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HUMAN GENETICS AS A TOOL TO IDENTIFY PROGRANULIN REGULATORS

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Abstract

Frontotemporal lobar degeneration (FTLD) is a common neurodegenerative disorder that predominantly affects individuals under the age of 65. It is known that the most common pathological subtype is FTLD with TAR DNA-binding protein 43 inclusions (FTLD-TDP). FTLD has a strong genetic component with about 50% of cases having a positive family history. Mutations identified in the progranulin gene (*GRN*) have been shown to cause FTLD-TDP as a result of progranulin haploinsufficiency. These findings suggest a progranulin-dependent mechanism in this pathological FTLD subtype. Thus, identifying regulators of progranulin levels is essential for new therapies and treatments for FTLD and related disorders. In this review, we discuss the role of genetic studies in identifying progranulin regulators, beginning with the discovery of pathogenic *GRN* mutations and additional *GRN* risk variants. We also cover more recent genetic advances, including the detection of variants in the *transmembrane protein 106 B* gene that increase FTLD-TDP risk presumably by modulating progranulin levels and the identification of a potential progranulin receptor, sortilin. This review highlights the importance of genetic studies in the context of FTLD and further emphasizes the need for future genetic and cell biology research to continue the effort in finding a cure for progranulin-related diseases.

Keywords

progranulin; genetics; FTLD; TDP-43; TMEM106B; sortilin

Introduction

Frontotemporal dementia (FTD) is a presenile neurodegenerative disorder that is clinically characterized by distinct changes in personality and behavior that are often accompanied by a gradual loss of language skills. The clinical presentations associated with FTD are a result of various pathological manifestations in the frontal and temporal cortices, collectively termed frontotemporal lobar degeneration (FTLD). Although the brain areas affected by FTLD are consistent, the pathological presentation can vary among FTLD patients. For the last 10 years, several research efforts have focused on the form of FTLD in which patients display immunoreactive inclusions for the hyperphosphorylated microtubule associated protein tau (FTLD-tau). However, more recently as a result of improved immunohistochemical techniques it was determined that the most common pathological subtype of FTLD includes ubiquitin-positive, tau-negative inclusions in both the cytoplasmic and nuclear cell fractions. In 2006, the TAR DNA-binding protein 43 (TDP-43) was identified as the major constituent of these ubiquitin-positive aggregates (Arai et al.,

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2006; Neumann et al., 2006), which led to further classification of this pathological subtype as FTLT-TDP (Mackenzie et al., 2006).

Although the various forms of FTD have been shown to initiate sporadically, nearly 50% of cases present with a positive family history, suggesting a strong genetic component of this neurodegenerative disease (Graff-Radford and Woodruff, 2007). In the late 1990's, extensive linkage analyses uncovered a region on chromosome 17 as an FTLT linkage region in which a pathological mutation was probable (Foster et al., 1997; Poorkaj et al., 1998; Spillantini et al., 1998). Shortly after this finding, mutations in the tau gene (*MAPT*) were uncovered which explained the inheritance of FTLT-tau in a subset of familial patients (Hutton et al., 1998; Rizzu et al., 1999; Spillantini et al., 1998). However, it was not until 2006 when the first mutations were discovered to explicate FTLT with TDP-43 pathology. The gene in which these mutations were found (*GRN*) encodes for the progranulin protein and is located only 1.7 Mb away from *MAPT* (Baker et al., 2006; Cruts et al., 2006). All pathogenic *GRN* mutations reported to date are heterozygous loss-of-function mutations which cause disease by haploinsufficiency, and all *GRN* mutation carriers invariably present with TDP-43 pathology. This evidence strongly suggests the importance of progranulin levels in mediating one's risk for developing FTLT-TDP. Investigations into the role of progranulin in TDP-43 proteinopathy are underway, though the exact mechanism of progranulin-induced TDP-43 dysfunction currently remains unknown. Nevertheless, understanding the regulation of progranulin levels as a disease modifier could lead to more promising therapies and treatments for FTLT-TDP patients.

Here we review what is known regarding the regulation of progranulin in the context of FTLT-TDP. More specifically, we focus on how the use of genetics has advanced the FTLT-TDP field with regard to identifying mechanisms by which progranulin is controlled in a diseased state.

