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TDP-43 Frontotemporal Lobar Degeneration and Autoimmune Disease

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Abstract

Background—The aetiology and pathogenesis of non-genetic forms of frontotemporal dementia (FTD) is unknown and even with the genetic forms of FTD, pathogenesis remains elusive. Given the association between systemic inflammation and other neurodegenerative processes, links between autoimmunity and FTD need to be explored.

Objective—To describe the prevalence of systemic autoimmune disease in semantic variant primary progressive aphasia (svPPA), a clinical cohort, and in progranulin (PGRN) mutation carriers compared to neurologically healthy normal controls (NC) and Alzheimer's disease (AD) as dementia controls.

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Design—Case control.

Setting—Academic medical centres.

Participants—129 svPPA, 39 PGRN, 186 NC, and 158 AD patients underwent chart review for autoimmune conditions. A large subset of svPPA, PGRN, and NC cohorts underwent serum analysis for tumor necrosis factor α (TNF-α) levels.

Outcome Measures—Chi-square comparison of autoimmune prevalence and follow up logistic regression.

Results—There was a significantly increased risk of autoimmune disorders clustered around inflammatory arthritides, cutaneous disorders, and gastrointestinal conditions in the svPPA and PGRN cohorts. Elevated TNF-α levels were observed in svPPA and PGRN compared to NC.

Conclusions—svPPA and PGRN are associated with increased prevalence of specific and related autoimmune diseases compared to NC and AD. These findings suggest a unique pattern of systemic inflammation in svPPA and PGRN and open new research avenues for understanding and treating disorders associated with underlying transactive response DNA-binding protein 43 (TDP-43) aggregation.

BACKGROUND

An inflammatory contribution to neurodegenerative disease pathogenesis has long been hypothesized.(1) Alzheimer's disease (AD), frontotemporal dementia (FTD), and many other neurodegenerative conditions are united by pathological protein misfolding and aggregation accompanied by synaptic and neuronal loss and inflammatory markers around the site of pathological injury. Several studies have reported a lower prevalence of AD among those taking anti-inflammatory medications, suggesting a potential role for inflammation in AD.(1) Nevertheless, it remains unclear whether inflammation plays a primary or secondary role in the major neurodegenerative conditions.

Frontotemporal lobar degeneration (FTLD) shows pathological abnormalities that are distinct from AD and thus provides an alternative disorder to investigate the relationship between inflammation and neurodegeneration. Previous studies of environmental risk factors in sporadic behavioral variant FTD found a significant association with head trauma and a close to significant association with thyroid disease, although that study lumped all of the FTD subtypes together without regard for neuropathological subsets.(2) Furthermore, elevations in cerebrospinal fluid cytokines, notably TNF-α, have previously been demonstrated in FTD.(3) While provocative, these studies were performed before the full spectrum of FTLD pathological subtypes had been elucidated. Consequently, the patient population examined represented a heterogeneous mix of pathologies, predominantly FTLD due to tau aggregation (FTLD-tau) and FTLD with abnormal cytoplasmic localization of TDP-43 (FTLD-TDP). Therefore, it remains unclear whether systemic inflammatory illness was overrepresented among patients with any clinical or pathological subtype.

In contrast to the heterogeneity of most of the FTD subtypes, semantic variant primary progressive aphasia (svPPA) is nearly always associated with underlying TDP-43 aggregates (75–100% in clinicopathological correlation series).(4,5) In our pathology confirmed cases at the University of California San Francisco (UCSF) Memory and Aging Center, 21/23 svPPA patients showed TDP-43 type C aggregates making this a clinical disorder with which the underlying neuropathology can be predicted. Furthermore, among FTD syndromes, svPPA is the least likely to be familial,(6) making it an ideal disorder to study the prevalence of non-genetic factors, such as chronic inflammation. Another TDP-43 associated FTLD subtype, caused by mutations in granulin (*GRN*) leading to a systemic deficiency in the progranulin (PGRN) protein, is associated with immune alterations.(7)

