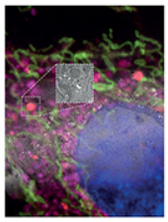
Autophagy



Autophagy

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# A burning question from the first international BPAN symposium: is restoration of autophagy a promising therapeutic strategy for BPAN?

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MEETING REPORT



# A burning question from the first international BPAN symposium: is restoration of autophagy a promising therapeutic strategy for BPAN?

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**ABSTRACT**

Beta-propeller protein-associated neurodegeneration (BPAN) is a rare neurodegenerative disease associated with severe cognitive and motor deficits. BPAN pathophysiology and phenotypic spectrum are still emerging due to the fact that mutations in the *WDR45* (WD repeat domain 45) gene, a regulator of macroautophagy/autophagy, were only identified a decade ago. In the first international symposium dedicated to BPAN, which was held in Lyon, France, a panel of international speakers, including several researchers from the autophagy community, presented their work on human patients, cellular and animal models, carrying *WDR45* mutations and their homologs. Autophagy researchers found an opportunity to explore the defective function of autophagy mechanisms associated with *WDR45* mutations, which underlie neuronal dysfunction and early death. Importantly, BPAN is one of the few human monogenic neurological diseases targeting a regulator of autophagy, which raises the possibility that it is a relevant model to directly assess the roles of autophagy in neurodegeneration and to develop autophagy restorative therapeutic strategies for more common disorders.

**Abbreviations:** ATG: autophagy related; BPAN: beta-propeller protein-associated neurodegeneration; ER: endoplasmic reticulum; KO: knockout; NBIA: neurodegeneration with brain iron accumulation; PtdIns3P: phosphatidylinositol-3-phosphate; ULK1: unc-51 like autophagy activating kinase 1; WDR45: WD repeat domain 45; WIPI: WD repeat domain, phosphoinositide interacting.

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## Introduction

BPAN, previously known as static encephalopathy of childhood with neurodegeneration in adulthood (SENDA), is an X-linked dominant neurogenerative disease that has been classified as a neurodegeneration with brain iron accumulation (NBIA) disorder (OMIM 300,894). BPAN is the most recently identified NBIA disorder, and with the increase of BPAN patients diagnosed in the last few years, BPAN has emerged as the most common NBIA disorder with prevalence higher than pantothenate kinase-associated neurodegeneration (PKAN) disease [1,2]. Human and cellular studies have proposed that *WDR45* (OMIM 300,526) variants are causative of a specific NBIA phenotype associated with early developmental delay, autism, and seizures in childhood, with intellectual disability and neurological deterioration (parkinsonism, dystonia, and dementia) in early adulthood [3–5]. An important genetic hallmark of BPAN is that most mutations are *de novo*, which when associated with the specific clinical features, allows clinicians to establish a BPAN diagnosis. Nevertheless, some ambiguity may remain, in particular with *WDR45* missense mutations, which may require further studies of pathogenicity at the cellular level. Hence, further analyses of derived lymphoblastoid cells or fibroblasts from people with BPAN can be used to establish that *WDR45* variants lead to protein loss and defective autophagy similar to engineered *WDR45* knockout (KO) cells.

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Since the initial discovery of the role of WDR45 in BPAN, research has rapidly grown with several animal and cellular models available to study the function of human WDR45 and its animal homologs. This includes published and ongoing studies in mice [6–9], *Drosophila melanogaster* (BM, MC, SA and LW personal communication), and *Caenorhabditis elegans* [10], *Dictyostelium* [11], as well as several human cell lines carrying *WDR45* mutations (fibroblast, lymphoblast, neuroblastoma) [4,12–14] and induced pluripotent stem cells/iPSCs generated from BPAN human fibroblasts [12]. One reason for this rapid establishment of numerous BPAN models is that WDR45 is a known regulator of autophagy, which raises important questions about the role of autophagy in the central nervous system development and maintenance [15]. Indeed, several researchers who participated in the BPAN symposium and others have previously published in the autophagy field [16–30]. *WDR45/WIPI4* belongs to the family of WIPI (WD repeat domain, phosphoinositide interacting) proteins also known as beta-propellers that bind phosphoinositides/PROPPINs, including WIPI1, WIPI2, WDR45B/WIPI3 and WDR45, which are all known regulators of autophagy [31,32]. WIPI proteins all contain a conserved F/

