Increased prevalence of non-thyroid autoimmune disease in patients with familial frontotemporal dementia associated with progranulin mutations

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Background

- Familial frontotemporal dementia (FTD) is most commonly due to mutations in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), or chromosome 9 open reading frame 72 (*C9orf72*).
- Mouse models of *GRN* or *C9orf72* mutations exhibit immune dysfunction, including excessive systemic inflammatory responses and neuroinflammation [1-7], inflammatory arthritides [8] and upregulated auto-antibody production [5,6]. Patients with FTD due to *GRN* mutations have elevated levels of several pro-inflammatory cytokines in serum and cerebrospinal fluid [9-11]. Patients with systemic vasculitides that develop anti-GRN antibodies have more active disease [12].
- Autoimmune thyroid disease is relatively common in the general population. However, recent research has observed an increased prevalence of *non-thyroid autoimmune* disease in patients with 'TDP-43-opathies' such as semantic dementia [9], as well as *GRN* mutation associated FTD [9] and *C9orf72* mutation associated FTD and motor neuron disease [13]. However, the prevalence of autoimmune disease has not been assessed in patients with FTD secondary to *MAPT* mutations, who have definite tau, rather than TDP-43, pathology.
- We analysed the prevalence of systemic autoimmune disease across a well-characterised cohort of symptomatic familial FTD patients with *GRN, MAPT* or *C9orf72* mutations, and healthy controls. We show that non-thyroid autoimmune disease is more prevalent in individuals with *GRN* mutations, but not *C9orf72* or *MAPT* mutations, suggesting that GRN haploinsufficiency is most closely linked to systemic immune dysregulation.

Methods

- Retrospective review of medical notes or research visit clinical report forms for all symptomatic familial FTD cases with a *GRN, C9orf72* or *MAPT* mutation, in previous or ongoing studies at UCL Dementia Research Centre, including the UCL Genetic Frontotemporal Dementia Initiative (GENFI) cohort. Control group data were obtained from case report forms of healthy controls recruited into the Longitudinal Investigation of FTD (LIFTD) study, all of whom had had genetic testing and were negative for FTD-associated mutations. Notes were reviewed as per Figure 1 using autoimmune conditions in Table 1, based on previous similar studies [9,13].

Figure 1: Process used in retrospective notes review

Table 1: Autoimmune conditions used in retrospective notes review

Rheumatology	Gastroenterology	Neurology	Dermatology	Endocrinology	Haematology	Cardiology
Behcet's disease	Coeliac disease	Chronic inflammatory demyelinating polyneuropathy	Alopecia areata, totalis or universalis	Addison's disease	Autoimmune haemolytic anaemia	Chronic rheumatic heart disease/rheumatic fever
Inflammatory arthritides: Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, reactive arthritis	Inflammatory bowel disease: Crohn's disease Ulcerative colitis	Guillain Barre syndrome	Discoid lupus	Hypothyroidsm (and cause if known e.g. Hashimoto's)	Immune thrombocytopaenic purpura	
Polymyalgia rheumatica	Chronic lymphocytic colitis	Inclusion body myositis	Localised scleroderma	Hyperthyroidisim (and cause if known e.g. Graves' disease):		
Polymyositis, dermatomyositis	Lupoid hepatitis	Myasthenia gravis	Lichen sclerosus	Type 1 diabetes		
Sarcoidosis	Pernicious anaemia	Multiple sclerosis, neuromyelitis optica or other demyelinating disease	Pemphigus vulgaris/bullous pemphigoid			
Sjogren's syndrome	Primary biliary cirrhosis	Sydenham's chorea (chorea minor)	Psoriasis			
Systemic lupus erythematosus	Primary sclerosis cholangitis	Transverse myelitis	Vitiligo			
Systemic sclerosis						
Vasculitides: Wegener's granulomatosis, Churg Strauss syndrome, Polyarteritis nodosa						

- Prevalence of any autoimmune disease ('total') and gender were compared between groups using Chi squared or Fisher's exact tests. Sub-analyses were carried out for presence of thyroid disease and non-thyroid disease. Age at onset (age at research visit for controls) was compared using ANOVA with Bonferroni post hoc tests. Significance threshold was $p<0.05$ for all analyses.
- All analyses were performed initially including three patients who had dual mutations (2 with *GRN/C9orf72* mutations, 1 with *C9orf72/SQSTM1*), then excluding them, to investigate for effect of possessing two different TDP-43 pathology-related mutations on autoimmune disease prevalence.

Results

- Demographics are shown in **Tables 2 and 3.** There was no significant difference in gender between any group. Age at onset (AAO) (age at data collection for controls) significantly differed between all groups ($p<0.001$), except between the *GRN* and *C9orf72* mutation groups. The *MAPT* group had a significantly younger AAO (49.3 years) than other mutation groups.

Table 2 (includes dual mutation carriers)

Mutation	Number of patients (includes dual mutations)	Male/ Female (%)	Diagnosis (N)	Mean age at onset (FTD) or visit (controls) in years (range)	Total auto-immune disease N (%)	Thyroid disease N (%)	Non-thyroid disease N (%)
GRN	31	48.4/51.6	bvFTD = 16 /PNFA = 10 CBS = 2 PSP = 0 FTD-MND = 3	57.4 (45.0-67.0)	11 (35.5%)	5 (16.1%)	6 (19.4%)
MAPT	40	65.0/35.0	bvFTD = 36 PNFA = 0 CBS = 2 PSP = 1 FTD-MND = 1	49.3 (33.0-70.0)	3 (7.5%)	2 (5.0%)	1 (2.5%)
C9orf72	36	55.6/44.4	bvFTD = 23 PNFA = 3 CBS = 0 PSP = 0 FTD-MND = 10	55.5 (40.0-68.0)	8 (22.2%)	5 (13.9%)	3 (8.3)
Healthy controls	24	45.8/54.2	N/A	68.5 (52.1-72.9)	3 (12.5%)	3 (12.5%)	0 (0%)