PGRN knockout mice develop inflammatory arthritis and PGRN has demonstrated antagonistic effects on TNF-α signaling.(7) Recently, antibodies to PGRN have been demonstrated in patients with histories of particular autoimmune conditions, lowering systemic PGRN levels by half, similar to levels found in PGRN mutation carriers.(8,9)

As with neurodegenerative disease, autoimmune disease is increasingly correlating syndromic presentation with underlying pathomechanism. In some cases, autoimmune conditions that were considered unrelated, now reveal networks that detail closer underlying genetic and pathological ties, so called ‘clusters’, while in others such links are not present. (10–12) Given the associations between PGRN and inflammation, we hypothesized that, compared to normal controls (NC) and AD, the TDP-43-associated diseases (svPPA and PGRN mutation carriers) would display evidence of specific inflammatory signaling, as measured by an increased prevalence of particular clusters of autoimmune disorders and elevated TNF-α signaling.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

All subjects underwent informed consent to share their clinical data for research purposes. The study of patients’ clinical data was approved by the human research committee at UCSF and Mayo.

Participants

All participants underwent a thorough and standardized history and physical exam including the collection of past medical history. We retrospectively identified 94 svPPA patients from UCSF with complete records and whose clinical features conformed to revised consensus diagnostic criteria for svPPA.(13) An additional 35 svPPA patients were contributed by Mayo Clinic Jacksonville (MCJ) all of whom met consensus diagnostic criteria for svPPA for a total cohort of 129 patients with svPPA. We identified 23 PGRN mutation carriers from UCSF and 16 from MCJ with complete records for a total of 39 PGRN patients. Patients were included in the PGRN group if they had a mutation in *GRN*,(9) regardless of whether they were symptomatic, and all clinical phenotypes were included for symptomatic patients. Two of the PGRN patients also had been identified in our clinical svPPA cohort.

Age, gender, and education-matched NC subjects were selected from a larger set recruited into a study of normal aging. Subjects were included into the healthy aging cohort if they had a normal neurologic exam, MRI scans without clinically evident strokes, and were without cognitive deficits or diagnosis of major psychiatric disease. With the exception of untreated multiple sclerosis, past history of autoimmune disease was not exclusionary for the NC subject group. Subjects were consecutively chosen from those most recently enrolled, and any with incomplete medical history were excluded. With the addition of 60 subjects from MCJ, a total of 186 older healthy controls were included in the study.

We obtained age, gender, and education-matched AD subjects who met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association) criteria for Alzheimer’s disease (AD) (NINCDS-ADRDA).(14) Any subjects with incomplete charts or diagnoses of comorbid Lewy Body and or vascular disease were excluded. 35 additional AD subjects were contributed by MCJ leading to a total of 158 AD subjects.

Identification and Classification of Autoimmune Conditions

UCSF and MCJ charts were reviewed in a retrospective manner by a rater blinded to neurological diagnosis, screening for any evidence of autoimmune disease. Using the same established criteria at both sites,(15) we searched medical records for evidence of individual autoimmune conditions and modified the criteria by removing motor neuron disease and including only type 1, but not type 2, diabetes mellitus as autoimmune conditions. Furthermore, we added chronic lymphocytic colitis, lichen sclerosis, and vitiligo for which there is evidence of autoimmune aetiology (16–18) to Rugbjerg's criteria after having encountered these conditions in the medical records (Table 1). The physicians' notes in the review charts represented data that spanned over a decade in many cases and employed the standard thorough history taking typical of a behavioral neurology encounter. Only notes with reference of past medical history were included.

Determination of TNF-α Concentrations in Plasma

Because progranulin has been shown to have antagonistic effects on TNF-α signaling, we attempted to obtain more direct evidence of TNF-α mediation in subjects for whom this data was available. TNF-α concentration in frozen-EDTA plasma samples were measure in a subset of patients with svPPA (n=26), PGRN (n=24), and healthy controls (n=37) was determined by use of a commercial ELISA, the Human TNF-alpha Ultra-Sensitive Plate (Meso Scale Discovery). Lower limit of detection: 0.036 pg/mL; lower limit of quantification: 0.6 pg/mL.