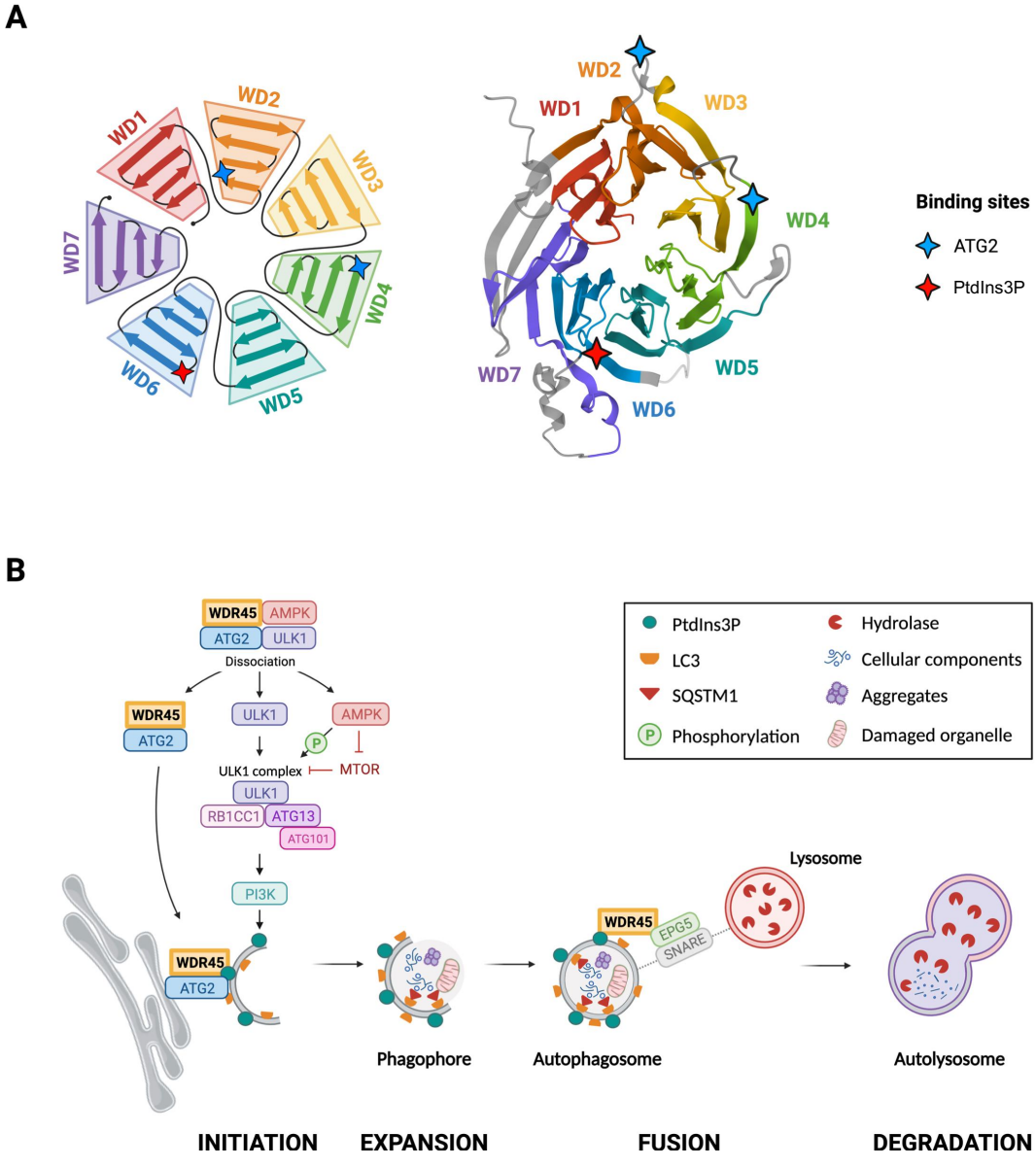


**Figure 1.** The role of WDR45 in autophagy. (A) Schematic representation and 3D structure of WDR45. The 3D structure was generated by Alpha fold structure prediction. The 3D structure of WDR45 and WIPI1, WIPI2 and WDR45B/WIPI3 are similar in which the 7 WD repeats of WDR45 fold into a beta propeller [22]. WD1 to WD7 repeats are represented with the same color codes in the schematic and the 3D structure representation. Mutated residues localized in the PtdIns3P and ATG2 binding domains are shown with red and blue stars, respectively. The mapping of the reported *WDR45* variants is not shown but those variants are distributed throughout the protein domains with no particular hotspots [33]. WDR45 variants all lead to BPAN, with a broad phenotypic spectrum and varied severity. (B) Schematic representation of the autophagy process and WDR45 interaction partners. Under fed conditions, WDR45 interacts with ATG2 in a complex with AMPK and ULK1. In this complex, ULK1 is inactive. Upon starvation and activation of AMPK by STK11/LKB1, the AMPK-ULK1-ATG2-WDR45 complex dissociates. On the one hand, AMPK activates the ULK1 complex by its phosphorylation and also inhibits MTOR. This results in the activation of the class III phosphatidylinositol 3-kinase complex and PtdIns3P production. On the other hand, the WDR45-ATG2 part of the complex is dissociated from the rest of the complex and localizes at the nascent autophagosome, where it presumably promotes maturation. In addition, WDR45 by interacting with EPG5 favors the fusion of autophagosomes with lysosomes.

LRRG motif, for phosphoinositide binding that allows their association with the cytoplasmic leaflet of organelle membranes (Figure 1A). The detailed comparison of WIPI protein homologies has been recently reported [33]. Based on their amino acid sequence identity, WIPI proteins can be classified into two distinct clades. One clade includes WIPI1 and WIPI2, and the other WDR45B/WIPI3 and WDR45. The strong similarities between the members of the same clade explains their redundant roles in autophagy. In contrast, it was proposed that the function of WDR45 in autophagy could be due to specific interacting partners that are distinct from other WIPI and WDR45 proteins [33–36]. Supporting the fact that the function of WDR45 is distinct from the other WIPI proteins, variants in *WIPI1*, *WIPI2* and *WDR45B/WIPI3* genes do not clearly lead to phenotypes resembling