitochondrial dysfunction and defective mitophagy are common pathological findings in autophagy and lysosomal storage disorders. Evidence of impaired mitophagy has long been recognized in patient samples and disease models of a variety of different autophagy disorders [189]. Deficits in mitochondrial form and function are also critical contributors to progressive neurodegeneration, as observed in PINK1- and PRKN-related early-onset PD [190]. Defective mitophagy induced by defects in the PINK1-PRKN pathway, which normally involves a complex interplay of PINK1-dependent phosphorylation and PRKN-mediated ubiquitination events on the outer mitochondrial membrane resulting in the selective sequestration of ubiquitinated mitochondria within autophagosomes, leads to accumulation of damaged mitochondria and subsequent neuronal cell death [191,192]. Defective mitophagy has also been observed in association with mutations in OPTN encoding optineurin [193].

Another important group of conditions that show marked clinical overlap with disorders of autophagy are disorders of intracellular (vesicular) trafficking, probably reflective of the fact that some of the proteins implicated in congenital disorders of autophagy, such as EPG5, do have genuinely multiple roles in both autophagy but also other, in particular endosomal/endocytic trafficking pathways [194]. Indeed, it may be very difficult to distinguish which of the phenotypical expressions of a mutated protein may be due to its role in autophagic or other closely related vesicular trafficking processes. Based on the assumption that multisystem disorders linked in the same molecular pathways do share a recognizable “clinical” signature, a reverse search on Human Dysmorphology databases applying the key features of EPG5-related Vici syndrome reveals indeed a number of clinically similar conditions due to mutations affecting proteins that are implicated in cellular trafficking processes in a wider sense, but that may also give rise to secondary autophagy abnormalities. For example, Marinesco-Sjogren syndrome (MSS) [195] and related disorders share cataracts, a skeletal muscle myopathy and, in some cases, sensorineural deafness with EPG5-related Vici syndrome, although other neurological features and the degree of multisystem involvement are usually less pronounced. Corresponding to the observed clinical overlap, impaired autophagy and nuclear abnormalities similar to those observed in primary autophagy disorders have been described in muscle tissue from SIL1-deprived mice, an animal model of MSS [195–197]; although the precise basis for this observation remains uncertain, disturbance of the autophagy pathway at the phagophore stage is
one plausible hypothesis, considering the prominent role of S1L1 at the ER. Another group of conditions that show considerable overlap with EPG5-related Vici syndrome are Chediak-Higashi syndrome (CHS) [198] and related primary immunodeficiency syndromes, with common features of hypopigmentation, immune defects, variable neurological involvement, and, in some cases, a vacuolar myopathy. Corresponding to the observed clinical overlap, mutations in LYST, the causative gene, have been shown to affect lysosome size and quantity but also to cause autophagic abnormalities, although evidence for the latter has been discussed controversially [199].

The hypothesis of disorders linked in connected autophagy and trafficking pathways sharing the same “clinical signature” was recently supported by the identification of an interaction between EPG5 and RAB3GAP1, the protein mutated in Warburg Micro syndrome [200], as outlined above a clinical phenocopy of EPG5-related Vici syndrome. Furthermore, WMS can also be caused by mutations in RAB3GAP2 (RAB3 GTPase activating non-catalytic protein subunit 2), RAB18 and TBC1D20 (TBC1 domain family member 20). In addition to their primary trafficking functions, both RAB3GAP2 and RAB18 also play an important role in autophagosome formation, while TBC1D20 is needed for autophagosome maturation [200–203]. The clear link between the autophagy pathway and cellular trafficking due to mutations in those genes may thus explain the observed clinical similarities between WMS and EPG5-related Vici syndrome.

There are a number of other human multisystem disorders, which show considerable overlap with congenital disorders of autophagy, including glycogen storage disorders, congenital disorders of glycosylation, ciliopathies and peroxisomal disorders.