Statistical Analysis

Analysis of variance (ANOVA) was used to test for significance for continuous variables such as age, education, Mini Mental State Examination (MMSE) score, Clinical Dementia Rating (CDR) Total score, and CDR Sum of Boxes score across diagnostic groups. For categorical variables such as gender and ethnicity, chi-square tests were used. Prevalence and comparison of autoimmune disease among the diagnostic groups were assessed for statistical significance using chi-square tests. In order to determine whether non-thyroid autoimmune conditions were predictive of diagnosis, we conducted follow-up hierarchical bivariate logistic regressions in which the dependent variable was a dichotomous diagnostic variable. In step one, we entered nuisance covariates including age, gender, and education. In step two, we entered presence of thyroid disease, and in step three, we entered our primary independent variable of interest, presence of non-thyroid disease. This approach enabled us to examine whether the presence of a non-thyroid condition was a significant predictor of diagnostic status after accounting for other demographic factors and even thyroid disease. Odds ratios for the non-thyroid autoimmune conditions among the diagnostic groups were also computed. The above analyses were performed using SPSS v20.0 (IBM Corp., Armonk, NY, USA). A t-test was employed to compare TNF-α levels in the svPPA and PGRN versus NC cohorts.

RESULTS

Study 1 - svPPA vs. NC vs. AD

The patient groups were matched for gender, education, and race. The control group had a significantly higher MMSE at presentation and significantly lower CDR Total and Sum of Boxes scores, as expected (Table 2).

In the svPPA cohort, 18% (n=23) were positive for past medical history of autoimmune disease. Thyroid disease was the largest contribution to autoimmune disease in the svPPA cohort, 9% (n=11) total. Of this group, 6% (n=7) had only thyroid disease. The four individuals with thyroid disease and another autoimmune condition had diagnoses of chronic

lymphocytic colitis (n=1), type 1 diabetes mellitus (n=1), and vitiligo (n=2). The remaining 9% (n=12) presented with non-thyroid autoimmune disorders included: discoid lupus and systemic lupus erythematosus (n=1), lichen sclerosis (n=1), psoriasis (n=1), rheumatoid arthritis (n=3), sarcoidosis (n=2), Sjögren's syndrome (n=2), Sjögren's syndrome and systemic lupus erythematosus (n=1), and vitiligo (n=1). Analysis of the non-thyroid autoimmune conditions revealed significantly greater prevalence of disease in the svPPA cohorts compared to NC and AD (p=0.004) on chi-square analysis. In contrast, there were no significant differences in total autoimmune disease among the svPPA, NC, and AD cohorts. Analysis of thyroid disease revealed no statistical differences in the prevalence of this condition across all groups and at rates comparable to general population estimates (8.9–10.3%).(19,20)

Separate logistic regressions found that the presence of non-thyroid autoimmune disease predicted svPPA status above and beyond other variables for svPPA vs. NC (OR=3.15, 95% CI: 1.31–7.6) and svPPA vs. AD (OR=3.59, 95% CI: 1.36–9.46) (Figure 1). No other variables in the model, including the presence of thyroid disease, were significant predictors of diagnostic status in either regression analysis.

Study 2 - PGRN vs. NC vs. AD

Comparison of the PGRN cohort with the previously obtained NC and AD groups revealed that the PGRN cohort was significantly younger. The groups were no different for education, gender, and race. As was the case above, both the PGRN and AD cohort had significantly lower MMSE and significantly higher CDR Total and Sum of Boxes at presentation (Table 3).

