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REVIEW

Progranulin axis and recent developments in frontotemporal lobar degeneration

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Abstract

Frontotemporal lobar degeneration (FTLD) is a devastating neurodegenerative disease that is the second most common form of dementia affecting individuals under age 65. The most common pathological subtype, FTLD with transactive response DNA-binding protein with a molecular weight of 43 kDa inclusions (FTLD-TDP), is often caused by autosomal dominant mutations in the progranulin gene (*GRN*) encoding the progranulin protein (PGRN). *GRN* pathogenic mutations result in haploinsufficiency, usually by nonsense-mediated decay of the mRNA. Since the discovery of these mutations in 2006, several groups have published data and animal models that provide further insight into the genetic and functional relevance of PGRN in the context of FTLD-TDP. These studies were critical in initiating our understanding of the role of PGRN in neural development, degeneration, synaptic transmission, cell signaling, and behavior. Furthermore, recent publications have now identified the receptors for PGRN, which will hopefully lead to additional therapeutic targets. Additionally, drug screens have been conducted to identify pharmacological regulators of PGRN levels to be used as potential treatments for PGRN haploinsufficiency. Here we review recent literature describing relevant data on *GRN* genetics, cell culture experiments describing the potential role and regulators of PGRN in the central nervous system, animal models of PGRN deficiency, and potential PGRN-related FTLD therapies that are currently underway. The present review aims to underscore the necessity of further elucidation of PGRN biology in FTLD-related neurodegeneration.

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Introduction

Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative disorder accounting for 5 to 10% of all dementia patients [1]. After Alzheimer's disease, FTLD is the most common cause of early-onset neurodegenerative dementia in cases before 65 years of age [2]. As the name suggests, FTLD patients develop severe atrophy of the frontal and temporal lobes. Consequently, associated neurodegeneration leads to various symptoms that are clinically organized into different subtypes. The first subtype, behavior variant frontotemporal dementia, is associated with behavioral changes and personality dysfunction [3,4]. Secondly, FTLD patients can present with language dysfunctions, or primary progressive aphasia in particular, with nonfluent/agrammatic variant primary progressive aphasia and semantic primary progressive aphasia [3,5]. Some patients display motor neuron impairments co-associated with frontotemporal dementia, termed frontotemporal dementia motor neuron disease, resembling amyotrophic lateral sclerosis (ALS) [6].

Neuropathologically, FTLD patients are divided into two main classes: those with tau-positive inclusions, and those with ubiquitin-positive but tau-negative inclusions. The ubiquitinated protein inclusions in FTLD with ubiquitin-positive inclusions are comprised of the fused-in sarcoma protein in some cases; however, the majority of FTLD brains with ubiquitin-positive inclusions contain transactive response DNA-binding protein with a molecular weight of 43 kDa (TDP-43) in the inclusions, now referred to as FTLD-TDP [7]. TDP-43, an RNA/DNA binding protein with multiple roles in RNA metabolism and transcriptional repression, becomes hyperphosphorylated, is cleaved into C-terminal fragments, and translocates from the nucleus to the cytoplasm in FTLD-TDP patients [8,9]. Moreover, TDP-43-positive inclusions are also found in ALS, suggesting that ALS and FTLD-TDP constitute a broad disease continuum [8].

FTLD has strong genetic influence, with 10 to 40% of patients having a positive family history [10]. Mutations in the microtubule-associated protein tau (*MAPT*) gene were first identified to cause FTLD [11]. The brains of individuals with *MAPT* mutations invariably present with hyperphosphorylated tau accumulation in affected

