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Prevalence of immunological diseases in a Finnish frontotemporal lobar degeneration cohort with the C9orf72 repeat expansion carriers and non-carriers

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Abstract

Recent studies have suggested a role for immune dysregulation behind the etiology of frontotemporal lobar degeneration (FTLD). Here, we have investigated the prevalence of immunological diseases in FTLD (N=196) with and without the C9orf72 repeat expansion, Alzheimer’s disease (AD) (N=193) and not cognitively impaired (NCI) subjects (N=92). The prevalence was 16.3% in FTLD, 13.5% in AD and 15.2% in NCI. Although differences between the groups did not reach statistical significance, the frequency of immunological diseases was the highest in FTLD without the C9orf72 expansion (22/117, 18.8%) and the lowest in FTLD with the expansion (6/56, 10.7%), suggesting that the C9orf72 expansion possibly influences immunological pathways in FTLD.

Key words: Frontotemporal lobar degeneration, Frontotemporal dementia, immunological disease, C9orf72, comorbidity, immunology
1. Introduction

Frontotemporal lobar degeneration (FTLD) is a group of progressive neurodegenerative syndromes mainly affecting the frontal and temporal lobes of the brain. Clinically FTLD can be divided into two major clinical subgroups: 1) Behavioral variant frontotemporal dementia (bvFTD) characterized by personality changes (Rascovsky et al., 2011), and 2) primary progressive aphasias (PPA), a group of disorders that manifest as progressive loss of language functions (Gorno-Tempini et al., 2011). PPAs are further divided into three subgroups based on the clinical profile: non-fluent variant primary progressive aphasia (nfvPPA), semantic variant primary progressive aphasia (svPPA) and logopenic variant primary progressive aphasia (lvPPA), of which the last one is mainly associated with Alzheimer’s disease (AD) (Gorno-Tempini et al., 2011).

FTLD is a neuropathologically and genetically heterogeneous group of diseases. The most common neuropathological subtypes are TDP-43- and Tau-positive FTLD (FTLD-TDP and FTLD-Tau, respectively) (Sieben et al., 2012). Familial forms of the disease are mainly associated with mutations in C9orf72, MAPT and GRN genes. Hexanucleotide repeat expansion in chromosome 9 open reading frame 72 -gene (C9orf72) is the most common genetic cause for familial FTLD and amyotrophic lateral sclerosis (ALS) (DeJesus-Hernandez et al., 2011; Renton et al., 2011). The C9orf72 repeat expansion and GRN mutations lead predominantly to TDP-43 neuropathology (DeJesus-Hernandez et al., 2011; Renton et al., 2011; Rohrer et al., 2009), while mutations in MAPT are associated with tau pathology (Rohrer et al., 2009). Notably, more than half of the FTLD cases are sporadic without any known genetic alterations (Rohrer et al., 2009), but show similar neuropathological features to familial FTLD cases (Cairns et al., 2007). Despite the recognized pathogenic mutations and different characteristic pathological features, the exact molecular pathogenic mechanisms of FTLD have remained unclear.
Recently, several preclinical and clinical studies have suggested a potential involvement of immune system dysfunction behind the etiology of FTLD (Atanasio et al., 2016; Burberry et al., 2016; Ferrari R, Hernandez DG, Nalls MA, Rohrer JD, Ramasamy A et al., 2014; Miller et al., 2016, 2013). Therefore, our aim here was to determine whether immunological diseases, and especially autoimmune diseases, are more common in FTLD patients when compared to patients with AD or not cognitively impaired (NCI) participants. We also investigated the prevalence of immunological diseases within the FTLD patient group in relation to the presence or absence of the C9orf72 repeat expansion.

2. Materials and methods

2.1. Ethical considerations:

The study was performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from the participants. The study protocol was approved by the research ethics committees of Northern Savo hospital district and Northern Ostrobothnia hospital district.

