Review

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Progranulin in neurodegenerative disease

Terri L. Petkau[1] and Blair R. Leavitt[1,2,3]

[1] Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, and Children's and Women's Hospital, 980 West 28th Avenue, Vancouver, BC, Canada V5Z 4H4
[2] Division of Neurology, Department of Medicine, University of British Columbia Hospital, S 192, 2211 Wesbrook Mall, Vancouver, BC, Canada V6T 2B5
[3] Brain Research Centre, University of British Columbia, Vancouver, BC V6T 1Z3, Canada

Loss-of-function mutations in the progranulin gene are a common cause of familial frontotemporal dementia (FTD). The purpose of this review is to summarize the role of progranulin in health and disease, because the field is now poised to begin examining therapeutics that alter endogenous progranulin levels. We first review the clinical and neuropathological phenotype of FTD patients carrying mutations in the progranulin gene, which suggests that progranulin-mediated neurodegeneration is multifactorial and influenced by other genetic and/or environmental factors. We then examine evidence for the role of progranulin in the brain with a focus on mouse model systems. A better understanding of the complexity of progranulin biology in the brain will help guide the development of progranulin-modulating therapies for neurodegenerative disease.

Progranulin in neurodegenerative disease

Loss-of-function mutations in the progranulin (*GRN*) gene are a common cause of familial FTD (see Glossary). Genetic variation in progranulin has now been linked to multiple neurodegenerative conditions, making it an attractive and potentially valuable therapeutic target. We summarize the clinical and neuropathological phenotype of FTD patients carrying *GRN* mutations and discuss the genetic evidence supporting a role for *GRN* in other neurodegenerative disorders. We then examine the role of progranulin in the brain based on literature from *in vitro* and *in vivo* model systems, with a focus on mouse models of progranulin deficiency.

Frontotemporal lobar degeneration (FTLD)

FTLD is a collective term describing a group of neurodegenerative disorders that cause selective atrophy of the frontal and temporal lobes of the brain and are clinically referred to as FTD. Clinical FTD can be divided into three subtypes based on the predominant early clinical features: behavioral variant, characterized by progressive decline in behavior and executive function; semantic dementia, characterized by loss of knowledge of semantic language; and progressive non-fluent aphasia, characterized by deficits in expressive or motor speech. In addition, FTD may overlap clinically with motor neuron disease/amyotrophic lateral sclerosis (FTD-MND) and the parkinsonian syndromes progressive supranuclear palsy and corticobasal syndrome (reviewed in [1]).

FTLD cases are classified into subtypes based on the main component(s) of pathological protein aggregates. Tau pathology, defined by deposits of hyperphosphorylated tau protein primarily in neurons and astrocytes, was the earliest pathology to be recognized [2]. Most tau-negative cases have neuronal cytoplasmic inclusions that are immunoreactive for ubiquitin, previously referred to as FTLD-U. FTLD-U is further broken down into

Glossary

AD (Alzheimer's disease): a progressive neurodegenerative condition and the most common cause of dementia. *GRN* mutation carriers occasionally present clinically with AD, but AD is distinguished from FTLD by characteristic neuropathology that includes amyloid plaques and neurofibrillary tangles.
ALS (amyotrophic lateral sclerosis): a progressive neuromuscular disorder that causes degeneration of upper and lower motor neurons. ALS shares some clinical and neuropathological characteristics with FTLD but is rare as a clinical presentation in *GRN* mutation carriers.
FTD (frontotemporal dementia): a collective term used to describe a diverse set of clinical syndromes associated with degeneration of the frontal and temporal lobes of the brain.
FTLD (frontotemporal lobar degeneration): a collective term that refers to the pathological processes underlying the clinical syndromes of FTD.
Haploinsufficiency: a disease mechanism brought about by the loss of a single functional copy of a gene in a diploid organism. If the single remaining gene copy is not sufficient to maintain wild type function of the resultant protein, that gene is referred to as haploinsufficient.
Lipofuscin: an autofluorescent pigment that accumulates with age in post-mitotic cells. It is composed of lipids, sugars, and metals, and is often associated with mitochondrial or lysosomal dysfunction.
Modifier gene: a gene that, when expressed, can alter the expression of another gene or phenotypes associated with the expression of another gene.
NCL (neuronal ceroid lipofuscinosis): a group of very early onset neurodegenerative, lysosomal storage disorders that cause motor symptoms, psychological abnormalities, and early death. Multiple genetic forms exist, mostly due to mutations in different components of the lysosome, which leads to exaggerated accumulation of the aging pigment lipofuscin.
PD (Parkinson's disease): a neurodegenerative disorder causing motor dysfunction due to the loss of dopaminergic neurons of the substantia nigra.
PET (positron emission topography): a nuclear medical imaging technique that requires the introduction of a tracer coupled to a biologically active molecule into the body.
SNP (single nucleotide polymorphism): DNA sequence variation between two alleles at a single nucleotide position.
TDP-43: trans-activating response element with an approximate molecular weight of 43 kDa, the protein encoded by the *TARDBP* gene. It is the major ubiquitinated protein in many cases of FTLD, Alzheimer's disease, and ALS.