brain regions characteristic of FTLD with tau pathology [12]. On the other hand, several genes have been shown to cause FTLD-TDP, such as mutations in genes encoding the valosin-containing protein (*VCP*) [13,14], transactivation response DNA binding protein gene (*TARDBP*) [15,16], or the recently identified chromosome 9 open reading frame 72 (*C9ORF72*) [17,18]. Additionally, in 2006, the first mutations in the progranulin gene (*GRN*) were discovered after thorough examination of chromosome 17q21 [19,20]. Patients with *GRN* mutations also consistently present with intracellular TDP-43 accumulation upon autopsy, with primarily neuronal cytoplasmic inclusions as well as some neuronal intranuclear inclusions characteristic of FTLD-TDP type A as defined by the harmonized classification system [8,21]. Typically, *GRN* mutations include heterozygous frame-shift, nonsense, and splice-site alterations promoting premature termination of the coding sequence, subsequently leading to degradation of the mutant *GRN* mRNA via nonsense-mediated decay [22]. The resulting 50% loss in progranulin protein (PGRN) leads to disease by haploinsufficiency, suggesting that decreased PGRN levels might account for some patients' risk of developing FTLD-TDP. The role of PGRN in the central nervous system (CNS) and its link to TDP-43 pathology are currently being investigated, as addressed in the present review.

PGRN is recognized to date as a precursor protein composed of 7.5 tandem repeats separated by interlinked spacer regions [23]. A signal sequence allows PGRN to be secreted as a glycosylated 88 kDa protein [24]. In the periphery, studies reveal that full-length PGRN is proteolytically cleaved into mature 6 kDa granulins. This proteolytic processing is regulated by secretory leukocyte protease inhibitor (SLPI), which prevents cleavage by binding to PGRN itself or binding to and inhibiting the protease elastase [25]. Although it is unclear whether these mechanisms occur in the CNS, it has been hypothesized that elastase is released from activated microglia that cleaves extracellular PGRN, whereas SLPI is thought to be released from astrocytes thereby inhibiting this cleavage event [26,27].

PGRN expression occurs in a variety of body tissues, including epithelial, immune and neuronal cells in adult rats and mice [28]. During development, PGRN is widely expressed in the forebrain, retinal ganglia, olfactory bulbs, and spinal cord [29]. In mature rodent brains, Pgrn expression is prominent in cerebellar Purkinje cells, pyramidal neurons throughout the cerebral cortex, and hippocampus, as well as activated microglia [29], suggesting roles in brain function. However, the main role of PGRN in the CNS remains relatively unknown, requiring additional work to understand PGRN-related mechanisms in the brain.

PGRN is a widely secreted growth factor involved in multiple biological functions such as cell growth and survival, embryogenesis, wound repair, and inflammation [24,29-31]. Recent work also established that PGRN and granulin E exhibit neurotrophic properties [32,33]. Collectively, PGRN has been linked to proper neuronal morphology and survival, inflammation, and TDP-43 pathology within the CNS. In the present review we highlight key findings related to PGRN and its role in FTLD-related neurodegeneration. Further, we discuss how PGRN might be a valuable target for developing potential FTLD-TDP treatments and therapies.

Genetics of progranulin gene

In 2006 *GRN* was identified as a second FTLD gene on chromosome 17q21, explaining the disease in the FTLD families linked to this region in which mutations in *MAPT*, located only 1.7 Mb away from *GRN*, had been excluded [19,20]. Since then, 70 different *GRN* mutations have been identified in 232 families worldwide (Figure 1) [34,35]. The disease mechanism associated with *GRN* mutations is uniform; all mutations are heterozygous and result in the loss of 50% functional PGRN, causing disease through haploinsufficiency [19,20]. Most mutations lead to premature stop codons, either directly as a result of nonsense mutations or indirectly through a shift in the normal reading frame by splice-site mutations or small insertions and deletions, thereby inducing the degradation of mutant RNA by nonsense-mediated decay – although other mechanisms have been observed [22,36,37]. In addition to these typical *GRN* loss-of-function mutations, a large number of silent and missense mutations in *GRN* have also been reported, although their role in neurodegenerative disease pathogenesis has remained less clear [38]. In fact, most of these mutations have been observed in both patients and control individuals and are predicted to be nonpathogenic. Based on *in vitro* functional studies and *in vivo* PGRN expression analysis in patients carrying these mutations, however, four potential pathogenic missense mutations were identified that were uniquely seen in patients (p.C139R, p.P248L, p.R432C, and p.C521Y) (Figure 1) [39-44]. It is expected that at least some of these mutations cause disease through a partial loss of PGRN function, potentially by making neurons more vulnerable to neurodegeneration through subtle decreases in neurotrophic support.