In the PGRN cohort, 28% (n=11) were positive for past medical history of autoimmune disease. Thyroid disease was the largest contribution to autoimmune disease in the PGRN cohort (n=6, 15%). Five other individuals (13%) presented with autoimmune diseases including: coeliac disease (n=1), psoriasis (n=2), sarcoidosis (n=1), and type I diabetes mellitus with thyroid disease (n=1). As with the svPPA group, analysis of the non-thyroid autoimmune conditions revealed significantly higher rates of disease in the PGRN cohorts compared to NC and AD (p=0.0002) on chi-square analysis. There were no significant differences in total autoimmune disease among the PGRN, NC, and AD cohorts. Subgroup analysis of thyroid disease revealed no statistical differences in the prevalence of this condition across all groups and at rates comparable to general population estimates of thyroid disease (8.9–10.3%).(19,20)

Bivariate logistic regression found that the presence of non-thyroid autoimmune disease predicted PGRN status above and beyond other variables for PGRN vs. NC (OR=3.27, 95% CI: 1.009–10.6) and PGRN vs. AD (OR=3.73, 95% CI: 1.1–12.9) (Figure 1). No other variables in the model, including the presence of thyroid disease, were significant predictors of diagnostic status in either regression analysis.

PGRN and svPPA

Two PGRN patients in this collection also had clinical diagnoses of svPPA, this included an individual without any history of autoimmune disease and an individual with type I diabetes mellitus and thyroid disease. Both groups possess significant overlap with the types of rheumatologic conditions, thyroid disease, inflammatory arthritides, cutaneous conditions, and gastrointestinal disorders. Combining the PGRN and svPPA cohorts reveals that nearly all the non-thyroid conditions occur at higher rates than estimated rates in the general population (Table 4).

TNF-α Analysis

Plasma concentrations of TNF-α were determined in all subjects for whom samples were available (PGRN, n=24, 62%; svPPA, n=26, 22.4%; NC, n=37, 21.5%). Compared to NC, plasma TNF-α concentrations were elevated in the PGRN and svPPA cohort. TNF-α for NC was 4.1±1.7 pg/mL vs. 6.0±3.8 pg/mL in PGRN ($p = 0.0075$, *t* test) and vs. 8.4±11pg/mL in svPPA ($p = 0.012$, *t* test) (Figure 2).

DISCUSSION

We observed a higher prevalence of specific autoimmune conditions in svPPA and in PGRN carriers compared to matched cohorts. Both svPPA and PGRN patients showed elevated levels of TNF-α compared to controls. These findings suggest a strong relationship between inflammation signaling, immune-mediated illness, and two neurodegenerative conditions, svPPA and progranulin mutations.

Literature on autoimmune pathogenesis finds that diseases tend to cluster in groups, although these groups have not yet been consistently defined.(10–12) These clusters are determined by epidemiological overlap, conditions co-occurring in the same individual or within first-degree relatives at rates higher than expected for the general population, and by shared genetic risk alleles. In addition to showing similarities in autoimmune pathogenesis within clusters, some studies have also begun to show significant differences between various clusters.(30)

Thyroid disease is considered an archetype autoimmune disease cluster with particularly strong overlap with pernicious anemia and diabetes.(10) An in-depth meta-analysis of genome-wide-association studies by Sirota et al. revealed an inverse relationship between thyroid disease and rheumatoid arthritis clusters, providing further justification for considering thyroid disease separately from the other immune conditions found in our cohorts.(30) Thyroid disease is the most prevalent autoimmune condition in the general population (16) occurring at rates of nearly 10% of an elderly population.(19,20) In our study, thyroid disease was the single greatest contribution to autoimmune disease across all cohorts, at rates statistically similar to each other and rates found in the general population. This argues against a specific association between thyroid disease and either svPPA or PGRN. This finding contrasts with a near significant association of bvFTD with thyroid disease previously reported by others.(2)

Another autoimmune cluster, defined by inflammatory arthritides rheumatoid arthritis, systemic lupus erythematosus, and psoriasis,(10–12) appeared prominently in both svPPA and PGRN cohorts. There are well documented convergences between Sjögren's syndrome and sarcoidosis with rheumatoid arthritis, systemic lupus erythematosus, and psoriasis including highly significant associations with increased TNF-α signaling, an abnormality found in svPPA and PGRN carriers.(11,31–33)

Other clusters prominently appearing in both svPPA and PGRN cohorts, cutaneous and gastrointestinal, have been less well characterized in the literature. Supporting a cutaneous cluster are the co-occurrences of and common T cell activation pathogenesis shared among discoid lupus, lichen sclerosis, psoriasis, and vitiligo.(18,34,35) Supporting the existence of a gastrointenstinal cluster, chronic lymphocytic colitis shares genetic and pathologic features with coeliac disease.(17) Taken together, autoimmune disorders belonging to each of these non-thyroid clusters were found to have higher rates in the svPPA and PGRN cohorts than in NC or AD controls and occur at rates greater than general population estimates.