Corresponding author: Leavitt, B.R. (bleavitt@cmmt.ubc.ca).

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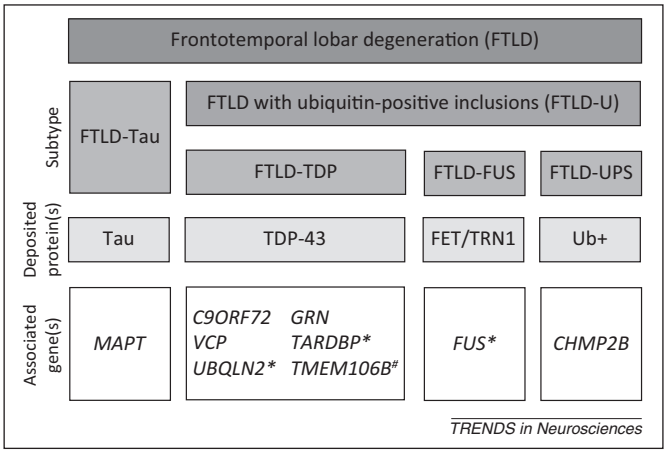

Figure 1. A summary of the subtypes of frontotemporal lobar degeneration (FTLD) and their respective underlying pathologies and genetics. **TARDBP* (encoding trans-activating response element with an approximate molecular weight of 43 kDa, TDP-43), *UBQLN2* (ubiquilin 2), and *FUS* (fused in sarcoma) are common causes of familial amyotrophic lateral sclerosis (ALS) and only rarely cause FTLD. #*TMEM106B* (encoding transmembrane protein 106B) is a genetic risk factor for FTLD that works indirectly by affecting progranulin levels. Box sizes do not reflect the relative frequency of the different pathologies or genetic mutations.

subtypes depending on the major ubiquitinated protein present. Trans-activating DNA binding protein with a molecular weight of 43 kDa (TDP-43) is the major ubiquitinated protein in the majority of cases of FTLD [3]. The distribution and relative abundance of these inclusions defines a further classification level referred to as Types A–D [4]. Notably, TDP-43 pathology is not unique to FTLD; it is a common pathology in amyotrophic lateral sclerosis (ALS) and also present in 25–50% of cases of Alzheimer's disease (AD) [5]. Fused in sarcoma (*FUS*) and other protein family members (known as FET proteins) are the major ubiquitinated proteins in cases of FTLD-U that are tau- and TDP-43-negative, including the majority of sporadic cases [6]. There remain a small number of patients with FTLD-U pathology where the major ubiquitinated protein(s) are still unidentified. This pathology is currently referred to as the FTLD-ubiquitin proteasome system, or FTLD-UPS.

FTLD represents a significant cause of early-onset dementia with 75–80% of cases presenting between 45 and 64 years of age. The disease has a large familial component, with approximately 30–50% of cases reporting family history of disease. Mutations in five known disease genes cause FTLD. Current knowledge of the clinical, neuropathological, and genetic components of FTLD and their relationships to each other have been recently reviewed [7] and are summarized in Figure 1.