The role of common *GRN* variants in the development of FTLD and related neurodegenerative diseases such as ALS, Alzheimer's disease, and Parkinson's disease has also been studied. In a series of pathologically confirmed FTLD-TDP patients, it was shown that carriers homozygous for the T allele of rs5848, located in a miRNA binding site in the 3' untranslated region of *GRN*,

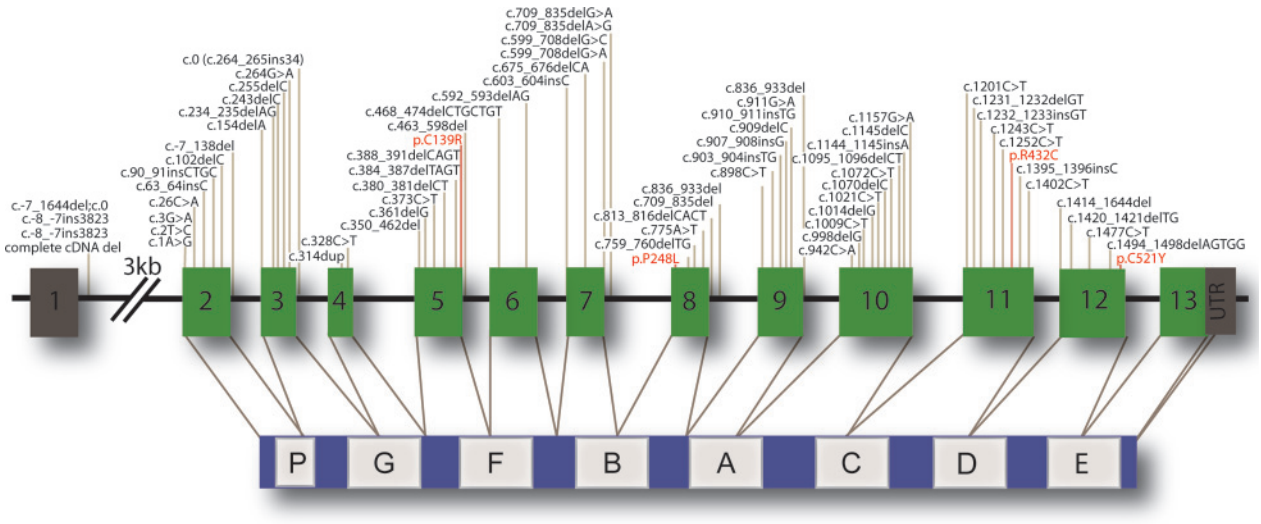

Figure 1. Overview of pathogenic loss-of-function mutations and potential pathogenic missense progranulin mutations in frontotemporal lobar degeneration. Mutations in the progranulin gene (*GRN*) are a common cause of frontotemporal lobar degeneration with transactivation response DNA binding protein molecular weight of 43 kDa pathology (FTLD-TDP). Schematic representation of the genomic structure of *GRN* (top) and progranulin protein (PGRN) (bottom). The gray numbered boxes in the genomic structure indicate the noncoding exon 1 and the 3' untranslated region; the green numbered boxes indicate coding exons 2 to 13. The white lettered boxes in PGRN refer to the individual granulin domains. A total of 70 different loss-of-function mutations scattered over all *GRN* exons, except exon 13, have been reported. These mutations are indicated with vertical brown lines on the *GRN* exons and listed above the exons with their cDNA numbering relative to the largest *GRN* transcript (GenBank accession number NM_002087.2). Four potential pathogenic missense mutations are indicated in red with their protein numbering according to the largest PGRN isoform GenPept accession number NP_002078.1).