Increased glycogen is common on muscle biopsies from patients with EPG5-related Vici syndrome, and, in conjunction with occasionally observed organomegaly, may give rise to the suspicion of one of the glycogen storage disorders [204], another group of conditions that is closely linked with both abnormal autophagy and lysosomal pathology [205]. The accumulation of autophagic debris, glycogen-containing lysosomes as well as exocytosed vesicles observed in those muscle biopsies share common pathological features with the severe metabolic myopathy observed in one of the GSDs, Pompe Disease [84,206].

Clear links are also emerging between congenital disorders of glycosylation [207,208] and the autophagy pathway: For example, various key autophagy proteins such as SNAP29 and BECN1 require post-translational O-GlcNAc glycosylation for their proper functioning [208,209], suggesting that any primary defect in these pathways will also have downstream functional consequences on autophagy. Furthermore, glycoconjugates have also been described as inducers of autophagy by decreasing the activity of the MTOR pathway [105], and probably play an important role in autophagosome formation, considering their localization on the ER and leading edges of the phagophore. Lastly, the interaction between the two pathways is bi-directional, as autophagy regulates the turnover of free glycans, which can accumulate in the cytosol [207,209].

Given the number of interactions between autophagy and glycosylation as outlined above, the strong clinical overlap with shared features of developmental delay, failure to thrive, neurological and neuromuscular abnormalities, and cardiac involvement [79,207], is thus not unexpected.

Ciliopathies, the summary term for a variety of diseases caused by impairment of the formation or function of primary cilia [210–213], are another clinically similar group of disorders that may feature multiorgan involvement but also neurological and structural CNS abnormalities including agenesis of the corpus callosum. Recently strong bi-directional interactions between autophagy and cilia have been described, in which ciliary pathways control autophagy and conversely autophagy is important for regulating ciliogenesis [213,214]. Both inducers (e.g., IFT20) and suppressors (e.g., OFD1) of ciliogenesis can be degraded through autophagy, stressing its influence on the formation of cilia and its potential role in the cause of ciliopathies. Vice versa, it has been shown that autophagy is decreased in cells with compromised cilia, possibly via activation of the MTOR pathway, again indicating their close interaction [213,214].

In conclusion, the vast clinical overlap between the above-mentioned groups of disorders and congenital disorders of autophagy is not very surprising, giving the clear mechanistic links between the different pathways (summarized in Table 4). Many of the proteins causing these diseases have multiple roles in several cellular pathways, making it sometimes difficult to pinpoint the specific cause of a disease or a particular symptom. Understanding autophagy and its crosstalk with other cell type-specific homeostatic pathways, in particular

| Table 4. Differential diagnosis of congenital disorders of autophagy. |
|---------------------------------------------------------------|
| Group of conditions                                           | Molecular basis for clinical overlap with autophagy disorders                                      |
| Lysosomal storage disorders                                   | Close connections between autophagic and lysosomal pathways; Retrorge autophagic abnormalities in lysosomal storage disorders; Anterograde lysosomal abnormalities in autophagy disorders |
| Mitochondrial disorders                                       | Secondary mitochondrial dysfunction due to defective mitophagy                                     |
| Glycogen storage disorders                                    | Retrorge autophagic abnormalities due to abnormal glycogen storage                                |
| Vesicular trafficking disorders                                | Close connection between autophagic and endosomal/endocytic trafficking pathways; Involvement of mutated genes in multiple pathways |
| Glycosylation disorders                                        | Glycosylation important for normal functioning of certain autophagy proteins; Role of glycoconjugates in autophagy induction; Role of autophagy in turnover of free cytosolic glycans |
| Ciliopathies                                                  | Role of ciliary pathways in controlling autophagy; Association between ciliary dysfunction and impaired autophagy |
membrane and vesicle trafficking, lysosomal pathways and autolysosome consumption [215], will probably help to unravel additional aspects of autophagy specific to neurons, and explain their specific vulnerability to defects affecting these processes.

