Increased prevalence of non-therapeutic 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 arthritis [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-therapeutic autoantibodies in patients with ‘TDP-43opathies’ 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 controls, to show that non-therapeutic autoimmune disease is more prevalent in individuals with GRN mutations, but not C9orf72 or MAPT mutations, suggesting that GRN haplosufficiency 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 Genetics 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].

Results

- Demographics are shown in Tables 2 and 3. There was no significant difference in gender between any group. Age at onset (AO) (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 AO (49.3 years) than other mutation groups.

- Table 2 (includes dual mutation carriers)

- Table 3 (excludes dual mutation carriers)

Discussion

- FTD patients with GRN mutations have a particularly high prevalence of non-therapeutic 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 haplosufficiency 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 taupathy (progressive supranuclear palsy) [9].

- GRN haplosufficiency 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


Figure 1: Process used in retrospective notes review

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-therapeutic autoimmune diseases present in the GRN mutation group included: 11 (35.5%) cases had Hashimoto’s thyroiditis, 2 (6.2%) cases had rheumatoid arthritis, 1 (3.1%) case had primary biliary cirrhosis, 1 (3.1%) case had systemic lupus erythematosus, and 1 (3.1%) case had vitiligo.

Table 1: Autoimmune conditions used in retrospective notes review

Table 2: (includes dual mutation carriers)

Table 3: (excludes dual mutation carriers)