bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Immune-related genetic enrichment in frontotemporal dementia

Iris Broce[1], Celeste M. Karch[2], Natalie Wen[2], Chun C. Fan[3], Yunpeng Wang[4], Chin Hong Tan[1], Naomi Kouri[5], Owen A. Ross[5], Günter U. Höglinger[6], Ulrich Muller[7], John Hardy[8], International FTD-Genomics Consortium (IFGC) °, Parastoo Momeni[9], Christopher P. Hess[1], William P. Dillon[1], Zachary A. Miller[10], Luke W. Bonham[10], Gil D. Rabinovici[10], Howard J. Rosen[10], Gerard D. Schellenberg[11], Andre Franke[12], Tom H. Karlsen[13], Jan H. Veldink[14], Raffaele Ferrari[8], Jennifer S. Yokoyama[10], Bruce L. Miller[10], Ole A. Andreassen[7], Anders M. Dale[3,15], Rahul S. Desikan[1,10], and Leo P. Sugrue [1]

[1]Neuroradiology Section, Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, USA
[2]Department of Psychiatry, Washington University, St. Louis, MO, USA
[3]Department of Cognitive Sciences, University of California, San Diego, La Jolla, CA, USA
[4]NORMENT; Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[5]Department of Neuroscience, Mayo Clinic College of Medicine, Jacksonville, Florida 32224, USA
[6]Department of Neurology, Technical University of Munich, Munich, Germany; German Center for Neurodegenerative Diseases (DZNE), Munich, Germany; and Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
[7]Institut for Humangenetik, Justus-Liebig-Universität, Giessen, Germany
[8]Department of Molecular Neuroscience, Institute of Neurology, UCL, London WC1N 3BG, UK
[9]Laboratory of Neurogenetics, Department of Internal Medicine, Texas Tech University Health Science Center, Lubbock, Texas, USA
[10]Memory and Aging Center, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA
[11]Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
[12]Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel, Kiel, Germany.
[13]Norwegian PSC Research Center and K.G.Jebsen Inflammation Research Centre, Research Institute of Internal Medicine, Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital Rikshospitalet, 0407 Oslo, Norway; Division of Gastroenterology, Institute of Medicine, University of Bergen, 5000 Bergen, Norway
[14]Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands.
[15]Departments of Radiology and Neurosciences, University of California, San Diego, La Jolla, CA, USA

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

#Correspondence:
Iris J. Broce, PhD
Department of Radiology and Biomedical Imaging
University of California, San Francisco
185 Berry Street
San Francisco, CA 94158
Email: iris.broce@ucsf.edu
Phone: (619) 847-5568
Fax: (415) 502-7588

Rahul S. Desikan, MD, PhD
Department of Radiology and Biomedical Imaging
Neuroradiology Section, L-352
University of California, San Francisco
505 Parnassus Avenue
San Francisco, CA 94143-0628
Email: rahul.desikan@ucsf.edu
Phone: (415) 353-4616
Fax: (415) 353-8593

Leo P. Sugrue, MD, PhD
Department of Radiology and Biomedical Imaging
Neuroradiology Section, L-352
University of California, San Francisco
505 Parnassus Avenue
San Francisco, CA 94143-0628
Email: leo.sugrue@ucsf.edu
Phone: (415) 353-9467
Fax: (415) 353-8593

° IFGC collaborators are listed below:

R Ferrari; D G Hernandez; M A Nalls; J D Rohrer; A Ramasamy; J B J Kwok; C Dobson-Stone; P R Schofield; G M Halliday; J R Hodges; O Piguet; L Bartley; E Thompson; E Haan; I Hernández; A Ruiz; M Boada; B Borroni; A Padovani; C Cruchaga; N J Cairns; L Benussi; G Binetti; R Ghidoni; G Forloni; D Albani; D Galimberti; C Fenoglio; M Serpente; E Scarpini; J Clarimón; A Lleó; R Blesa; M Landqvist Waldö; K Nilsson; C Nilsson; I R A Mackenzie; G-Y R Hsiung; D M A Mann; J Grafman; C M Morris; J Attems; T D Griffiths; I G McKeith; A J Thomas; P Pietrini; E D Huey; E M Wassermann; A Baborie; E Jaros; M C Tierney; P Pastor; C Razquin; S Ortega-Cubero; E Alonso; R Perneczky; J Diehl-Schmid; P Alexopoulos; A Kurz; I