have a 3.2-fold increased risk to develop FTLD-TDP compared with homozygous C-allele carriers [45]. *In vitro* studies confirmed that miR-659 can regulate PGRN expression, with miR-659 binding more efficiently to the high-risk T allele, thereby reducing PGRN levels. Although this genetic association could not be replicated in two series of largely clinical FTLD patients [46,47], these results are consistent with PGRN loss as the disease mechanism associated with FTLD-TDP. SNP rs5848 was also reported as a genetic risk factor for the development of hippocampal sclerosis in older people and for the development of Alzheimer's disease in a Taiwanese population [48,49]. Genetic association studies using several other common polymorphisms in the *GRN* genomic region further identified significant association of *GRN* variants in Belgian and Finnish Alzheimer's disease populations [40,50], in Belgian and Dutch ALS populations [51], and in an Italian FTLD population [52]. Although additional studies are needed to fully resolve the role of *GRN* variability on the development of FTLD and related neurodegenerative disorders, these studies suggest an important role for PGRN dysfunction in a range of neurodegenerative diseases.

Cell studies of progranulin protein

The identification of disease-causing *GRN* mutations highlighted the importance of PGRN haploinsufficiency in the onset of FTLD-TDP and related TDP-43 proteinopathies. Understanding the role of PGRN in the CNS and its link to TDP-43 pathology has thus been the focus of many researchers in the neurodegenerative disease field. Since PGRN is known to be a secreted protein, experiments have been conducted to determine the potential role of extracellular PGRN in neuronal development and survival. Such studies have shown that addition of PGRN to stressed or PGRN-depleted neuronal cells promoted neurite outgrowth [32,33,53,54]. Moreover, the addition of SLPI abrogated these effects [32], suggesting SLPI as a likely regulator in PGRN processing and/or function. Two of these studies also described enhanced neuronal survival under stress conditions when recombinant PGRN was present [32,53]. The neuroprotective effects of PGRN might be due, at least in part, to the activation of cell signaling pathways involved in cell survival: such as the extracellular regulated kinase and/or phosphatidylinositol-3 kinase/Akt pathways [33,55-57]. Additional data for PGRN downstream signaling were recently published, indicating that PGRN loss induces the activation of the Wnt signaling pathway well before observable inflammation, microgliosis, or neurodegeneration [58]. More specifically, the Wnt receptor, frizzled family receptor 2 (Fzd2), was found to be upregulated in $Grn^{-/-}$ mice as a potential compensatory mechanism due to the role of Fzd2 as a neuroprotective

factor [58]. These data not only implicate Fzd2 as a potential early marker of disease progression, but also suggest that therapeutic Fzd2 upregulation could be a promising FTLD treatment.

In addition to its role in neuronal cell survival and development, PGRN has also been speculated to play a role in excitotoxicity and synaptic transmission. Depletion of PGRN in cultured neurons by siRNA infection led not only to enhanced caspase-3 activation, but also to vulnerability to *N*-methyl-D-aspartic acid-induced excitotoxicity [59]. Another recent publication presented data in which reduced PGRN levels caused a decrease in dendritic arborization, spine density, and presynaptic density that occurred concomitantly with an increase in synaptic vesicles per synapse – some of which was also observed in the brains of FTLD patients with *GRN* mutations [54]. These data indicated that while there is an overall decrease in the number of synapses under conditions of PGRN deficiency, glutamatergic transmission in the remaining synapses is enhanced, potentially as a compensatory mechanism. Taken together, PGRN seems to be a critical player in neuronal development and synaptic maintenance, both of which could result in the increased susceptibility to neuronal death, potentially leading to the neurodegeneration observed in patients with FTLD.