Progranulin and its function in the brain

The *GRN* gene spans approximately 8 kb of the genomic sequence on chromosome 17q21. Of its 13 exons, exon 1, and part of exons 2 and 13 are non-coding. The progranulin coding region is translated into a 593 amino acid-containing precursor protein with 7.5 non-identical, cysteine-rich granulin domains arranged in tandem (Baba et al., 1993; Bhandari and Bateman, 1992; Bhandari et al., 1992; Plowman et al., 1992). The progranulin protein has been shown to function in its full-length form or to be proteolytically processed to form 7 individual granulins of ~6 kDa.

Both the granulins and their precursor are reportedly expressed in several tissues of the periphery, as well as in cells of the central nervous system; however, their exact functions are still unclear. The granulins were found to play both agonistic and antagonistic roles for cellular proliferation in peripheral tissues. Moreover, progranulin has been implicated as an important potential growth factor during embryogenesis and has also been found to be upregulated in several different forms of cancer (Bateman and Bennett, 2009). Though it has been known for over 10 years that progranulin and granulins are expressed in brain tissue (Daniel et al., 2000), little attention was focused on their roles in the brain until the link between progranulin and dementia was evident. Within the brain, progranulin is a secreted protein expressed in both neurons and microglia. While progranulin expression increases with age in neurons, the level of progranulin in glial cells depends on their state of activation; thus, progranulin is upregulated in activated microglia as a part of the proliferative and inflammatory response to various forms of tissue injury (Petkau et al., 2010). Interestingly, progranulin-deficient mice portray exaggerated inflammation in response to various inflammatory activators, suggesting a regulatory role of this protein in mediating inflammatory responses in the central nervous system (CNS) (Yin et al., 2010).

Although the exact role of progranulin in neurons in the context of neurodegeneration is still unclear, several reports have suggested progranulin to be important for neuronal development. In 2008, Van Damme and colleagues reported that progranulin and granulin E both enhanced neurite outgrowth and survival in a neuron culture system (Van Damme et al., 2008). Further investigations into the mechanisms by which progranulin might support neuronal development and survival resulted in data that implicated several downstream players likely involved in progranulin-dependent signaling. First, the treatment of mouse neurons with progranulin stimulated neurite outgrowth that occurred concomitantly with phosphorylation of glycogen synthase kinase-3 beta (GSK3 β) (Gao et al., 2010). Similarly, cultured progranulin-null mouse embryonic fibroblasts and neurons showed decreased pro-survival signaling such as Akt and Erk1/2 phosphorylation, which was completely or partially rescued with recombinant progranulin, respectively (Kleinberger et al., 2010). These progranulin-deficient cells also showed reduced cell viability and increased caspase-mediated apoptosis, further supporting a role for progranulin in neuronal viability. Finally, this same publication established a direct link between progranulin and TDP-43 dysfunction. The authors reported that neurons lacking progranulin expression have significantly increased TDP-43 fragmentation and accumulation of insoluble TDP-43 (Kleinberger et al., 2010). These findings support the data included in other recent studies that implicated progranulin as an upstream mediator of TDP-43 pathology (Guo et al., 2010; Zhang et al., 2007). Collectively, progranulin seems to be important in regulating inflammatory responses, neuronal development, and neuronal survival in the CNS. Furthermore, progranulin insufficiency has been directly linked to TDP-43 dysfunction and aggregation in a neuron culture model of disease.

***GRN* mutations cause FTLTDP through haploinsufficiency**

Over 65 *GRN* mutations have been found in more than 150 unrelated FTLTDP cases, the earliest of which were reported in 2006 (www.molgen.ua.ac.be/ftldmutations). The first publications described splice-site, frame-shift, and nonsense mutations- all of which result in *GRN* nonsense-mediated mRNA decay and subsequent haploinsufficiency (Baker et al., 2006; Cruts et al., 2006). The mRNA destruction occurs as a result of the mutation-dependent introduction of a premature termination codon that, when identified by the cell's quality control mechanism, is consequently destroyed to prevent the accumulation of a truncated protein (Behm-Ansmant et al., 2007). However, this is not the only means by which *GRN* mutations cause reduced cellular progranulin levels. For example, loss of mRNA translation is also observed when mutations arise in the Kozak sequence of the *GRN* gene (Baker et al., 2006; Cruts et al., 2006; Gass et al., 2006; Le Ber et al., 2008) or as a result of a heterozygous deletion of the complete *GRN* locus (Gijssels et al., 2008). Finally, some mutations, including the p.A9D mutation identified in the large H4D2 family (Mukherjee et al., 2006), have been shown to affect the signal peptide sequence of GRN, resulting in a significant reduction in the amount of secreted progranulin (Gass et al., 2006; Kelley et al., 2010; Le Ber et al., 2008; Mukherjee et al., 2006; Mukherjee et al., 2008; Shankaran et al., 2008). The role of a larger group of *GRN* missense mutations in the development of FTLTDP and related neurodegenerative diseases remains the topic of active debate. However, it is clear that at least some of these mutations, especially those uniquely found in patients including p.C139R, p.R432C, p.P248L, and p.C521Y, might contribute to disease through a partial loss of progranulin function (Shankaran et al., 2008; van der Zee et al., 2007; Wang et al., 2010).