2.2. Study cohort:

Altogether 196 patients with FTLD were classified between the years 1999-2016 at the memory outpatient clinics of Kuopio University Hospital and Oulu University Hospital. An experienced neurologist, specialized in cognitive disorders, examined all of the patients and divided them into clinical subgroups. In total, 132 patients were diagnosed with bvFTD, 19 with FTLD-motoneuron disease (FTLD-MND), 37 with nfvPPA and eight with svPPA. The patients with bvFTD were diagnosed according to the latest diagnostic criteria by Rascovsky and colleagues (Rascovsky et al., 2011), and patients with PPAs were diagnosed according to the Gorno-Tempini diagnostic criteria (Gorno-Tempini et al., 2011). A retrospective review based on these same criteria was used for the patients that were originally diagnosed before the Rascovsky or Gorno-Tempini criteria were
published. All patients with bvFTD, nfvPPA or svPPA fulfilled the criteria with either probable or definite diagnosis. Patients with FTLD-MND had at least probable diagnosis of bvFTD, nfvPPA or svPPA and also a lucid manifestation of motoneuron disease. None of the patients in our cohort were diagnosed with lvPPA.

In addition to the FTLD clinical subgroups, patients with FTLD were further divided into two subgroups based on whether they carry or not the C9orf72 repeat expansion: the C9orf72 repeat expansion carriers (N=56) and the C9orf72 repeat expansion non-carriers (N=117). Within the clinical subgroups, 40 bvFTD, six nfvPPA, one svPPA and nine FTLD-MND patients carried the C9orf72 repeat expansion. Genotyping data of the C9orf72 repeat expansion was not available for 11.7% (23/196) FTLD patients (16 bvFTD, four nfvPPA, one svPPA and two FTLD-MND). Six patients without the C9orf72 repeat expansion genotyping were neuropathologically confirmed as FTLD (5/6 FTLD-TDP and 1/6 FTLD-Tau), leading to a total of 62 patients with definite and 134 with probable FTLD according to the latest criteria (Gorno- Tempini et al., 2011; Rascovsky et al., 2011).

For comparison, an age- and sex-matched group of patients (N=193) with at least probable AD according to the McKhann criteria (McKhann et al., 1984) were identified during the years 1999-2017 at the memory outpatient clinics in Kuopio University Hospital and Oulu University Hospital. Patients were diagnosed by an experienced neurologist specialized in cognitive disorders and the diagnoses were based on clinical and neuropsychological examination, brain imaging and cerebrospinal fluid AD biomarkers.

Another control group was gathered from the memory outpatient clinic of Kuopio University Hospital, comprising of individuals who had undergone the same evaluations for cognitive disorders as the AD group, but who were eventually classified as not cognitively impaired (NCI) and without any diagnosed neurodegenerative disorder (N=92).
2.3. Genetic analyses

The repeat-primed polymerase chain reaction assay (RP-PCR) (Renton et al., 2011) was used to indicate the presence or absence of the C9orf72 repeat expansion in the FTLD patients. The results of PR-PCR were confirmed using Amplicon length analysis (van der Zee et al., 2013). Six patients in the C9orf72 repeat expansion carrier group had an intermediate expansion (20-40 repeats) and the rest (N=50) had a full expansion (more than 40 repeats). All FTLD patients in the C9orf72 repeat expansion non-carrier group had fewer than five repeats. Based on our previous reports showing that other known FTLD mutations (GRN, MAPT, CHMP2B) are extremely rare in Finnish population, these genes were not systematically sequenced (Kaivorinne et al., 2008, 2010; Krüger et al., 2009).

2.4. Clinical review

Medical histories were retrospectively reviewed for evidence of immunological diseases by using a modified classification from previous similar studies (Table 1) (Miller et al., 2016, 2013; Rugbjerg et al., 2009). Immunological diseases were further divided into different disease clusters (1. Cutaneous conditions, 2. Inflammatory arthritides, 3. Gastrointestinal disorders, 4. Connective tissue disorders, 5. Endocrine disorders, 6. Vasculitides, 7. Ocular disorders, and 8. Hematologic disorders) for a cluster analysis. Hypothyreosis and asthma were analyzed separately from other immunological disorders since their etiology can be rather heterogenous and cannot be confirmed retrospectively. Within thyroid diseases, only the diagnoses of autoimmune thyreoiditis and
Basedow’s disease were included with other autoimmune conditions in the endocrine disorders cluster.