With regards to the relationship between autoimmune disease and PGRN, an analysis of PGRN knockout mice revealed a susceptibility to inflammatory arthritis and high levels of TNF-α.(7) Although this association has yet to be established in human *GRN* mutation carriers, our data would appear to support this link. *GRN* mutations result in FTLD-TDP, type A neuropathology, and clinicopathological studies demonstrate that svPPA is most often associated with underlying FTLD-TDP, type C pathology.(36) Both of these FTLD-TDP disorders appear to be linked by autoimmunity. Our observation of a related pattern of systemic inflammatory disorders between PGRN and svPPA, suggests that FTLD-TDP, type C, might have similar pathomechanisms. Finding increased TNF-α levels in both our PGRN and svPPA cohort further strengthens this potential link, as an effective magnification of TNF-α signaling was hypothesized as a probable mechanism of this rheumatologic disease vulnerability in the PGRN knockout mice.

Lastly, a recent publication revealed the presence of anti-PGRN antibodies in around 40% of screened rheumatoid arthritis (16/44) and systemic lupus erythematosus patients (39/91). These antibodies had the direct effect of lowering plasma PGRN levels by about 50% compared to NC,(8) mirroring the haploinsufficiency effects of *PGRN* mutations.(9) The presence of anti-PGRN antibodies in autoimmune disease provides a direct mechanism of action for how sustained autoimmune pathology would precipitate FTLD-TDP disease and supports our findings of increased rates of these related autoimmune disorders in FTLD-TDP populations.

Based on the present work and previous studies, we propose a model in which an imbalance of anti- and pro-inflammatory factors results in systemic inflammation and susceptibility to specific neurodegenerative diseases (Figure 3). In this model increased TNF-α signaling, either via primary decreased PGRN expression (as seen in patients with *GRN* mutations or patients with autoimmune disease who develop anti-PGRN antibodies) and secondary increased TNF-α or primary increased TNF-α expression (which can occur in the setting of autoimmune disease as well as in chronic disease unrelated to autoimmune mechanisms), increases susceptibility to certain types of FTLD-TDP. These two mechanisms are not mutually exclusive and likely interact with each other. Currently, this model relates only to FTLD-TDP types A and C, however, it should be noted that the other well-known FTLD-TDP -causing mutations, *C9ORF72* and valosin containing protein (*VCP*), which are accompanied by FTLD-TDP types B (as well as A) and D, respectively, (36,37) also have intriguing links to immune function, although these links require further study.

If confirmed, these findings may help delineate how specific patterns of systemic inflammation predispose to discrete forms of neurologic disease. It will be exciting to see if, with larger numbers, patterns arise that allow for the prediction of specific underlying TDP-43 subtypes and whether the neurodegenerative disease will prove amenable to anti-inflammatory approaches. TDP-43 proteinopathy has become increasingly recognized as co-pathology in many neurodegenerative diseases, found in up to 50% of AD, 60% of Parkinson's disease, and occasionally in patients with Huntington disease.(38) As such, further study using PGRN and svPPA as model systems may help clarify TDP-43 pathobiology generally.