Table 3 (excludes dual mutation carriers)

Mutation	Number of patients (excludes dual mutations)	Male/ Female (%)	Diagnosis (N)	Mean age at onset (FTD) or visit (controls) in years (range)	Total auto-immune disease N (%)	Thyroid disease N (%)	Non-thyroid disease N (%)
GRN	29	51.7/48.3	bvFTD = 16 /PNFA = 10 CBS = 2 PSP = 0 FTD-MND = 1	57.8 (45.0-67.0	9 (31.0%)	5 (17.2%)	4 (13.8%)
MAPT	40	65.0/35.0	bvFTD = 36 PNFA = 0 CBS = 2 PSP = 1 FTD-MND = 1	49.3 (33.0-70.0)	3 (7.5%)	2 (5.0%)	1 (2.5%)
C9orf72	33	60.6/39.4	bvFTD = 23 PNFA = 3 CBS = 0 PSP = 0 FTD-MND = 7	56.0 (40.0-68.0)	6 (18.2%)	5 (15.2%)	1 (3.0%)
Healthy controls	24	45.8/54.2	N/A	68.5 (52.1-72.9)	3 (12.5%)	3 (12.5%)	0 (0%)

- Prevalence of autoimmune disease within the cohort is summarized in **Tables 2 and 3 above** and displayed **below in Figure 2.** The majority of cases of autoimmune disease across all groups, and all cases in the healthy control group, were thyroid related. Total autoimmune disease was significantly more prevalent in the ***GRN* mutation group** than the *MAPT* group (35.5% vs. 7.5%; p=0.003), with a trend towards a greater prevalence when compared with controls (35.5% vs. 12.5%; p=0.052), but not compared with the *C9orf72* mutation group (22.2%). This was due to an increased prevalence of **non-thyroid**, rather than thyroid, disease in the *GRN* group (19.4%) compared with the *MAPT* group (2.5%; p=0.038) and controls (0.0%; p=0.030). The greater prevalence in the *GRN* group compared with the *MAPT* group was seen even if the dual *GRN*/*C9orf72* mutation carriers were excluded (31.0% vs. 7.5%; p=0.011). Prevalence of total, thyroid and non-thyroid autoimmune disease was not significantly different between any other group.

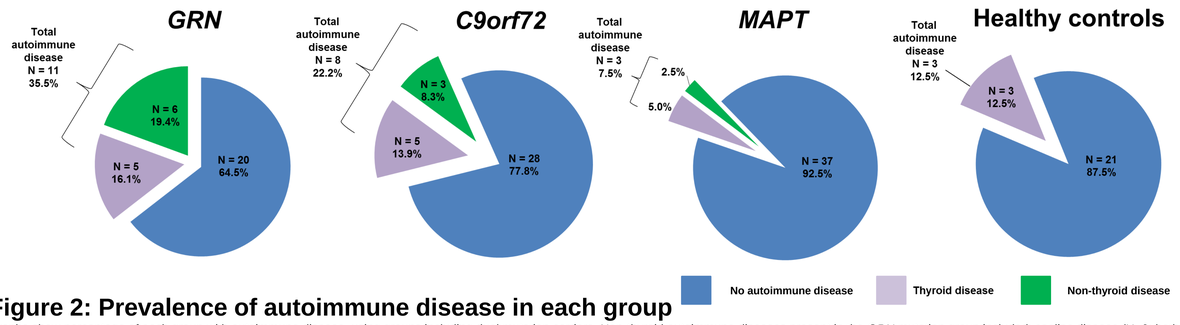

Figure 2: Prevalence of autoimmune disease in each group

Graphs show percentage of each group with autoimmune disease, using groups including dual mutation carriers. Non-thyroid autoimmune diseases present in the *GRN* mutation group included: coeliac disease (N=2; both cases had dual *GRN/ C9orf72* mutations), sarcoidosis (N=1), ankylosing spondylitis (N=1), recurrent polyarthritis and fever (N=1) and persistent eosinophilia with pericardial effusion (N=1). The *C9orf72* group had coeliac disease (N=2, both had dual *GRN/C9orf72* mutations) and psoriasis (N=1) The *MAPT* mutation carriers had 1 case with rheumatoid arthritis.

Discussion

- FTD patients with *GRN* mutations have a particularly high prevalence of non-thyroid systemic autoimmune disease, confirming observations from previous research [9]. Previous observations of a high prevalence of autoimmune disease in individuals with the *C9orf72* mutation [13] were not replicated in our study. GRN haploinsufficiency may therefore be more closely linked to systemic autoimmunity than underlying TDP-43 pathology.
- Patients with *MAPT* mutations have a similar prevalence of autoimmune disease to healthy controls, suggesting tau pathology is not associated with increased systemic autoimmunity. This is consistent with previous research on patients with assumed tauopathy (progressive supranuclear palsy) [9].
- GRN haploinsufficiency could cause systemic and cerebral immune dysregulation from an early age in *GRN* mutation carriers, leading to higher rates of systemic autoimmune disease and excess neuroinflammation, accelerating neurodegeneration. Future work will focus on replicating analyses across a larger group of individuals with familial FTD across multiple GENFI sites, and examining inflammatory biomarkers in blood and cerebrospinal fluid samples from symptomatic and pre-symptomatic individuals both with and without autoimmune diseases.

References & Acknowledgements

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