FTLD patients were compared to the AD and NCI groups. Comparison was also made within the FTLD group based on the presence or absence of the C9orf72 repeat expansion and the clinical subtypes.

2.5. Statistical analyses

All statistical analyses were performed by using SPSS statistic version 23 (IBM corp. USA). Independent sample t-test was used to compare continuous variables (age and number of immunological diseases per participant) and chi square test (or Fisher’s exact test when frequencies were less than five) for categorical variables, such as gender and occurrence of immunological diseases (dichotomous variables). P-values < 0.05 were considered statistically significant.
3. Results

The number of immunological diseases per subject varied between 0 and 3 (Table 2, Figure 1). The prevalence of the immunological diseases in total was 16.3% in FTLD, 13.5% in AD and 15.2% in NCI, and there were no statistically significant differences between the groups. However, within the FTLD group, patients without the C9orf72 repeat expansion showed a trend (not statistically significant) towards a higher prevalence of immunological diseases as compared to the C9orf72 repeat expansion carriers (18.8% in C9orf72 repeat expansion non-carriers vs. 10.7% in C9orf72 repeat expansion carriers, Chi-square p=0.177). Moreover, when compared to AD and NCI groups, FTLD patients without the C9orf72 repeat expansion showed the highest prevalence and the expansion carriers the lowest prevalence of immunological diseases. The most evident difference in the prevalence of immunological diseases within the FTLD group between the C9orf72 repeat expansion carriers and non-carriers was observed in the gastrointestinal disorder cluster (C9orf72 expansion non-carriers 6.0% vs. C9orf72 expansion carriers 0.0% vs., p=0.098), but this did not reach statistical significance. In the other disease cluster analyses, differences were observed in the endocrine disorder cluster (FTLD C9orf72 repeat expansion non-carriers 6.8% vs. NCI 2.2%, p=0.191, FTLD C9orf72 repeat expansion non-carriers 6.8% vs. AD 2.6%, p=0.084). In addition, the prevalence of asthma was the highest in FTLD patients without the C9orf72 repeat expansion and the lowest in patients with AD (13.7% vs. 8.3%, p=0.131). However, these differences were not statistically significant.

Comparison between the different FTLD clinical subgroups indicated that the prevalence for immunological diseases (asthma and hypothyreosis were excluded) in general was 18.9% in bvFTD (N=132), 16.2% in nfvPPA (N=37), 0.0% in svPPA (N=8) and 5.3% in FTLD-MND (N=19), showing no statistically significant differences between the groups in either the prevalence of immunological diseases in general or in the disease cluster analyses.
None of the five pathologically confirmed FTLD-TDP patients had any immunological diseases.
4. Discussion

We have studied here the prevalence of different types of immunological diseases in patients with FTLD and compared the prevalence within the FTLD group between C9orf72 repeat expansion carriers and non-carriers. In addition, we have compared the prevalence of these diseases between FLTD, AD and NCI groups. We did not find any statistically significant differences in the prevalence of immunological diseases in general when comparing the FTLD group (all patients) to AD or NCI groups. However, the prevalence of immunological diseases in patients without the C9orf72 repeat expansion was nearly twice as high as in the C9orf72 repeat expansion carriers, even though the difference did not reach statistical difference. In addition, the prevalence of immunological diseases was the highest in the FTLD patients not carrying the C9orf72 repeat expansion when compared to all the other groups.