FTLTDP risk factors associated with progranulin levels

Loss-of-function mutations in *GRN* only account for approximately 20% of all FTLTDP cases (Baker et al., 2006; Cruts et al., 2006; Gass et al., 2006; Gijssels et al., 2008). Since the pathological presentation in the remaining FTLTDP cases is the same as *GRN*

mutation carriers, and because several of these cases show a family history, it is likely that other genetic factors are involved in mediating progranulin levels- either within the *GRN* gene or elsewhere in the genome. One such variant was identified by Rademakers and colleagues in 2008. In this study, the authors demonstrated that a common genetic variant located in the 3'-untranslated region of *GRN*, rs5848, is a risk factor for FTL-D-TDP (Rademakers et al., 2008). Homozygosity for the minor T-allele occurred three times as often in FTL-D-TDP patients as compared to controls. SNP rs5848 is located at a predicted microRNA (miRNA) binding site for miR-659. MiRNAs have been shown to play an integral part in gene regulation (Hobert, 2008; Nilsen, 2007; Ouellet et al., 2006), and the authors were able to show that rs5848 was a functional variant that regulated progranulin levels by miR-659 binding to the *GRN* 3'-UTR. Consistent with these findings, significantly reduced progranulin levels were observed in brain lysates of FTL-D cases carrying two copies of the rs5848 risk 'T' allele, to about 70% of the levels observed in cases carrying two copies of the rs5848 'C' allele. In an independent study, the rs5848 polymorphism was shown to significantly influence serum progranulin levels with rs5848 TT carriers having a lower level of serum progranulin than CT and CC carriers (Hsiung et al., 2011). Regardless of the mechanism by which *GRN* variants reduce functional levels of progranulin, these genetic studies have provided a significant foundation indicating progranulin levels as a potential therapeutic target for FTL-D-TDP. Whether progranulin levels also play a role in the general FTL-D population (with unknown underlying pathology) remains uncertain, since two largely clinical FTL-D case-control series failed to identify significant association of rs5848 with FTL-D (Rollinson et al., 2009; Simon-Sanchez et al., 2009).

It was not until 2010 that Van Deerlin et al. were able to identify FTL-D-TDP risk variants other than those in *GRN*. These authors performed a genome-wide association study (GWAS) of over 500 FTL-D-TDP cases and 2000 controls to determine potential risk factors for this form of FTL-D (Van Deerlin et al., 2010). The GWAS showed significant association with three SNPs in linkage disequilibrium mapping to 7p21, which were located near or within the gene for *TMEM106B*. This gene encodes an uncharacterized transmembrane protein with unknown function. In addition, these SNPs were shown to regulate *TMEM106B* expression, with the risk alleles showing higher *TMEM106B* mRNA levels. Of note, the strongest association of *TMEM106B* SNPs was observed in the subgroup of *GRN* mutation carriers, suggesting that *TMEM106B* variants might increase the risk for FTL-D-TDP by modulating progranulin levels or function.

A replication study performed by Finch and colleagues also found these SNPs to be highly associated with FTL-D-TDP in an independent cohort of *GRN* mutation carriers (Finch et al., 2011). In their study, individuals homozygous for the minor C-allele of *TMEM106B* SNP rs1990622 accounted for 19.1% of the control population and only 2.6% of people with FTL-D-TDP with *GRN* mutations, suggesting that the C-allele might be protective against FTL-D-TDP in *GRN* mutation carriers. Additionally, a significant association was observed between rs1990622 and progranulin levels in plasma of unaffected controls, with higher levels of progranulin in C-allele carriers (Finch et al., 2011). In an independent study, Cruchaga et al. showed an association of rs1990622 with age at onset in *GRN* mutation carriers, with the C-allele delaying the age at onset by 13 years (Cruchaga et al., 2011). These authors also showed higher plasma progranulin levels in *GRN* mutation carriers and healthy adults carrying the rs1990622 C-allele. Taken together, the identification of protective *TMEM106B* SNPs (such as the rs1990622 C-allele) further supports the therapeutic potential of progranulin level regulation in the context of FTL-D. Notably, association of *TMEM106B* SNPs was also reported in a Flanders-Belgian cohort of primarily clinically diagnosed FTL-D patients without *GRN* mutations; however a modifying effect of *TMEM106B* on disease onset was not observed in this study (van der Zee et al., 2011).