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Rainero; E Rubino; L Pinessi; E Rogaeva; P St George-Hyslop; G Rossi; F Tagliavini; G Giaccone; J B Rowe; J C M Schlachetzki; J Uphill; J Collinge; S Mead; A Danek; V M Van Deerlin; M Grossman; J Q Trojanowski; J van der Zee; M Cruts; C Van Broeckhoven; S F Cappa; I Leber; D Hannequin; V Golfier; M Vercelletto; A Brice; B Nacmias; S Sorbi; S Bagnoli; I Piaceri; J E Nielsen; L E Hjermind; M Riemenschneider; M Mayhaus; B Ibach; G Gasparoni; S Pichler; W Gu; M N Rossor; N C Fox; J D Warren; M G Spillantini; H R Morris; P Rizzu; P Heutink; J S Snowden; S Rollinson; A Richardson; A Gerhard; A C Bruni; R Maletta; F Frangipane; C Cupidi; L Bernardi; M Anfossi; M Gallo; M E Conidi; N Smirne; R Rademakers; M Baker; D W Dickson; N R Graff-Radford; R C Petersen; D Knopman; K A Josephs; B F Boeve; J E Parisi; W W Seeley; B L Miller; A M Karydas; H Rosen; J C van Swieten; E G P Dopper; H Seelaar; Y A L Pijnenburg; P Scheltens; G Logroscino; R Capozzo; V Novelli; A A Puca; M Franceschi; A Postiglione; G Milan; P Sorrentino; M Kristiansen; H-H Chiang; C Graff; F Pasquier; A Rollin; V Deramecourt; T Lebouvier; D Kapogiannis; L Ferrucci; S Pickering-Brown; A B Singleton; J Hardy; P Momeni

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

ABSTRACT

Background

Converging evidence suggests that immune-mediated dysfunction plays an important role in the pathogenesis of frontotemporal dementia (FTD). Although genetic studies have shown that immune-associated loci are associated with increased FTD risk, a systematic investigation of genetic overlap between immune-mediated diseases and the spectrum of FTD-related disorders has not been performed.

Methods and findings

Using large genome-wide association studies (GWAS) (total n = 192,886 cases and controls) and recently developed tools to quantify genetic overlap/pleiotropy, we systematically identified single nucleotide polymorphisms (SNPs) *jointly* associated with 'FTD-related disorders' namely FTD, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and amyotrophic lateral sclerosis (ALS) – and one or more immune-mediated diseases including Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), type 1 diabetes (T1D), celiac disease (CeD), and psoriasis (PSOR). We found up to 270-fold genetic enrichment between FTD and RA and comparable enrichment between FTD and UC, T1D, and CeD. In contrast, we found only modest genetic enrichment between any of the immune-mediated diseases and CBD, PSP or ALS. At a conjunction false discovery rate (FDR) < 0.05, we identified numerous FTD-immune pleiotropic SNPs within the human leukocyte antigen (*HLA)* region on chromosome 6. By leveraging the immune diseases, we also found novel FTD susceptibility loci within *LRRK2* (Leucine Rich Repeat Kinase 2), *TBKBP1* (TANK-

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

binding kinase 1 Binding Protein 1), and *PGBD5* (PiggyBac Transposable Element Derived 5). Functionally, we found that expression of FTD-immune pleiotropic genes (particularly within the *HLA* region) is altered in postmortem brain tissue from patients with frontotemporal dementia and is enriched in microglia compared to other central nervous system (CNS) cell types.