The disease cluster analysis revealed a trend for a higher prevalence of endocrine diseases in the FTLD group (especially in patients without the C9orf72 repeat expansion) compared to AD or NCI groups. Also, specifically the FTLD patients not carrying the C9orf72 repeat expansion showed a trend for an increased prevalence of gastrointestinal diseases and asthma when compared to the C9orf72 repeat expansion carriers, AD patients and NCI subjects. Intriguingly, several extremely rare diseases (such as Churg-Strauss vasculitis, Addison’s disease, bullous pemphigoid, localized scleroderma and immune thrombocytopenic purpura) were detected in our FTLD and AD cohorts, which was surprising given our relatively small cohort sizes. Accumulating data suggest a plausible relationship between systemic inflammation and the pathogenesis of FTLD. Several studies have demonstrated that the loss of function of the C9orf72 gene in murine models recapitulates human autoimmune disease with a severe autoimmune phenotype, high mortality rate, and increased levels of inflammatory cytokines (Atanasio et al., 2016; Burberry et al., 2016; O’Rourke et al., 2016; Sudria-Lopez et al., 2016). In addition, PGRN
(protein encoded by the GRN gene) knockout mice have been reported to develop inflammatory arthritis and the PGRN protein is able to regulate inflammation through TNF-α signaling (Tang et al., 2011). A recent genome wide association study (GWAS) by Ferrari et al. reported an association of the HLA-DRA/DRB5 locus with FTLD regardless of the genetic background. The HLA-DRA/DRB5 region encodes several major histocompatibility complex class II proteins involved in adaptive immunity and has been implicated to play a role in autoimmune disease pathogenesis (Ferrari R, Hernandez DG, Nalls MA, Rohrer JD, Ramasamy A et al., 2014). Previously, a higher prevalence of autoimmune diseases has been reported in FTLD patients compared to controls, AD patients and patients with progressive supranuclear palsy (Miller et al., 2016, 2013). Interestingly, the contribution of an autoimmune mechanism in FTLD was also suggested in a recent study, which proposed a pathogenic role for the anti-AMPA GluA3 autoantibodies in FTLD (Borroni et al., 2017).

So far, the autoimmune disease prevalence in FTLD patients has been evaluated in two previous studies, both conducted by the same research group (Miller et al., 2016, 2013). These studies aimed to evaluate the prevalence of autoimmune diseases in FTLD patients especially characterized by TDP-43 brain pathology, including only participants with either GRN mutations, svPPA, or FTLD patients with the C9orf72 repeat expansion (DeJesus-Hernandez et al., 2011; Hodges et al., 2010; Tang et al., 2011). These studies together indicated that the prevalence of non-thyroid autoimmune diseases was higher in the FTLD-TDP43 cohort (12%) compared to AD cohort (3.8%), progressive supranuclear palsy cohort representing tau pathology (3.7%) and control subjects (4.3%). No differences were found between the groups in the prevalences of autoimmune diseases when thyroid diseases were included. Since these studies included a large amount of FTLD patients with probable TDP-43 pathology, the authors suggested an association between TDP-43 pathophysiology and immune dysfunction (Miller et al., 2016, 2013). In the latter study, patients with FTLD-MND had a high prevalence of autoimmune diseases regardless of the presence of the C9orf72 repeat
expansion. However, patients with bvFTD carrying the C9orf72 repeat expansion without MND manifestation had a very low prevalence of autoimmune diseases (Miller et al., 2016).