BPAN. However, some levels of redundancy exist between *WIPI* genes, particularly between *WIPI1* and *WIPI2*, and between *WDR45B/WIPI3* and *WDR45* [33,37]. In support of a redundant function of *WIPI* genes in the central nervous system, mutations in *WIPI2* and *WDR45B/WIPI3* genes lead to neurodevelopmental pathologies. These include developmental delay, microcephaly, seizures and progressive neurological deterioration in those harboring *WDR45B/WIPI3* mutations, although reports are still relatively limited and the associated phenotypes are likely to change while larger patient cohorts are being described [38].

## What is known so far about the role of WDR45 in autophagy?

Autophagy is an evolutionarily conserved process degrading and recycling cellular contents such as protein aggregates, damaged organelles, and other cytoplasmic materials [39]. Autophagy is characterized by the formation of a phagophore membrane, which expands, resulting in a double-membrane vesicle named an autophagosome. After the fusion of the autophagosome with lysosomes that contain proteases, the sequestrated cytoplasmic contents are degraded and recycled [40]. Autophagy is mediated by ATG (autophagy related) proteins in several steps, first the initiation, followed by the phagophore formation and expansion, which sequesters cytoplasmic cargos within the autophagosome (Figure 1B). Essential regulators of autophagy include the nutrient-sensing MTOR (mechanistic target of rapamycin kinase) and AMP-activated protein kinase (AMPK), which phosphorylate ULK1 (unc-51 like autophagy activating kinase 1), the upstream activator of autophagy, leading to its inhibition or activation, respectively. An important upstream complex is the class III phosphatidylinositol 3-kinase complex, which induces the synthesis of phosphatidylinositol-3-phosphate (PtdIns3P) on the phagophore membrane [41]. Another key autophagy protein is MAP1LC3/LC3 (microtubule associated protein 1 light chain 3; Atg8 in yeast), which after conjugation with phosphatidylethanolamine/PE allows the expansion and closure of the phagophore to form an autophagosome. This step is followed by the fusion between the autophagosome and the lysosome, which is mediated by the interaction of the soluble N-ethylmaleimide-sensitive-factor attachment protein receptor/SNARE complex and EPG5 (ectopic P-granules 5 autophagy tethering factor) proteins, allowing the degradation of cytoplasmic cargos by hydrolytic enzymes within the autolysosome.