While this study has limitations -- svPPA is a relatively uncommon disease and the cohort described here remains small despite our multi-centre approach; PGRN carriers are even rarer -- our analyses represents among the largest collection of these patients to date and displays adequate power to detect significant increases in inflammatory disease prevalence in separate svPPA and PGRN cohorts. The collection of past medical history was performed in a retrospective manner based on previous physician diagnoses and obtained in open-ended questioning, rather than by direct laboratory-based evaluations of autoimmune

markers. This suggests that we may have underrepresented the prevalence of autoimmune disease in this sample. While all our patients receive the same attention regarding history and physical examination, NC and dementia patients alike, both UCSF and MCJ are tertiary care centres with specialty dementia care clinics. As such, it is possible that previous to visiting with our centres, the subjects in the PGRN and svPPA cohort may have received greater medical attention than the NC cohort. Nonetheless, our NC group showed a roughly similar prevalence of overall autoimmune disease to the other cohorts arguing against systematic ascertainment bias. The younger age of the PGRN cohort was driven by the inclusion of asymptomatic carriers. As rates of autoimmune disease increase with age, a younger experimental group with older controls would only bias against our hypothesis. TNF-α signaling was chosen as a marker of inflammation in an exploratory manner and in the future we hope to broaden the analysis of inflammatory markers to include additional cytokines, autoimmune antibodies, and other measures of inflammation.

Despite these limitations, the present findings build on previous work (39,40) and warrant careful review for a history of autoimmunity in all patients with neurodegenerative disease with particular emphasis on FTLD pathologies. These findings may open up a suite of new diagnostic tools and therapeutic approaches to FTLD-TDP. Whether systemic inflammation creates risk for TDP-43 disease or both autoimmune and TDP-43 disorders reflect shared underlying pathogenic mechanisms remains undetermined and should be pursued in future studies. Furthermore, we should entertain the possibility that autoimmunity may in some instances represent a preclinical disruption of neuroimmunological function.

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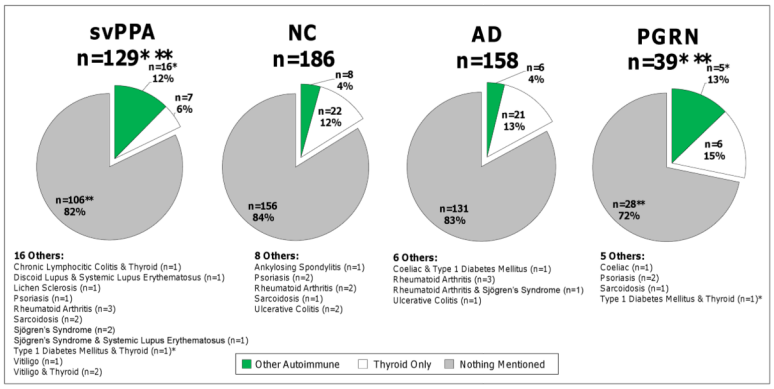

Figure 1.

Prevalence of Autoimmune Disease among Diagnostic Groups.

Abbreviations: AD = Alzheimer's disease; NC = normal controls; PGRN = progranulin; svPPA = semantic variant primary progressive aphasia. Retrospective chart review of autoimmune conditions in AD, NC, PGRN, and svPPA subjects. Other Autoimmune refers to all other autoimmune conditions on the collection instrument that were not thyroid disease. When an individual had a thyroid disorder and another autoimmune disease they were assigned to the Other Autoimmune category, so as to avoid being counted twice. Thyroid Only refers to those who had only thyroid spectrum disorders affecting subjects. Nothing Mentioned refers to individuals where there was no mention of any condition found within the screening collection instrument. * ** Two patients in the collection overlapped between the PGRN and svPPA cohort (one had type 1 diabetes and thyroid disease and the other had no mentioned autoimmune disorder).