**Animal models of congenital disorders of autophagy**

Animal models emulating human pathologies allow insights into disease mechanisms on cell biological level, which are often hard or impossible to gather otherwise.

The best-characterized animal model for Vici syndrome is the epg5−/− mouse model. epg5−/− mice show a clear neurodegenerative phenotype as observed in humans, however this only arises in adulthood, while the majority of Vici syndrome patients present with very early-onset neurodegeneration [79,128]. Another difference is the lack of neurodevelopmental features in the epg5−/− mice, although they do have a reduced (but not absent) corpus callosum, a myopathy and retinitis pigmentosa [128,216]. These differences between the human and the murine phenotype suggest that caution is required when investigating complex human multisystem disorders in relevant animal models, which are however still indispensable for the development and pre-clinical testing of new therapies.

Although development of specific therapies for congenital disorders of autophagy is still at a very early stage, lessons may be learned from recent more advanced developments concerning disorders, which are not strictly part of this group but where defective autophagy is a prominent feature. For example, a number of different (including pharmacological, genetic and enzyme replacement) approaches have been investigated for XLMTM due to X-linked recessive mutations in myotubularin, a regulator of the Ptdlns3P pool essential for phagophore formation in the early stages of autophagy [217,218]. Some of these approaches are currently reaching the stage of clinical application and may serve as models for therapy development in congenital disorders of autophagy.

Interestingly, there are a number of phenotypes in animal models with primary defects in autophagy for which no corresponding human phenotype has been identified yet, for example those affecting the cysteine protease ATG4, which is required for c-terminal hydrolysis of ATG8 family proteins including LC3 [219]. ATG4B-deficient mice show slightly abnormal cerebellar morphology and mild motor impairment [220] while a point mutation in the ATG4D gene has been identified as the cause of a hereditary neurodegenerative disease in Lagotto Romagnolo dogs, associated with decreased autophagic flux under basal conditions [221,222]. Another congenital disease of autophagy identified in dogs is hereditary ataxia caused by mutations in RAB24 [223]. RAB24 functions in the clearance of autolysosomes in basal autophagy [224].

Identification of disease-causing mutations in animal models like these could help to shed more light on human disease for which no causative genes have been pinpointed yet, in particular in the context of the wealth of genetic data currently generated in the context of diagnostic next-generation sequencing.

**Neurodevelopmental and neurodegenerative disorders due to defective autophagy – a lifetime continuum of neurological disease**

As outlined in the preceding paragraphs, there is mounting and multiple clinical and molecular evidence for a continuum between congenital disorders of autophagy and adult-onset neurodegenerative disease: 1) while essentially neurodevelopmental disorders at the outset, most congenital disorders of autophagy follow a biphasic course, with a phase of accelerated deterioration following an initial period of apparent stability. Such a period of accelerated deterioration, characterized by progressive dementia, epilepsy and movement disorders (often of a Parkinsonian nature) is typical in WDR45-associated BPAN and SNX14-associated cerebellar ataxia, but also in EPG5-related Vici syndrome, as evidenced by rapidly progressive microcephaly and an evolving movement disorder in long-term survivors. 2) Animal models of defective autophagy show CNS features mimicking adult-onset neurodegenerative disorders, as demonstrated in a conditional Epg5 Drosophila knockdown showing severe retinal neurodegeneration [84], by clinical and pathological features of human ALS in the epg5−/− mouse [129], and by similar findings in a range of murine models of Atg deficiency [225]. 3) Other early-onset neurodevelopmental disorders linked in related vesicular trafficking and lysosomal pathways, for example LYST-related CHS [226–228] but also SIL1-related MSS [229], also demonstrate a higher incidence of early-onset (Parkinsonian) movement disorder. 4) Risk variants in the EPG5 [172] but also SIL1 gene [230] have been identified as modifiers of adult-onset neurodegenerative disorders including dementia, PD and ALS. 5) An increasing number of adult-onset neurodegenerative disorders including dementia, PD and ALS have now been linked to components of the autophagy pathway (Table S1). Taken together, these observations suggest a continuum between early-onset neurodevelopmental and adult-onset neurodegenerative disorders connected in intricately linked intracellular vesicle trafficking pathways and underline that the thorough investigation of rare genetic childhood disorders may be of relevance for the understanding of much more common age-related conditions (Figure 3).