Conclusions

We show considerable immune-mediated genetic enrichment specifically in FTD, particularly within the *HLA* region. Our genetic results suggest that for a subset of patients, immune dysfunction may contribute to risk for FTD. These findings have potential implications for clinical trials targeting immune dysfunction in patients with FTD.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

INTRODUCTION

Frontotemporal dementia (FTD) is a fatal neurodegenerative disorder and the leading cause of dementia among individuals younger than 65 years of age [1]. Given rapid disease progression and absence of disease modifying therapies, there is an urgent need to better understand FTD pathobiology to accelerate development of novel preventive and therapeutic strategies.

Converging molecular, cellular, genetic, and clinical evidence suggests that neuroinflammation plays a role in FTD pathogenesis. Complement factors and activated microglia, key components of inflammation, have been established as histopathologic features in brains of patients [2] and in mouse models of FTD [3,4]. Genome-wide association studies (GWAS) have shown that single nucleotide polymorphisms (SNPs) within the immune-regulating human leukocyte antigen (*HLA)* region on chromosome 6 are associated with elevated FTD risk [5]. Importantly, there is increased prevalence of immune-mediated diseases among patients with FTD [6,7]. Together, these findings suggest that immune-related mechanisms may contribute to and potentially drive FTD pathology.

Recent work in human molecular genetics has emphasized 'pleiotropy', where variations in a single gene can affect multiple, seemingly unrelated phenotypes [8]. In the present study, we systematically evaluated genetic pleiotropy between FTD and immune-mediated diseases. Leveraging large neurodegenerative GWASs and recently developed tools to estimate polygenic pleiotropy, we sought to identify SNPs *jointly* associated with 'FTD-related disorders' [9,10] – namely FTD, corticobasal degeneration (CBD),

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

progressive supranuclear palsy (PSP), and amyotrophic lateral sclerosis (ALS) – and one or more immune-mediated diseases including Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), type 1 diabetes (T1D), celiac disease (CeD), and psoriasis (PSOR).

METHODS

Participant samples

We evaluated complete GWAS results in the form of summary statistics (p-values and odds ratios) for FTD, CBD, PSP, and ALS and 6 immune-mediated diseases, including CD [11], UC [12], RA [13], T1D [14], CeD [15], and PSOR [16] (see Table 1). We obtained FTD GWAS summary statistic data from phase I of the International FTD-Genomics Consortium (IFGC), which consisted of 2,154 clinical FTD cases and 4,308 controls with genotyped and imputed data at 6,026,384 SNPs (Table 1, for additional details, see [5]). The FTD dataset included multiple clinically diagnosed FTD subtypes: behavioral variant (bvFTD), semantic dementia (sdFTD), primary nonfluent progressive aphasia (pnfaFTD), and FTD overlapping with motor neuron disease (mndFTD). These FTD cases and controls were recruited from forty-four international research groups and diagnosed according to the Neary criteria [17]. We obtained CBD GWAS summary statistic data from 152 CBD cases and 3,311 controls at 533,898 SNPs (Table 1, for additional details see [18]). The CBD cases were collected from eight institutions and controls were recruited from the Children's Hospital of Philadelphia Health Care Network. CBD was neuropathologically diagnosed using the National Institute of Health

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Office of Rare Diseases Research criteria [19]. We obtained PSP GWAS summary statistic data (stage 1) from the NIA Genetics of Alzheimer's Disease Storage Site (NIAGADS), which consisted of 1,114 individuals with autopsy-confirmed PSP and 3,247 controls at 531,451 SNPs (Table 1, for additional details see [20]). We obtained publicly-available ALS GWAS summary statistic data from 12,577 ALS cases and 23,475 controls at 18,741,501 SNPs (Table 1, for additional details see [21]). The relevant institutional review boards or ethics committees approved the research protocol of the individual GWAS used in the current analysis, and all human participants gave written informed consent.