Our present study does not provide support for the hypothesis for a specific association of TDP-43 pathophysiology and autoimmune disorders. This is suggested by the fact that our patients having potential or confirmed TDP-43 pathology (56 C9orf72 repeat expansion carriers and 5 neuropathologically confirmed FTLD-TDP cases) showed a lower prevalence of immunological diseases than C9orf72 repeat expansion non-carriers, AD, or NCI groups (6/56 C9orf72 repeat expansion carriers and 0/5 neuropathologically confirmed FTLD-TDP patients had an immunological disease). Notably, some of our patients not carrying the C9orf72 repeat expansion are also likely to have TDP-43 neuropathology, which makes the relationship between the TDP-43 neuropathology and the prevalence of immunological disease only suggestive. Furthermore, contrary to the previous studies (Miller et al., 2016, 2013), we did not detect a significantly higher prevalence of immunological diseases in the whole FTLD group (containing both C9orf72 repeat expansion carriers and non-carriers) when compared to AD and NCI groups, even when the non-thyroid autoimmune diseases were evaluated separately. This result is likely influenced by the fact that our FTLD group included the C9orf72 repeat expansion carriers, who showed the lowest prevalence and the C9orf72 repeat expansion non-carriers, who on the other hand showed the highest prevalence of immunological diseases. Moreover, both the AD and NCI groups had a relatively high prevalence of immunological diseases when compared to the FTLD group. These differences between the groups (for example our AD cohort vs. the AD cohort in the previous study (Miller et al., 2016)) could be explained by the differences between the US and Finnish populations, or selection bias when collecting the groups. Notably, a recent epidemiologic study showed an elevated risk for dementia (AD or vascular dementia) in patients with autoimmune disease (Wotton and Goldacre, 2017), suggesting that the relatively high prevalence of immunological diseases in our AD cohort is in accordance with the previous study. Moreover, diseases that were particularly
associated with AD in that study included Addison’s disease, SLE and psoriasis, all of which were detected also in our cohort (the only SLE case and the only Addison’s disease case were both AD patients). These facts may explain the lack of statistically significant differences when comparing the immunological disease prevalence in the FTLD group to the AD group. An interesting observation in our study, which is in line with previous findings (Miller et al., 2016), was that the C9orf72 carriers with bvFTD phenotype specifically without the MND-component had a low prevalence of autoimmune diseases.

The strengths of our study include the fact that all the patients were systematically examined and carefully diagnosed into different diagnostic groups by an experienced neurologist specialized in neurodegenerative disorders. Moreover, our cohort forms one of the largest and most accurately identified and well-characterized FTLD cohorts reported so far. The proportion of the C9orf72 repeat expansion carriers and neuropathologically confirmed cases in our cohort is remarkably high, which increases the validity of this study and allows reliable comparison between the C9orf72 repeat expansion carriers and non-carriers. Mutations in GRN or MAPT genes have been excluded in approximately half of the cases in this FTLD cohort in our previous studies (Kaivorinne et al., 2008, 2010; Krüger et al., 2009). In these studies, mutations in GRN or MAPT were found to be extremely rare in Finnish FTLD cases (no mutations in GRN or MAPT genes were detected). However, we cannot completely rule out that individual GRN or MAPT carriers would not exist in our cohort, but the possible presence of such single cases is unlikely affect the outcome of our analyses. In addition, differences in the socio-economic background do not have an impact on our cohort population in Finland, since all the patients with FTLD in our area are diagnosed at the university hospital. Immunological diseases screened in this study are diagnosed and treated in either central or university hospitals, and the completeness of the electronic health record system in Finland allows reliable retrospective observation.
The limitations of our study include the retrospective nature of the study, potentially leading to under-estimations of some non-severe autoimmune conditions. Since the group studied was relatively small for epidemiologic data, the results are more suggestive than definite. The small group sizes may also partially explain the lack of statistically significant differences between the groups. Of note, the low prevalence of observed immunological diseases in the C9orf72 repeat expansion carrier group may partially result from the fact that the patients within this group were slightly younger than those in the other groups included in the study. However, most of the differences between the patients with and without the C9orf72 repeat expansion were observed related to diseases that usually occur before the mean age of our C9orf72 repeat expansion carrier group (for example gastrointestinal and endocrine diseases), indicating that these observed differences are not likely due to age bias.

In conclusion, our study describes a relatively high prevalence of immunological diseases especially in FTLD patients not carrying the C9orf72 repeat expansion. On the contrary, the C9orf72 repeat expansion carriers had the lowest prevalence of immunological diseases in comparison with all the other groups, suggesting that the C9orf72 repeat expansion may have an impact on immunoregulation. However, none of the differences observed between the different groups in our study reached statistical significance. In the future, more defined and larger scale studies as well as studies aiming at understanding the underlying molecular mechanisms are therefore needed to clarify the role of the C9orf72 repeat expansion in immunological pathways in FTLD.