**Therapeutic perspectives**

Given the key role of autophagy in many human diseases, this fundamentally important intracellular pathway has been under intense investigation for therapeutic exploitation [148]. While in the cancer field, most attempts have focused on blocking autophagy, in neurodevelopmental and neurodegenerative disorders, the agreed consensus is that what is desirable is the stimulation rather than the blockade of autophagy. Most approaches so far have focused on neurodegenerative disorders and on targeting the regulatory signaling pathways upstream of autophagy rather than the autophagy process itself. Therapeutic approaches utilizing small molecules and focusing on upstream regulatory pathways such as the MTOR pathway can be grossly divided into those acting in an MTOR-dependent and those acting in an MTOR-independent
manner. Amongst the MTOR-dependent approaches, Rapamycin (which induces autophagy through its MTOR antagonism) has been shown to ameliorate the phenotype of models for AD, PD and HD [231–233]. An alternative, MTOR-independent approach is autophagy stimulation via the AMPK pathway utilizing molecules such as trehalose [234]. However, stimulation of autophagy initiation is not always helpful and there are examples where a detrimental effect has been observed in animal models of neurodegeneration in which the clearance step is stalled [235,236]. It is also worth noting that autophagy may be protective or pathogenic depending on the disease stage [135]. Moreover, many neurodegenerative diseases but in particular neurodevelopmental disorders such as EPG5-related Vici syndrome, display defects in the actual autophagy cycle, leading to a slower or impeded clearance. It is reasonable to expect that this blockage is not overcome by merely increasing the levels of autophagy initiation upstream, as evidenced by the absence of any survival benefit in a large phase III trial of the putative autophagy enhancer (lithium) in patients with ALS. A plausible alternative would be to rather increase all pathways of lysosomal clearance, including autophagy and lysosomal biogenesis, controlled by the transcription factor TFEB and related members of the MiT/TFE family [237–239]. Several interventions based on TFEB-related gene therapy approaches have indeed been shown to be effective in numerous animal models of neurodegenerative diseases [240–243], and in GSDs such as Pompe disease. Most therapeutic approaches applied to date modify autophagy in a very general way, and small molecules that would target the autophagy pathway more specifically and tailored to the underlying molecular defect may represent a more effective approach to neurodevelopmental and neurodegenerative disease with defective autophagy in future.

As a general point concerning late-onset neurodegenerative disorders associated with defective autophagy but without a specific causative gene, it is still uncertain if autophagy as such is normal and is just overwhelmed over time leading to issues later in life, or if, alternatively, there is a primary issue present from birth that very slowly leads to problems after decades, as supported by the observation outlined above that mutation dosage appears to determine age of onset. Whatever the underlying scenario, it is likely that in late-onset neurodegenerative disorders, the process of defective autophagy is present for many years before becoming clinically evident, suggesting a prolonged window of opportunity for therapeutic intervention. Subtle clinical signs or symptoms may be present for years (if not decades) in susceptible patients, indicating markers that may allow identification of patients for early treatment [65].

Conclusions and outlook
Neurodevelopmental disorders with defective autophagy represent a novel and rapidly expanding group of inborn errors of metabolism. While the causative defects affect primarily the autophagy machinery and associated proteins, there is considerable overlap with other inborn multisystem disorders, in particular lysosomal disorders and those due to defects in vesicular and membrane trafficking [178].
of clinical features and communality of molecular mechanisms suggest a continuum of early-onset neurodevelopmental and adult-onset neurodegenerative disorders with defects in autophagy and intracellular trafficking throughout life. Considering that the autophagy pathway is highly amenable to pharmacological modification, the development of therapies tailored to specific underlying molecular mechanisms and the complex neuronal environment represents the ultimate goal [174].