Genetic Enrichment Statistical Analyses

To identify specific loci jointly involved with each of the four FTD-related disorders and the six immune-mediated diseases, we computed conjunction FDRs [22,23]. Conjunction FDR, denoted by $FDR_{trait1\&\ trait2}$ is defined as the posterior probability that a SNP is null for either trait or for both simultaneously, given the *p*-values for both traits are as small, or smaller, than the observed *p*-values. Unlike the *conditional* FDR which ranks disease/primary phenotype associated SNPs based on genetic 'relatedness' with secondary phenotypes [24], the *conjunction* FDR minimizes the possibility/likelihood of a single phenotype driving the common association signal. *Conjunction* FDR therefore tends to be more conservative and specifically pinpoints pleiotropic loci between the traits/diseases of interest. We used an overall FDR threshold of < 0.05, which means 5 expected false discoveries per hundred reported. We

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

constructed Manhattan plots based on the ranking of conjunction FDR to illustrate the genomic location of the pleiotropic loci. Detailed information on conjunction Q-Q plots, Manhattan plots, and conjunction FDR can be found in prior reports [22,23,25,26].

Functional evaluation of shared risk loci

To assess whether SNPs that are shared between FTD and immune-mediated disease modify gene expression, we identified *cis*-expression quantitative loci (eQTLs, defined as variants within 1 Mb of a gene's transcription start site) associated with shared FTD-immune SNPs and measured their regional brain expression in a publicly available dataset of normal control brains (UKBEC, http://braineac.org/) [27]. We also evaluated eQTLs using a blood-based dataset [28]. We applied an analysis of covariance (ANCOVA) to test for associations between genotypes and gene expression. We tested SNPs using an additive model.

Network based functional association analyses

To evaluate potential protein and genetic interactions, co-expression, co-localization, and protein domain similarity for the functionally expressed (i.e. with significant *cis*-eQTLs) overlapping genes, we used GeneMANIA (www.genemania.org), an online web-portal for bioinformatic assessment of gene networks [29]. In addition to visualizing the composite gene network, we also assessed the weights of individual components within the network [30].

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Gene expression alterations in FTD brains

To determine whether functionally expressed (i.e. with significant *cis*-eQTLs) pleiotropic genes are differentially expressed in FTD brains, we analyzed gene expression of overlapping genes in a publically available dataset [31]. Specifically, we analyzed gene expression data from the frontal cortex, hippocampus, and cerebellum of controls and patients with frontotemporal dementia (FTD-U with or without *progranulin* (*GRN*) mutations, total n =28) (Gene Expression Omnibus (GEO) dataset GSE13162) [31].

Evaluation of cell classes within the brain

Using a publicly available RNA-sequencing transcriptome and splicing database [32], we ascertained whether the functionally expressed (i.e. with significant *cis*-eQTLs) pleiotropic genes are expressed by specific cell classes within the brain. The eight cell types surveyed are neurons, astrocytes, oligodendrocyte precursor cells, newly formed oligodendrocytes, myelinating oligodendrocytes, microglia, endothelial cells, and pericytes (for additional details, see [32]).

RESULTS

Shared genetic risk between FTD and immune-mediated disease

Using progressively stringent *p*-value thresholds for FTD SNPs (i.e. increasing values of nominal $-\log_{10}(p)$), we observed considerable genetic enrichment for FTD as a function of several immune-mediated diseases (Figure 1A). More specifically, we found

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

strong (up to 270-fold) genetic enrichment between FTD and RA, and comparable enrichment between FTD and UC, T1D, and CeD, with weaker enrichment for PSOR and CD.

At a conjunction FDR $p < 0.05$, we identified 21 SNPs that were associated with both FTD and immune-mediated diseases (Figure 1B, Table 2). Fourteen of these SNPs mapped to the *HLA* region on chromosome 6 (Figure 1B). Of these, three pairs of SNPs showed strong linkage disequilibrium (LD), suggesting that they reflected the same signal: a) rs9261536 with rs3094138 (nearest genes: *TRIM15* and *TRIM26*, respectively, pairwise D' = 0.96, $r^2 = 0.8$), b) rs204991 with rs204989 (nearest gene: *GPSM3*, pairwise D' = 1, $r^2 = 1$), and c) rs9268877 with rs9268852 (nearest gene: *HLA-DRA*, pairwise D' = 1, $r^2 = 0.99$). After excluding those identified SNPs in LD, we found that 11 of the 18 identified loci mapped to the *HLA* region, suggesting that *HLA* markers were critical in driving our results. To test this hypothesis, we repeated our enrichment analysis after removing all SNPs in LD with $r^2 > 0.2$ within 1Mb of *HLA* variants (based on 1000 Genomes Project LD structure). After removing *HLA* SNPs, we saw considerable attenuation of genetic enrichment in FTD as a function of immune-mediated disease (Figure 2), suggesting that the observed overlap between immune-related diseases and FTD was largely driven by the *HLA* region.