Disclosure of interest

Declarations of interest: none.

Acknowledgements

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References


Table 1. Screened immunological diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease</th>
<th>Disease</th>
<th>Disease</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s disease</td>
<td>Chorea minor</td>
<td>Hashimoto’s thyroiditis</td>
<td>Pemphigus(^2)</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Alopecia areata(^2)</td>
<td>Chronic lymphocytic colitis</td>
<td>Henoch-Schönlein purpura(^2)</td>
<td>Pernicious anemia</td>
<td>Sjögren’s syndrome</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Chronic rheumatic heart disease or rheumatic fever</td>
<td>Hypothyreosis(^1,2)</td>
<td>Polyarteritis nodosa</td>
<td>Systemic lupus erythematosus (SLE)</td>
</tr>
<tr>
<td>Asthma(^1,2)</td>
<td>Crohn’s disease</td>
<td>Inclusion body myositis</td>
<td>Polymyalgia rheumatica</td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Churg-Strauss vasculitis(^2)</td>
<td>Immune thrombocytopenic purpura</td>
<td>Polymyositis</td>
<td>Temporal arteritis(^2)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Dermatomyositis</td>
<td>Latent autoimmune diabetes in adults(^2)</td>
<td>Primary biliary cirrhosis</td>
<td>Transverse myelitis</td>
</tr>
<tr>
<td>Autoimmune thyroiditis(^2)</td>
<td>Discoid lupus</td>
<td>Localized scleroderma</td>
<td>Primary sclerosing cholangitis(^2)</td>
<td>Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>Autoimmune urticaria(^2)</td>
<td>Goodpasture’s disease(^2)</td>
<td>Lichen planus(^2)</td>
<td>Psoriasis</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Granulomatosis with polyangiitis</td>
<td>Lichen sclerosus</td>
<td>Psoriatic arthritis(^2)</td>
<td>Uveitis (autoimmune)(^2)</td>
</tr>
<tr>
<td>Bullous pemphigoid(^2)</td>
<td>Graves’s disease</td>
<td>Multiple sclerosis</td>
<td>Reactive arthritis</td>
<td>Vitiligo</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Guillain-Barré syndrome(^2)</td>
<td>Myasthenia gravis</td>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) = Asthma and hypothyreosis were analysed separately