Abbreviations
AC: anterior commissure; AD: Alzheimer disease; ALR: autophagic lysosomal reformation; ALS: amyotrophic lateral sclerosis; AMBRA1: autophagy and beclin 1 regulator 1; AMPK: AMP-activated protein kinase; ASD: autism spectrum disorder; ATG: autophagy related; BIN1: bridging integrator 1; BPAN: beta-propeller protein associated neurodegeneration; CC: corpus callosum; CHMP2B: charged multivesicular body protein 2B; CHS: Chediak-Higashi syndrome; CMA: chaperone-mediated autophagy; CMT: Charcot-Marie-Tooth disease; CNM: centronuclear myopathy; CNS: central nervous system; DNMT2: dynamin 2; DPR: dipeptid repeat protein; DVL3: disheveled segment polarity protein 3; EPGS: ectopic P-granules autophagy protein 5 homolog; ER: endoplasmic reticulum; ESCRT: homotypic fusion and protein sorting complex; FIG4: FIG4 phosphoinositide 3-phosphatase; FTD: frontotemporal dementia; GBA: glucocerebrosidase; GD: Gaucher disease; GRN: progranulin; GSD: glycogen storage disorder; HC: hippocampal commissure; HD: Huntington disease; HOPS: homotypic fusion and protein sorting complex; HSPP: hereditary spastic paraparesis; LAMP2A: lysosomal associated membrane protein 2A; MEAX: X-linked myopathy with excessive autophagy; mHTT: mutant huntingtin; MSS: Marinesco-Sjogren syndrome; MTM1: myotubularin 1; MTOC: mechanistic target of rapamycin kinase; NBIA: neurodegeneration with brain iron accumulation; NCL: neuronal ceroid lipofuscinosis; NPC1: Niemann-Pick disease type 1; PD: Parkinson disease; PtdIns3P: phosphatidylinositol-3-phosphate; RAB3GAP1: RAB3 GTase activating protein catalytic subunit 1; RAB3GAP2: RAB3 GTase activating non-catalytic protein subunit 2; RBL1: RBL1-inducible coiled-coil protein 1; RHEB: ras homolog, mTORC1 binding; SCAR20: SNX14-related ataxia; SENDA: static encephalopathy of childhood with neurodegeneration in adulthood; SNX14: sorting nexin 14; SPG11: SPG11 vesicle trafficking associated, spatzacin; SQSTM1: sequestosome 1; TBC1D20: TBC1 domain family member 20; TECPR2: tectonin beta-propeller repeat containing 2; TSC1: TSC complex subunit 1; TSC2: TSC complex subunit 2; UBQLN2: ubiquilin 2; VCP: valosin-containing protein; VMA21: vacuolar ATPase assembly factor VMA21; WDFY3/ALFY: WD repeat and FYVE domain containing protein 3; WDR45: WD repeat domain 45; WDR47: WD repeat domain 47; WMS: Warburg Micro syndrome; XLMTM: X-linked myotubular myopathy; ZFYVE26: zinc finger FYVE-type containing 26

Acknowledgments
This work was supported by grants from the European Union’s Horizon 2020 Research and Innovation Programme (765912 — DRIVE — H2020-MSCA-ITN-2017) to CD, MR, ELE, MF and HJ, Action Medical Research (2446) to HJ and MF, Medical Research Council (G1002186) to MF, and the Myotubular Trust (12KCL01) to HJ and MG.

Disclosure statement
No potential conflict of interest was reported by the author(s).

ORCID
Celine Deneubourg http://orcid.org/0000-0002-8854-6619
Olga Baron http://orcid.org/0000-0002-0536-8678
Eeva-Liisa Eskelinen http://orcid.org/0000-0003-0006-7785
Manolis Fanto http://orcid.org/0000-0001-7807-2563

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