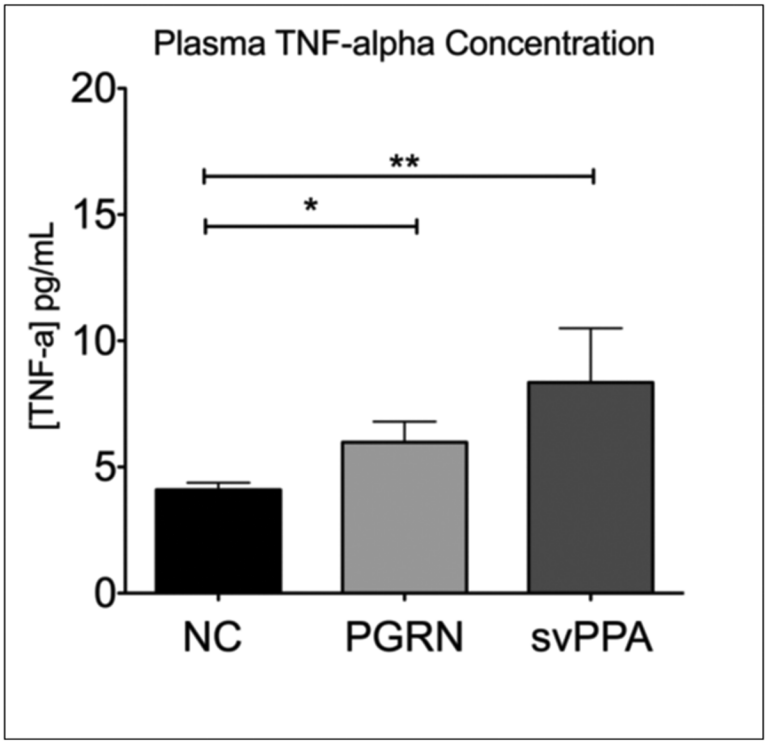

Figure 2.

TNF-α Levels in NC, PGRN, and svPPA.

Abbreviations: NC = normal control; PGRN = progranulin; svPPA = semantic variant primary progressive aphasia; TNF-α = tumor necrosis factor alpha. Samples from NC (37), PGRN (24), and svPPA (26) were analyzed for plasma TNF-α levels. * ** Statistical differences in TNF-α levels were found between NC and PGRN as well as NC and svPPA ($p = 0.0075$ and $p = 0.012$, respectively; *t* test)..

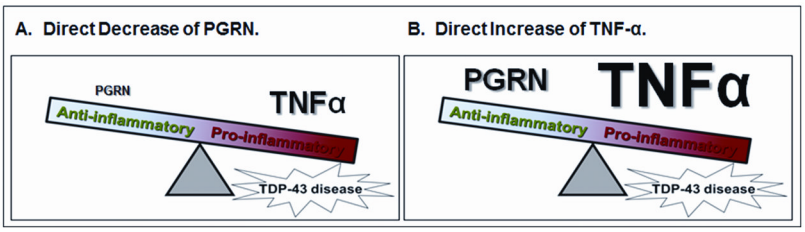

Figure 3.

Model of Relative Increased TNF-α Signaling in TDP-43 Disease, Via PGRN Depletion or TNF-α Elevation.

Abbreviations: PGRN = progranulin; TDP-43 = transactive response DNA-binding protein 43; TNF-α = tumor necrosis factor alpha. Proposed unifying schema for TDP-43 disease pathology mediated through the effects of TNF-α signaling. Above, (A) represents primary PGRN and secondary TNF-α mediated mechanisms while (B) represents a primary TNF-α mediated mechanism of TDP-43 disease. These two mechanisms likely interact with each other.

Table 1

Screen of Autoimmune Conditions.

- Addison disease
- Ankylosing spondylitis
- Autoimmune hemolytic anemia
- Behcet's disease
- Coeliac disease
- Chorea minor
- Chronic lymphocytic colitis
- Chronic rheumatic heart disease
- Crohn's disease
- Dermatomyositis
- Discoid lupus erythematosus
- Graves' disease
- Hashimoto thyroiditis
- Immune thrombocytopenic purpura
- Localized scleroderma
- Lichen sclerosis
- Lupoid hepatitis
- Multiple sclerosis
- Myasthenia gravis
- Pernicious anemia
- Polyarteritis nodosa
- Polymyalgia rheumatic
- Polymyositis
- Primary biliary cirrhosis
- Psoriasis
- Reactive arthritis
- Rheumatoid arthritis
- Sarcoidosis
- Sjögren's syndrome
- Systemic lupus erythematosus
- Systemic sclerosis
- Type 1 diabetes mellitus
- Ulcerative colitis
- Vitiligo
- Wegener granulomatosis

Modified listing of autoimmune conditions screened from Rugbjerg et al.(15)

Table 2

Population Demographics.