\(^2\) = Added to autoimmune disease collection (modified from Rugbjerg et al. (Rugbjerg et al., 2009)) that was used in previous studies (Miller et al., 2016, 2013)
Table 2. Clinical characteristics of the study subjects and the prevalence of observed concomitant immunological diseases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FTLD&lt;sup&gt;a&lt;/sup&gt; n=196</th>
<th>C9orf72 repeat expansion carriers&lt;sup&gt;b&lt;/sup&gt; n=56</th>
<th>C9orf72 repeat expansion non-carriers&lt;sup&gt;b&lt;/sup&gt; n=117</th>
<th>AD n=193</th>
<th>NCI n=92</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&lt;sup&gt;c&lt;/sup&gt;, mean (SD)</td>
<td>67.9 (8.0)</td>
<td>64.3 (8.2)</td>
<td>69.3 (7.5)</td>
<td>68.0 (7.8)</td>
<td>67.7 (9.9)</td>
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<tr>
<td>Gender, %female</td>
<td>49.0%</td>
<td>50.0%</td>
<td>51.3%</td>
<td>49.7%</td>
<td>54.3%</td>
</tr>
<tr>
<td>Immunological disease total n, (%)</td>
<td>32/196 (16.3%)</td>
<td>6/56 (10.7%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22/117 (18.8%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26/193 (13.5%)</td>
<td>14/92 (15.2%)</td>
</tr>
<tr>
<td>Cutaneous disorders n, (%)</td>
<td>10/196 (5.1%)</td>
<td>3/56 (5.4%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4/117 (3.4%)</td>
<td>4/193 (2.1%)</td>
<td>5/92 (5.4%)</td>
</tr>
<tr>
<td>Psoriasis, n</td>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
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<td>Alopecia areata, n</td>
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<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Bullous pemphigoid, n</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Localised scleroderma, n</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Lichen Planus, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chronic autoimmune urticaria, n</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Lichen sclerosis, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders n, (%)</td>
<td>7/196 (3.6%)</td>
<td>0/56 (0.0%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7/117 (6.0%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5/193 (2.6%)</td>
<td>3/92 (3.3%)</td>
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<td>Crohn’s disease, n</td>
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<tr>
<td>Ulcerative colitis, n</td>
<td>2&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>Lymphocytic colitis, n</td>
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<td>Celiac disease, n</td>
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<tr>
<td>Perianal anemia, n</td>
<td>1&lt;sup&gt;g&lt;/sup&gt;</td>
<td>0</td>
<td>1</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
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<tr>
<td>Connective tissue disorders n, (%)</td>
<td>1/196 (0.5%)</td>
<td>0/56 (0.0%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0/117 (0.0%)</td>
<td>5/193 (2.6%)</td>
<td>0/92 (0.0%)</td>
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<td>SLE, n</td>
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<td>Polymyalgia rheumatica, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>Sjögren’s syndrome, n</td>
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<tr>
<td>Inflammatory arthritides n, (%)</td>
<td>4/196 (2.0%)</td>
<td>1/56 (1.8%)</td>
<td>3/117 (2.6%)</td>
<td>5/193 (2.6%)</td>
<td>2/92 (2.2%)</td>
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<tr>
<td>Rheumatoid arthritis, n</td>
<td>4&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>Vasculitides n, (%)</td>
<td>2/196 (1.0%)</td>
<td>0/56 (0.0%)</td>
<td>2/117 (1.7%)</td>
<td>1/193 (0.5%)</td>
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<td>Churg-Strauss vasculitis, n</td>
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<td>Endocrine disorders n, (%)</td>
<td>10/196 (5.1%)</td>
<td>2/56 (3.6%)</td>
<td>8/117 (6.8%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5/193 (2.6%)</td>
<td>2/92 (2.2%)</td>
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<td>Basedow’s disease, n</td>
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<td>3</td>
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<tr>
<td>Autoimmune thyroiditis, n</td>
<td>4&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1</td>
<td>3</td>
<td>1&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
<td>Type 1 diabetes, n</td>
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<td>Latent autoimmune diabetes, n</td>
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<tr>
<td>Addison’s disease</td>
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<td>0</td>
<td>0</td>
<td>1&lt;sup&gt;i&lt;/sup&gt;</td>
<td>0</td>
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<tr>
<td>Hematologic disorders n, (%)</td>
<td>0/196 (0.0%)</td>
<td>0/56 (0.0%)</td>
<td>0/117 (0.0%)</td>
<td>2/193 (1.0%)</td>
<td>0/92 (0.0%)</td>
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<td>Autoimmune hemolytic anemia, n</td>
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<td>Immune thrombocytopenic purpura, n</td>
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<tr>
<td>Ocular diseases n, (%)</td>
<td>2/196 (1.0%)</td>
<td>0/56 (0.0%)</td>
<td>2/117 (1.7%)</td>
<td>1/193 (0.5%)</td>
<td>0/92 (0.0%)</td>
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<td>Uveitis, n</td>
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</tbody>
</table>

<sup>a</sup> Includes 10 patients with AD and 86 patients with NCI.

<sup>b</sup> N=56 for C9orf72 repeat expansion carriers.

<sup>c</sup> Data from Charpentier et al. 2018.

<sup>d</sup> Psoriasis includes 10 patients with AD and 86 patients with NCI.

<sup>e</sup> Alopecia areata includes 10 patients with AD and 86 patients with NCI.

<sup>f</sup> Bullous pemphigoid includes 10 patients with AD and 86 patients with NCI.

<sup>g</sup> Localised scleroderma includes 10 patients with AD and 86 patients with NCI.