Most studies from the last years have reported a role of WDR45 in bulk autophagy, although recent studies have also shown that it could also regulate the selective form of autophagy, ferritinophagy [14,33,37,42,43]. The first striking observation in the analysis of a mice model KO for *Wdr45*, is that the loss of *Wdr45* only led to a partial loss of autophagy, resulting in viable animals carrying neurological syndromes [6–9]. This led to the conclusion that *wdr45*-deficient animal models are useful to study the consequences of partial inhibition of autophagy or inhibition of selective autophagy on the development and maintenance of the nervous system in physiological and pathological conditions.

Mechanistically, WDR45 regulates the autophagy process at different steps. First, it carries conserved motifs that allows its binding to ATG2 and phosphoinositides [36]. By interacting with ATG2 and phosphatidylinositol-3-phosphate on autophagosome membranes, WDR45 favors lipid transfer and elongation of the phagophore controlling the size of the autophagosomes [36]. The importance of the ATG2-WDR45 interaction was challenged in a study showing that the interaction of ATG2 with GABARAP (GABA type A receptor-associated protein) but not with WDR45 plays a major role in autophagy [43]. Second, WDR45 interacts with EPG5, allowing its targeting to late endosomes/lysosomes, hence contributing to the fusion between autophagosome and lysosomes [44]. Thus, in contrast to WIPI1 and WIPI2, which regulate the initiation of autophagy, WDR45 appears to mostly regulate maturation of autophagosomes and their fusion with the lysosomes [35]. And third, WDR45 also interacts with the AMPK-ULK1-ATG2 complex suggesting that WDR45 could also play a role in the initiation of autophagy, although this remains to be functionally tested. Finally, in recent studies, it was observed that *WDR45* KO SH-SY5Y neuroblastoma cell line, BPAN patient primary skin culture, or derived cell line exhibited an accumulation of ferritin and cellular iron [14,42,45]. This accumulation suggests the involvement of WDR45 in ferritinophagy. During ferritinophagy, ferritin proteins are specifically targeted for degradation to the lysosomes through NCOA4 (nuclear receptor coactivator 4), resulting in the release of iron for cellular reuse [46]. However, it remains to be determined whether the binding of WDR45 to the lysosome contributes to the NCOA4-dependent targeting and degradation of ferritin.

Autophagy is particularly important for the homeostasis of non-dividing cells, and it has been proposed that autophagy is an essential mechanism allowing neuronal survival in adult organisms [17]. Hence mice lacking the essential autophagy genes *Atg5* or *Atg7* are not viable. In contrast, conditional KO of these genes in the nervous system provokes spontaneous neurodegeneration due to the lack of basal autophagy [47,48]. These finding, coupled with other studies showing impaired autophagy in neurodevelopmental and neurodegenerative disorders, have led to the hypothesis that restorating autophagy could serve as a putative therapeutic strategy to mitigate neurodegeneration [49,50]. Indeed, there are many (>20) early onset neurodevelopmental disorders and adult-onset

neurodegenerative disorders associated with defects in autophagy [51]. This includes common neurological disorders, such as amyotrophic lateral sclerosis and Parkinson disease but also a broad spectrum of congenital disorders. However, in the great majority of these diseases, autophagy impairment is one of multiple cellular dysregulations or may be the consequence of these dysregulations. For instance, Parkinson disease is considered as a multifactorial and heterogeneous disease. Very few monogenic disorders can be directly attributed to variations in an autophagy gene or a gene encoding a direct regulator of the autophagy pathway. However, there are specific cases where this holds true as BPAN, spinocerebellar ataxia, autosomal recessive 25 with *ATG5* variants, neurodevelopment disorders with *ATG7* variants and amyotrophic lateral sclerosis with SQSTM1/p62 (sequestosome 1) variants [30,52,53]. From these observations, we can hypothesize that the restoration of autophagy might be a particularly relevant strategy to treat those monogenic diseases.