Loss-of-function mutations in *GRN* as a cause of autosomal dominant familial FTLD were first reported in 2006 [8,9]. The *GRN* gene, located on chromosome 17q21, encodes a 593aa cysteine-rich, secreted protein composed of seven and a half tandem repeats of a conserved granulin domain (Figure 2). Mutations occur throughout the gene, but all pathological mutations reported to date are confirmed or predicted loss-of-function alleles [10], indicating haploinsufficiency as the disease mechanism. An approximately 50% reduction in mRNA level [8,11,12] and 33% reduction in protein level is reported in heterozygous *GRN* mutation carriers [8]. To date, there is only one published report of homozygous-null *GRN* mutation carriers [13], which, surprisingly, present with a markedly different clinical phenotype than FTD patients (Box 1).

The clinical and neuropathological phenotype of FTLD due to *GRN* mutations

FTLD due to *GRN* mutations is highly heterogeneous in terms of age of onset, disease duration, and clinical presentations [14], even among individuals or families carrying the same mutation. *GRN* mutation carriers may present with any of the defined clinical syndromes of FTD, including corticobasal syndrome, primary progressive aphasia, and FTLD with parkinsonism, although concomitant MND is rare (reviewed in [15]). The most defining neuroimaging feature of *GRN* mutation carriers

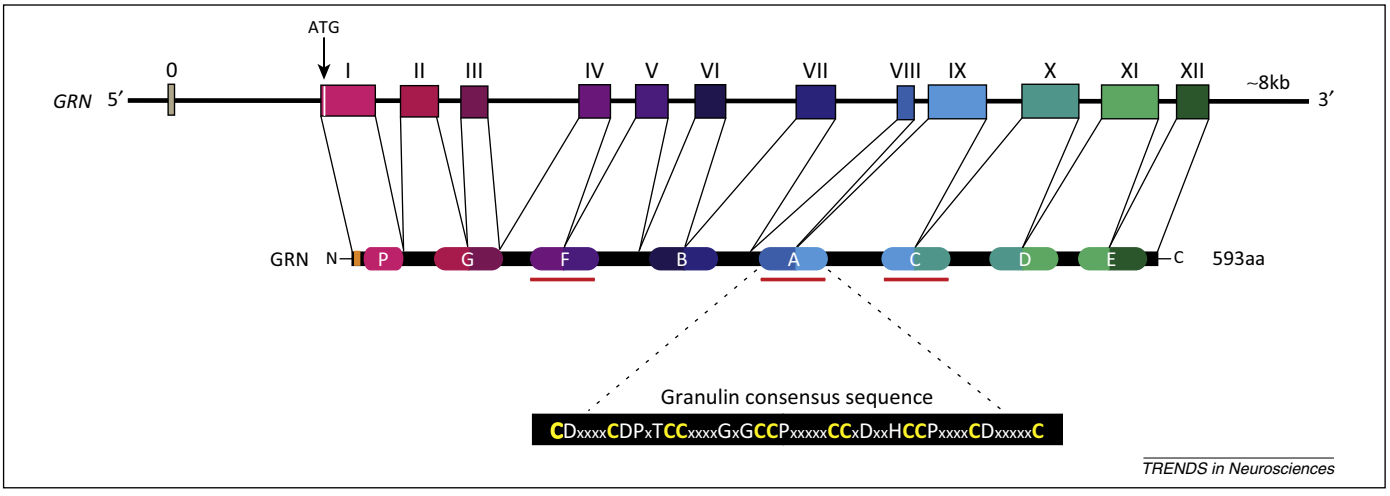

Figure 2. The structure of the human progranulin gene and protein. Progranulin (*GRN*), located on chromosome 17q21.32, consists of 13 exons, 12 of which are coding. The full-length protein (GRN) consists of a signal peptide (orange bar) followed by seven and a half tandem repeats of a conserved, 12-cysteine granulin motif separated by short spacer sequences that contain recognition sequences for extracellular proteases. The individual granulin peptides (~6 kDa each) are identified by sequential lettering in the order they were discovered. Exon 1 encodes the half-repeat, named paragranulin (P). The two halves of the other seven granulin peptides are encoded on separate exons, such that a full granulin peptide is always produced from two exons. Structural analysis of the individual granulin peptides has identified granulins A, C, and F as having stable tertiary structure (underlined in red), whereas granulins B, D, and E are poorly structured [119]. Mutations in *GRN* that cause FTLD occur throughout the gene; an updated list of pathological mutations is maintained at http://www.molgen.vib-ua.be/FTDMutations.