Although there is emerging evidence for an important role of PGRN in the CNS, the possible molecular mechanism(s) linking PGRN haploinsufficiency to TDP-43 dysfunction and/or pathology remain unclear; however, several publications have provided insight into such a mechanistic relationship. In 2007 Zhang and colleagues reported that PGRN suppression induced caspase-mediated cleavage of TDP-43 and mislocalization of TDP-43 from the nucleus to the cytoplasm in H4 cells, similar to that observed in the brains of FTLD-TDP patients [60]. On the other hand, this fragmentation and mislocalization was not observed in PGRN-deficient fibroblasts or other immortalized cell lines [42,56,61]. Nonetheless, PGRN-null cortical cultures did portray increased caspase activation and the production of TDP-43 cleavage products, although TDP-43 phosphorylation and solubility was unchanged [56]. Guo and colleagues additionally reported that PGRN knockdown in primary cortical cultures resulted in increased TDP-43 levels in the cytoplasm when these cells were cultured for 11 days post siRNA transfection [59]. The discrepancies that arise in studies of PGRN-induced TDP-43 dysfunction highlight the complexity and potentially cell-specific nature of the relationship between these two proteins. Further investigation is thus critical for uncovering the exact molecular mechanism underlying *GRN* haploinsufficiency and subsequent TDP-43 pathology in the context of FTLD.

Progranulin protein receptors

More information about the function of secreted proteins, such as PGRN, can be obtained by identifying their receptors. Such discoveries were made in the past year by three research groups.

Publications by Carrasquillo and colleagues and Hu and colleagues both independently identified sortilin-1 protein (SORT1), a member of the vacuolar protein-sorting defective domain with 10 conserved cysteine residues receptor family, as the first known receptor for PGRN [62,63]. SORT1 is an endocytic sorting receptor responsible for sorting its ligands between the Golgi apparatus and endosomes, as well as for targeting ligands to lysosomes [64]. As such, SORT1 overexpression significantly reduced extracellular levels of PGRN, after which SORT1 was found to bind the C-terminus of PGRN and deliver it to lysosomal compartments [62,63,65]. Interestingly, SORT1 was previously identified as the receptor for other neurotrophic factors in the brain, further supporting PGRN as a potential component of neuronal development and/or neuroprotection [66,67].

Shortly after these discoveries, Tang and colleagues reported their findings that showed TNF receptors as another group of proteins directly interacting with PGRN [68]. In fact, the presence of PGRN had an anti-inflammatory effect in PGRN-deficient mice due to outcompeting TNFα for receptor binding [68]. Collectively, the identification of SORT1 and TNF receptors as PGRN receptors will open new avenues in PGRN cell biology research and therapeutic development.

Animal models of progranulin protein

Development of animal models mimicking human disease is an invaluable tool for understanding the etiology as well as future therapies of disease. Since the first pathogenic *GRN* mutations were discovered, several *Grn* knockout animals have been generated in the hope of resolving our understanding of PGRN's involvement in neurodegeneration. The first *Grn* knockout mice were generated by Kayasuga and colleagues and displayed several features that correlated with FTLD [69]. First, $Grn^{-/-}$ mice showed significant decreases in survival compared with their $Grn^{+/+}$ and $Grn^{+/-}$ littermates [58]. Initial behavioral characterization of this model further determined that juvenile male $Grn^{-/-}$ mice exhibited an enhanced aggressive behavior after repeated encounters with intruders [69]. Follow-up studies reported that this aggressive characteristic disappeared as $Grn^{-/-}$ mice mature into middle age, and $Grn^{-/-}$ mice began to exhibit decreased social interactions determined by a resident–intruder test [58]. The differences in social interactions of these $Grn^{-/-}$ mice are an important feature that mimics changes in social behavior observed in FTLD patients. Additionally, Morris water maze trials have revealed that