## Current status of the autophagy restorative strategy

The fact that autophagy is impacted in BPAN opens the possibility that a pharmacological intervention aiming at restoring functional autophagy could slow down the progression of the disease. Indeed, there is already evidence that autophagy inducers by increasing autophagy activity can restore cellular dysregulations in BPAN cellular models. For example, rapamycin treatment increased autophagy and suppressed tunicamycin-induced apoptosis in HeLa sh*WDR45* cells [7]. In addition, torin treatment activated autophagy and suppressed iron accumulation in *WDR45* mutant human fibroblasts and dopaminergic neurons, respectively [12]. Because of the putative role of WDR45 in the regulation of ferritinophagy and cellular iron levels [14,42,45], it will be important to determine if autophagy stimulation can restore both ferritinophagy and iron dyshomeostasis in *WDR45* KO models. Although restoring autophagy seems a promising strategy to treat *WDR45* KO cells, further evidence indicates that the loss of WDR45 leads to multiple cellular defects, which in addition to iron accumulation, may not be solely due to bulk or selective autophagy impairments. This includes ER (endoplasmic reticulum) stress response [7,11,15] and mitochondrial dysfunction [8,12]. Currently, there is no evidence of a role of WDR45 in reticulophagy or mitophagy, which could suggest a more direct role of WDR45 at the ER or at the mitochondria to regulate ER stress and mitochondrial function, respectively. Therefore, future strategies targeting autophagy will need to carefully assess whether restoring autophagy is sufficient to suppress all cellular stresses, including iron dyshomeostasis, ER stress and mitochondrial dysfunction induced by *WDR45* mutation. Finally, if autophagy is the primary and causative event in the disease, we expect that autophagy restoration will result in the efficient suppression of neurodegeneration and an improved locomotor function. Such autophagy restoration approaches are awaited in animal models of the disease.

Monogenic rare diseases such as BPAN may also benefit from a gene-based therapy approach to restore *WDR45* expression or autophagy. A logical way to treat BPAN is to use gene-based therapy by importing a wild type *WDR45* to correct the origin of the disease. Several gene therapy vectors have already reached the market, including one to treat the rare monogenic disorder, Leber congenital amaurosis [54]. The relatively small size of the *WDR45* gene would make it amenable to being incorporated onto a viral vector, but the actual vector type and mode of delivery into the central nervous system and affected cells would have to be carefully considered.

Another possible approach is to induce the expression of an autophagy gene, similarly to what was previously done for spinocerebellar ataxia type 3 (SCA3). In SCA3 mouse models, studies have shown that the injection of a lentiviral vector carrying the *Ulk1* or *Ulk2* gene alleviate the aggregation and SCA3 neuropathology [55]. In BPAN however, the activation of autophagy initiation with ULK1 or ULK2 may not be as effective due to the fact *WDR45* KO cells exhibit a downstream blockade in autophagy at the steps of autophagosomes maturation and degradation by lysosomes [35,56]. A more efficient strategy in BPAN may be to boost lysosomal functions by expressing lysosomal enzymes or providing acidic nanoparticules, which is one current therapeutic strategy in lysosomal storage disorders [57,58]. However, a prior thorough characterization of the autophagy deficit and lysosomal function in *WDR45* KO cells and animal models will be required to envisage such a therapeutic strategy.

Finally, one of the remaining limitations of gene-based (and pharmacological) approaches is to overcome the blood brain barrier to allow the delivery of the molecules to the brain cells. Thus, one of the future challenges, which is currently the purpose of great efforts to treat neurological diseases, is to optimize the delivery of AAV (adeno-associated virus) or other compounds to brain cells [59,60].

Some other outstanding questions related to autophagy and mutations in *WDR45* remain, notably:

- Which tissues and cells are primarily affected by the partial loss of autophagy?
- What is the role of autophagy and WDR45 in animal neuronal development, and whether the developmental role of WDR45 contributes to disease in adult?
- What are the primary neuronal networks affected by *WDR45* mutations and whether defects in glial cells contribute the disease?

## Description of the symposiums

The first international symposium on BPAN was held on May 13$^{th}$-14$^{th}$ 2022 at ENS of Lyon, in France. The symposium was organized by the patient organization “Autour du BPAN”, the Hospices Civils of Lyon and researchers at LBMC (ENS-Lyon, CNRS, INSERM, University of Lyon, University of Claude Bernard Lyon 1). Susan J. Hayflick, MD, who discovered that mutations in the *WDR45* gene result in BPAN, was the keynote speaker of the symposium. The first day speakers from France, Germany, the Netherlands, Spain, and the United States reported their findings on

scientific advances on BPAN, followed by a round table. The second day dedicated to the family of patients focused on clinical studies and therapeutic perspectives. https://www.autourdubpan.fr/symposium/lang-en/

The second international symposium on BPAN was organized by the CNRS and Autour du BPAN at the University of Bordeaux, France, on May 12–13th, 2023. It focused on the mechanisms leading to iron accumulation in *WDR45* KO cells, as well as the development of biomarkers and natural history studies for future clinical management. A third symposium will be organized in Paris, for which the topic still remains to be defined.

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