Outside the *HLA* region, we found 7 other FTD-immune associated SNPs (Figure 2, Table 2), including two in strong LD, which mapped to the H1 haplotype of microtubule associated protein tau (*MAPT)* (LD: rs199533 with rs17572851; nearest genes: *NSF* and *MAPT*, pairwise D' = 1, $r^2 = 0.94$). Beyond *MAPT*, we found five

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

additional novel loci associated with increased FTD risk, namely: 1) rs2192493 (chr 7, nearest gene = *TWISTNB*), 2) rs7778450 (chr 7, nearest gene = *TNS3*), 3) rs10216900 (chr 8, nearest gene = *CR590356*), 4) rs10784359 (chr 12, nearest gene = *SLC2A13*), and 5) rs2134297 (chr 18, nearest gene = *DCC*) (see Table 2 for additional details).

Modest genetic enrichment between immune-mediated disease and PSP, CBD and ALS

To evaluate the specificity of the shared genetic overlap between FTD and immune-mediated disease, we also evaluated overlap between the 6 immune-mediated diseases and CBD, PSP, and ALS. For CBD and PSP a few of the immune-mediated diseases produced genetic enrichment comparable to that seen for FTD (Supplementary Figures 1A-C, Supplementary Tables 1-3). For example, we found 150-fold genetic enrichment between CBD and CeD, and 180-fold enrichment between PSP and RA. In contrast, we found minimal enrichment between ALS and the immune-mediated diseases tested, with the highest levels of enrichment between ALS and RA (up to 20-fold), and between ALS and CeD (up to 15-fold).

At a conjunction FDR< 0.05, we identified several SNPs associated with both CBD, PSP, or ALS and immune-mediated disease (Supplementary Figures 2A-C, Tables 1-3). Few of the SNPs shared between CBD, PSP, or ALS and immune-mediated disease mapped to the *HLA* region. Only two PSP-immune SNPs mapped to the region of *MLN* and *IRF4* on chromosome 6 and no CBD- and ALS-immune SNPs mapped to the *HLA* region (Supplementary Figures 2A-C, Tables 1-3).

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Beyond the *HLA* region, we found several overlapping loci between the immune-mediated diseases and CBD, PSP and ALS (Supplementary Figures 2A-C, Tables 1-3). For PSP: 1) rs7642229 with CeD (chr 3, nearest gene = *XCR1*, FDR $p = 1.74 \times 10^{-2}$); 2) rs11718668 with CeD (chr 3, nearest gene = *TERC*, FDR $p = 3.00 \times 10^{-2}$); 3) rs12203592 with CeD (chr 6, nearest gene = *IRF4*, FDR $p = 4.17 \times 10^{-2}$); 4) rs1122554 with RA (chr 6, nearest gene = *MLN*, FDR $p = 2.09 \times 10^{-2}$); 5) rs3748256 with RA (chr 11, nearest gene = *FAM76B*, FDR $p = 2.09 \times 10^{-2}$). For ALS: 1) rs3828599 with CeD (chr 5, nearest gene = *GPX3*, FDR $p = 2.27 \times 10^{-2}$); 2) rs10488631 with RA (chr 7, nearest gene = *TNPO3*, FDR $p = 3.42 \times 10^{-2}$).