older *Grn*$^{-/-}$ mice possess mildly impaired learning and memory performances, typical of later stages of FTLD [58]. Pathologically, *Grn*$^{-/-}$ mice also display characteristics often observed in FTLD patients, including enhanced microglial activation, astrogliosis, and progressive accumulation of ubiquitin aggregates [58,70]. Ahmed and colleagues further analyzed these ubiquitin aggregates and found that they are largely composed of lipofuscin granules, which are recognized to form in response to mitochondrial stress and lysosomal injury [70]. Interestingly, these lipofuscin-containing granules are not observed in the brains of FTLD patients. Further, *Grn*$^{-/-}$ mice ubiquitin aggregates do not contain TDP-43, the main protein found in FTLD-TDP patient brain inclusions [58,70].

Yin and colleagues independently generated a *Grn* knockout mouse model from which they discovered that Pgrn loss augmented inflammation, leading to an increase in the production of proinflammatory cytokines [71]. Various experiments revealed behavioral abnormalities in these mice, including increased depression-like and disinhibition-like behavior, in addition to impaired cognitive behavior in older animals, all of which are behavioral phenotypes observed in FTLD patients [72]. These mice also show an increase in microglial and astroglial activation with age, as well as ubiquitin staining [72]. Interestingly, this group determined that the ubiquitin aggregates within these animals contain TDP-43 pathology, which was not present in the previous animal model.

Alternative PGRN-deficient models have been developed in addition to the mouse model to further our knowledge of this protein using simpler organisms. Work in the nematode *Caenorhabditis elegans* brought new insight into the role of PGRN when data revealed that *pgrn-1* mutants have unaltered apoptotic initiation but increased clearance of apoptotic cells [73]. This finding was also replicated in Pgrn-deficient mouse macrophages [73], suggesting that apoptosis kinetics is disrupted with PGRN loss across different species. One potential explanation for such data is that PGRN-null apoptotic cells undergo clearance before the cell has adequate time to recover, potentially leading to the increased neuronal loss observed in FTLD patients with PGRN insufficiency. Additionally, zebrafish studies showed that knockdown of zfPGRN-A, the ortholog to human PGRN, caused abnormal motoneuron development due to truncation and inappropriate branching, further demonstrating the neurotrophic properties of PGRN [74]. Similar to many cell culture experiments, however, PGRN loss in zebrafish did not affect the localization of the TDP-43 orthologs Tardbp and Tardbpl [42]. Even though several pathological and biochemical differences occur between the animal models and FTLD patients, many essential commonalities exist. It is expected that these and newly developed PGRN models will further improve our understanding of PGRN in disease and will serve as useful tools to investigate possible therapies for PGRN loss.

Progranulin protein therapeutics

The discovery of FTLD-causing mutations in *GRN* leading to haploinsufficiency has since implicated PGRN and its potential regulators as promising drug targets for FTLD-TDP treatments and therapies. Although there are no current drugs available to directly affect *GRN* mRNA or protein levels, one recent study is paving the way to such a discovery. Cenik and colleagues performed a chemical library screen in which the US Food and Drug Administration-approved suberoylanilide hydroxamic acid (SAHA) was identified as an enhancer of *GRN* transcription and subsequent PGRN expression [75]. Additionally, SAHA treatment restored normal PGRN levels in human cell lines derived from pathogenic *GRN* mutation carriers [75]. Although SAHA has been implicated in transcriptional regulation as a histone deacetylase inhibitor, the exact mechanism by which this acid contributes specifically to increased *GRN* expression remains to be elucidated.