Genetic involvement in the identification of a progranulin receptor

Since progranulin is a secreted protein, the search for a progranulin receptor has been underway in both the field of genetics and cell biology. Within the past year, both fields were successful in such an attempt. The genetic finding was published by Carrasquillo and colleagues who conducted a GWAS to identify genetic variants that significantly associated with plasma progranulin levels (Carrasquillo et al., 2010). SNP rs646776, located on chromosome 1p13.3, was most significantly associated with plasma progranulin levels in two independent series of over 500 non-diseased individuals and a third series of nearly 200 people with FTLN-TDP. More specifically, each inherited copy of the minor allele showed a reduction in progranulin levels by 15%. SNP rs646776 is located near the gene encoding for the vsp10-domain-containing receptor, sortilin (*SORT1*), that has been shown to be a neuronal growth factor receptor (Jansen et al., 2007; Mazella et al., 1998; Nykjaer et al., 2004; Petersen et al., 1997; Teng et al., 2005). The authors used a cell culture model to support the hypothesis that SORT1 is a receptor for progranulin. Overexpression of SORT1 in HeLa cells significantly reduced extracellular levels of progranulin, while SORT1 knockdown increased extracellular progranulin (Carrasquillo et al., 2010). Of note, the authors determined that rs646776 regulated *SORT1* mRNA in a tissue specific manner, with no effect of rs646776 on *SORT1* levels in the brain. SNP rs646776 itself is therefore not a candidate risk factor for FTLN-TDP; however, future investigation into additional *SORT1* variants could reveal a *SORT1*-dependent genetic component to FTLN-TDP.

Interestingly, strong biochemical evidence supporting SORT1 as a progranulin receptor was simultaneously published by Hu et al. These authors identified SORT1 as the major progranulin interactor using an unbiased binding screen (Hu et al., 2010). Further investigation revealed that progranulin colocalized and interacted directly with SORT1 on the surface of neuronal cells and within the lysosome post endocytosis. Hu et al. also provided the first *in vivo* evidence that SORT1 mediates progranulin levels in mouse brain. Finally, a recent study showed that progranulin was also a ligand for the tumor necrosis factor receptor (TNFR) (Tang et al., 2011). Additional data in this paper revealed that subsequent to progranulin binding, TNF α signaling and inflammation was reduced in multiple arthritis mouse models (Tang et al., 2011). These findings provided further evidence for the role of progranulin *in vivo*, as well as identified another potential progranulin receptor. Collectively, these results not only open new potential therapeutic avenues for FTLN-TDP, but they also highlight the importance of both genetic and functional studies in the search for progranulin interactors.

Conclusions

The identification of *GRN* mutations opened a novel area of research in the field of FTLN in 2006. Loss-of-function mutations in *GRN* have since been identified in 10-20% of familial FTLN-TDP patients; however this does not exclude a role for progranulin in other patients with familial and sporadic FTLN-TDP. Indeed, in the last 5 years the neurogenetics field significantly advanced our understanding of FTLN-TDP and uncovered several potential and actual regulators of progranulin levels. First, genetic variants in *GRN* leading to a partial loss of progranulin function, including the common variant rs5848 and rare *GRN* missense mutations, were shown to play a role in developing FTLN-TDP. Second, *TMEM106B* SNPs modifying progranulin levels were identified as an important risk-factor for FTLN-TDP. The most significant association of *TMEM106B* SNPs was identified in FTLN-TDP patients with *GRN* mutations, further indicating the significance of TMEM106B in progranulin regulation. Third, genetic studies conducted in parallel to functional assessments led to the discovery of potential progranulin receptors, such as SORT1 and TNFR.

Despite these advances, more *in vitro* and *in vivo* data are required to uncover what remains unknown regarding the onset of FTLT-TDP. Researchers have yet to discover the direct link between loss of progranulin function and TDP-43 dysfunction. Additional investigations into the normal role of progranulin in the CNS are also needed to reveal additional players in these complex pathways. Furthermore, it would be interesting to discern to what extent progranulin levels regulate other TDP-43 proteinopathies, such as some pathological forms of Alzheimer's disease and amyotrophic lateral sclerosis. In sum, the quest for genetic factors involved in progranulin regulation is critical for a better understanding of the pathobiology of FTLT and other neurodegenerative disorders.

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