cis-eQTL expression

To investigate whether shared FTD-immune SNPs modify gene expression, we evaluated *cis*-eQTLs in both brain and blood tissue types. At a previously established conservative Bonferroni corrected p-value $< 3.9 \times 10^{-5}$ [33], we found significant *cis*-associations between shared SNPs and genes in the *HLA* region on chromosome 6 in peripheral blood mononuclear cells (PBMC), lymphoblasts, and the human brain (see Supplementary Table 4 for gene expression associated with each SNP). We also found that rs199533 and rs17572851 on chr 17 were significantly associated with *MAPT* ($p = 2 \times 10^{-12}$) expression in the brain. Beyond the *HLA* and *MAPT* regions, notable cis-eQTLs included rs10784359 and *LRRK2* ($p = 1.40 \times 10^{-7}$) and rs2192493 and *TBKBP1* ($p = 1.29 \times 10^{-6}$) (see Supplementary Table 4).

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Protein-protein and co-expression networks

We found physical interaction and gene co-expression networks for the FTD-immune pleiotropic genes with significant *cis*-eQTLs (at a Bonferroni corrected p-value $< 3.9 \times 10^{-5}$). We found robust co-expression between various *HLA* classes further suggesting that large portions of the *HLA* region, rather than a few individual loci, may be involved with FTD (Fig 3, Supplementary Table 5). Interestingly, we found that several non-*HLA* functionally expressed FTD-immune genes, namely *LRRK2*, *PGBD5*, and *TBKPB1*, showed co-expression with *HLA* associated genes (Figure 3).

Genetic expression in FTD brains compared to controls

To investigate whether the FTD-immune pleiotropic genes with significant *cis*-eQTLs are differentially expressed in FTD brains, we compared gene expression in FTD-U brains to brains from neurologically healthy controls. We found significantly different levels of *HLA* gene expression in FTD-U brains compared to controls (Table 3). This was true of FTD-U brains regardless of progranulin gene (*GRN*) mutation status. In spite of the fact that the FTD GWAS used to identify these genes was based on patients with sporadic FTD (without *GRN* mutations), *GRN* mutation carriers showed the greatest differences in *HLA* gene expression (Figure 4, Table 3). These findings are compatible with prior work showing microglial-mediated immune dysfunction in *GRN* carriers [3,35].

Microglial enrichment

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

For the FTD-immune pleiotropic genes with significant *cis*-eQTLs, across different CNS cell types, we found significantly greater expression within microglia compared to neurons or fetal astrocytes (Figure 5A). Interestingly, *HLA* genes showed the greatest degree of differential expression. Four of the FTD-immune *HLA* associated genes, namely *HLA-DRA, AOAH, HLA-A,* and *HLA-C*, showed highest expression in microglia (ranging from 10 to 60 FPKM, see Figure 5B). In addition, *MAPT* was predominantly expressed in neurons, *LRRK2* in microglia/macrophages, *PGBD5* in neurons, and *TBKBP1* in fetal astrocytes (Figure 5B and Supplemental Figures 3A-C).

DISCUSSION

We systematically assessed genetic overlap between 4 FTD-related disorders and several immune-mediated diseases. We found extensive genetic overlap between FTD and immune-mediated disease particularly within the *HLA* region on chromosome 6, a region rich in genes associated with microglial function. This genetic enrichment was specific to FTD and did not extend to CBD, PSP, or ALS. Further, we found that shared FTD-immune gene variants were differentially expressed in FTD patients compared with controls, and in microglia compared with other CNS cells. Beyond the *HLA* region, by leveraging the immune-mediated traits, we detected novel FTD susceptibility loci within *LRRK2, TBKBP1* and *PGBD5*. Considered together, these findings suggest that various microglia and inflammation-associated genes, particularly within the *HLA* region, play a critical and selective role in FTD pathogenesis.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