PGRN levels could also possibly be increased by pharmacologically targeting proteins involved in its regulation and/or function. Two potential candidates are SORT1 and TNF receptors; however, no drugs have been developed to target these PGRN receptors. Nevertheless, encouraging findings were reported by Capell and colleagues, who screened for compounds capable of selectively increasing PGRN levels by inhibiting its proteolytic degradation [76]. Of the compounds screened, the alkalizing reagent bafilomycin A1 was the only drug to significantly increase intracellular and secreted PGRN levels. The authors showed that bafilomycin A1 increased PGRN levels in a post-translational manner by selectively targeting vacuolar-type H^+-adenosine triphosphatase. Further, the data suggested that bafilomycin A1-dependent vacuolar-type H^+-adenosine triphosphatase inhibition might increase intracellular and extracellular PGRN by neutralizing the pH of intracellular compartments and/or the extracellular space [76]; however, the direct mechanism by which vacuolar-type H^+-adenosine triphosphatase inhibition leads to PGRN level alterations remains unclear.

Another protein identified as a potential PGRN regulator and, thus, a possible drug target is the transmembrane protein 106B (TMEM106B). Genetic variants in and near the *TMEM106B* gene were recently found in a genome-wide association study to protect individuals carrying pathogenic *GRN* mutations from developing FTLD-TDP [77]. The identified protective variants have been shown to correlate with increased plasma PGRN

levels, as well as an increased age of onset in FTLD-TDP patients [78,79]. Since not all replication studies showed significance of these TMEM106B variants with FTLD-TDP [80], additional experiments to assess the role of TMEM106B in FTLD-TDP are needed to validate this protein as a pharmacological target. Nonetheless, future drugs to modify TMEM106B levels and/or function could prove useful as an indirect means of altering PGRN levels in affected individuals.

Conclusion

Promising insights into the molecular mechanism of FTLD have been established since the discovery of *GRN* mutations. Since all known pathogenic *GRN* mutations cause haploinsufficiency, and since all *GRN* mutation carriers present with TDP-43 pathology in affected brain regions, PGRN levels and function probably play a predominant role in the FTLD-TDP disease subtype. The use of cell culture and animal modeling of PGRN depletion have uncovered only the surface of PGRN's role in the CNS. Although the link between PGRN and TDP-43 pathology still remains to be determined, recent studies have revealed critical information that could potentially lead to such a discovery. For example, some culture systems have begun to show that PGRN loss causes TDP-43 dysfunction, although not completely mimicking the dysfunction observed *in vivo*. Second, the identification of PGRN regulators such as TMEM106B and of the PGRN receptors such as SORT1 and TNF receptors will hopefully shed more light on PGRN intracellular signaling and additional therapeutic targets. In the last year, promising findings were reported implicating alkalizing agents and/or SAHA as possible drug candidates for increasing PGRN levels in FTLD patients. The continued search for more representative FTLD models and PGRN modifiers will prove imperative for the advancement of FTLD treatments and therapies.

Abbreviations

Akt, oncogene synonym for protein kinase B; ALS, amyotrophic lateral sclerosis; *C9ORF72*, chromosome 9 open reading frame 72 gene; CNS, central nervous system; FTLD, frontotemporal lobar degeneration; FTLD-TDP, frontotemporal lobar degeneration with transactivation response DNA binding protein molecular weight of 43 kDa pathology; Fzd2, frizzled family receptor 2; *GRN*, progranulin gene; *MAPT*, microtubule-associated protein tau gene; miRNA, microRNA; PGRN, progranulin protein; SAHA, suberoylanilide hydroxamic acid; siRNA, small interfering RNA; SLPI, secretory leukocyte protease inhibitor; SNP, single nucleotide polymorphism; SORT1, sortilin 1 protein; *TARDBP*, transactivation response DNA binding protein gene; TDP-43, transactivation response DNA binding protein molecular weight of 43 kDa; TMEM106B, transmembrane protein 106B; TNF, tumor necrosis factor; *VCP*, valosin-containing protein gene; Wnt, protein encoded by the vertebrate homolog of the *Drosophila wingless* gene.

Competing interests

The authors declare that they have no competing interests.

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