DIAGNOSTIC GROUP mean± SD (n)	svPPA	AD	NC	*p*
AGE AT FIRST VISIT yr.	65.2±7.7 (129)	65.7±9.8 (158)	65.6±9.9 (186)	n.s.
GENDER % female	49.6% (129)	48.7% (158)	53.8% (186)	n.s.
RACE % Caucasian	92% (124)	89.4% (151)	92.4% (185)	n.s.
EDUCATION yr.	15.6±2.9 (110)	15.7±3.7 (134)	16.2±2.4 (168)	n.s.
MMSE AT FIRST VISIT	20.9±8 (83)	20±6.3 (121)	29.2±1.5 (162)	<0.0001
CDR Total	0.93±0.66 (76)	0.84±0.44 (71)	0.01±0.08 (124)	<0.0001
CDR Sum of Boxes	5.0±3.9 (76)	4.7±2.4 (71)	0.03±0.14 (124)	<0.0001

Abbreviations: AD = Alzheimer's disease; CDR = clinical dementia rating scale; MMSE = Mini Mental State Examination; NC = normal control; svPPA = semantic variant primary progressive aphasia.

Table 3

Population Demographics.

DIAGNOSTIC GROUP mean± SD (n)	PGRN	AD	NC	*p*
AGE AT FIRST VISIT yr.	59.6±11.3 (39)	65.7±9.8 (158)	65.6±9.9 (186)	0.001
GENDER % female	59% (39)	48.7% (158)	53.8% (186)	n.s.
RACE % Caucasian	91% (34)	89.4% (151)	92.4% (185)	n.s.
EDUCATION yr.	15.7±3.6 (34)	15.7±3.7 (134)	16.2±2.4 (168)	n.s.
MMSE AT FIRST VISIT	25 ±5.1 (25)	20±6.3 (121)	29.2±1.5 (162)	<0.0001
CDR Total	0.79±0.89 (19)	0.84±0.44 (71)	0.01±0.08 (124)	<0.0001
CDR Sum of Boxes	4.2±4.9 (19)	4.7±2.4 (71)	0.03±0.14 (124)	<0.0001

Abbreviations: AD = Alzheimer's disease; CDR = clinical dementia rating scale; MMSE = Mini Mental State Examination; NC = normal control; PGRN = progranulin.

Table 4

Comparison of Autoimmune Prevalence.

AUTOIMMUNE DISEASE	PGRN + svPPA COHORT PREVALENCE	ESTIMATED GENERAL POPULATION PREVALENCE	ESTIMATED ODDS RATIO
Thyroid (Hypo & Hyper)	10.2% (n=17*)	**8.9–10.3%** (19,20)	0.99 – 1.15
Psoriasis	1.8% (n=3)	**0.1%** (21)	18
Rheumatoid Arthritis	1.8% (n=3)	**0.86%** (16,22,23)	2.1
Sjögren's	1.8% (n=3)	**0.014–0.32%** (16,24)	5.6 – 107.14
Sarcoidosis	1.8% (n=3)	**0.001–0.04%** (25)	45 – 1800
Vitiligo	1.8% (n=3)	**0.4%** (16,26)	4.5
Systemic Lupus Erythematosus	1.2% (n=2)	**0.024%** (16)	50
Coeliac Disease	0.6% (n=1)	**0.83–0.03%** (27)	0.72 – 20
Chronic Lymphocytic Colitis	0.6% (n=1)	**0.06%** (28)	10
Discoid Lupus	0.6% (n=1)	**0.4–0.8%** (29)	0.75 – 1.5
Lichen Sclerosis	0.6% (n=1)	**Unknown** (18)	N/A
Type 1 Diabetes Mellitus	0.6% (n=1*)	**0.19%** (16)	3.16

Abbreviations: PGRN = progranulin; svPPA = semantic variant primary progressive aphasia.

*Patient with clinical svPPA and PGRN carrier who has type 1 diabetes mellitus and thyroid disease.