<sup>h</sup> Chronic autoimmune urticaria includes 10 patients with AD and 86 patients with NCI.

<sup>i</sup> Lichen Planus includes 10 patients with AD and 86 patients with NCI.
<table>
<thead>
<tr>
<th>Immunological Disease</th>
<th>n, (%)</th>
<th>1/196 (0.5%)</th>
<th>1/56 (1.8%)</th>
<th>0/117 (0.0%)</th>
<th>0/193 (0.0%)</th>
<th>2/92 (2.2%)</th>
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<tbody>
<tr>
<td>Sarcoidosis n, (%)</td>
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<tr>
<td>Hypothyreosis j n, (%)</td>
<td></td>
<td>20/196 (10.2%)</td>
<td>9/56 (16.1%)</td>
<td>11/117 (9.4%)</td>
<td>24/193 (12.4%)</td>
<td>14/92 (15.2%)</td>
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<tr>
<td>Asthma j n, (%)</td>
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<td>23/196 (11.7%)</td>
<td>5/56 (8.9%)</td>
<td>16/117 (13.7%)</td>
<td>16/193 (8.3%)</td>
<td>10/92 (10.9%)</td>
</tr>
</tbody>
</table>

* = Age at the last visit in University Hospital; † = the whole FTLD group includes 23 FTLD patients without C9orf72 repeat expansion genotyping data; ‡ = C9orf72 repeat expansion carriers vs. non-carriers, total autoimmune diseases: p=0.177, gastrointestinal: p=0.098, ‡ = C9orf72 repeat expansion non-carriers vs. AD, endocrine: p=0.084, asthma: p=0.131; § = C9orf72 repeat expansion non-carriers vs. NCI, endocrine: p=0.191. Four patients (marked with superscript letters “c,d,e,f”) in the FTLD group had a diagnosis of two separate immunological diseases and one (marked with superscript letter “g”) of three separate diseases. Two AD patients (marked with superscript letters “h,i”) had a diagnosis of two separate immunological disorders. j = Asthma and hypothyreosis were not included in the “Immunological disease total” analysis.
Figure captions

**Figure 1.** The number of immunological diseases described in Table 2 per subject in each group. Asthma and hypothyreosis are excluded. Bars indicate number of immunological diseases for each subject and error bars the 95% confidence interval (CI). FTLD patients not carrying the C9orf72 repeat expansion had the highest prevalence of immunological diseases, whereas the C9orf72 repeat expansion carriers had the lowest prevalence. The number of immunological diseases (mean ± SD) in different groups: FTLD (N=196), 0.19 ± 0.48, (95% CI = 0.13-0.26, range = 0-3); the C9orf72 repeat expansion carriers (N=56), 0.13 ± 0.38 (95% CI = 0.02-0.23, range = 0-2); the C9orf72 repeat expansion non-carriers (N=117), 0.23 ± 0.53 (95% CI = 0.13-0.33, range = 0-3); AD (N=193), 0.15 ± 0.38 (95% CI = 0.09-0.20, range = 0-2); NCI (N=92), 0.15 ± 0.36 (95% CI = 0.08-0.23, range 0-1). Four patients in the FTLD group had a diagnosis of two separate immunological diseases and one for three separate disorders. Two AD patients had a diagnosis of two separate immunological diseases. No statistical significance was detected when comparing different groups (independent sample t-test).
Highlights:

- FTLD C9orf72 expansion carriers have less autoimmune diseases than the non-carriers
- FTLD patients may have elevated risk for endocrinal autoimmune diseases
- The overall autoimmune disease prevalence is not higher in FTLD vs. control groups
Prevalence of autoimmune diseases in FTLD patients

C9orf72 expansion non-carriers (N=117, n.s.)

C9orf72 expansion carriers (N=56, n.s.)

The difference between the groups did not reach statistical significance (n.s.).
Figure 1

Immunological diseases per subject

FTLD
FTLD C9orf72 carriers
FTLD C9orf72 non-carriers
AD
NCI