By combining GWAS from multiple studies and applying a pleiotropic approach, we identified genetic variants jointly associated with FTD-related disorders and immune-mediated disease. We found that the strength of genetic overlap with immune-mediated disease varies markedly across FTD-related disorders, with the strongest pleiotropic effects associated with FTD, followed by CBD and PSP, and the weakest pleiotropic effects associated with ALS. We identified eleven FTD-immune associated loci that mapped to the *HLA* region, a concentration of loci that was not observed for the other disorders. Indeed, only two PSP-immune pleiotropic SNPs and no CBD- or ALS-immune pleiotropic SNPs mapped to the *HLA* region. Previous work has identified particular *HLA* genes associated with CBD, PSP, and ALS [34,36]. In contrast, our current findings implicate large portions of the *HLA* region in the pathogenesis of FTD. Together these results suggest that each disorder across the larger FTD spectrum has a unique relationship with the *HLA* region.

Our results also indicate that functionally expressed FTD-immune shared genetic variants are differentially expressed in FTD brains compared to controls and in microglia compared to other CNS cell types (Figure 5). Microglia play a role in the pathophysiology of *GRN*+ FTD. Progranulin is expressed in microglia [35] and *GRN* haploinsufficiency is associated with abnormal microglia activation and neurodegeneration [3]. It is perhaps expected, therefore, that *GRN*+ brains show differential expression of FTD-immune genes, even though these genetic variants were derived from GWAS of patients with sporadic FTD (who lack *GRN* or other established FTD mutations). More surprising is the presence of similar enrichment in *GRN*- brains,

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

suggesting that dysfunction of microglial-centered immune networks may be a common feature of FTD pathogenesis.

By leveraging statistical power from the large immune-mediated GWASs, we identified novel FTD susceptibility loci within *LRRK2, TBKBP1* and *PGBD5* and confirmed previously shown FTD associated signal within the *MAPT* region. *LRRK2* mutations are a cause of Parkinson's disease [37] and Crohn's disease [38]. We previously described a potential link between FTD and the *LRRK2* locus [39] and another study using a small sample showed that *LRRK2* mutations may increase FTD risk [40]. Together these results suggest that the extended *LRRK2* locus might influence FTD despite common genetic variants within *LRRK2* not reaching genome-wide significance in large FTD-GWAS [5]. We suggest that increased expression of *LRRK2* in microglia results in proinflammatory responses, possibly by modulating TNF-alpha secretion (Tumor-Necrosis Factor) [41]. *TBKBP1* also modulates TNF-alpha signaling by binding to *TBK1* (*TANK*-binding kinase 1) [42]; rare pathogenic variants in *TBK1* cause FTD-ALS [43,44,45]. Importantly, elevated CSF levels of TNF-alpha are a core feature of FTD [6,46]. Building on these findings, in our bioinformatics 'network' based analysis, we found that both *LRRK2* and *TBKBP1* interact with genes within the *HLA* region (Figure 3). Further, physical interactions between *MAPT* and the *HLA* network are compatible with research suggesting that under different conditions reactive microglia can either drive or mitigate tau pathology [47,48]. *MAPT* mutations, which disrupt the normal binding of tau protein to tubulin, account for a large proportion of familial FTD

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

cases [49]. Together, these findings suggest that *LRRK2, TBKBP1,* and *MAPT* may, at least in part, influence FTD pathogenesis via *HLA*-related mechanisms.

This study has limitations. Particularly, in the original datasets that form the basis of our analysis, diagnosis of FTD was established clinically. Given the clinical overlap among neurodegenerative diseases, we cannot exclude the potential influence of clinical misdiagnosis. As such, our findings would benefit from confirmation in large pathologically confirmed cohorts. In addition, given the complex interconnectedness of the *HLA* region (see Figure 3), we were not able to define the specific gene(s) on chromosome 6 responsible for our pleiotropic signal. However, given the number of *HLA* loci associated with increased FTD risk, it may be the case that no single *HLA* variant will be clinically informative; rather, an *additive combination* of these microglia-associated genetic variants may better inform FTD risk.

In conclusion, across a large cohort (total n = 192,886 cases and controls), we leveraged pleiotropy between FTD-related disorders and immune-mediated disease to identify several genes within the *HLA* region that are expressed within microglia and differentially expressed in the brains of patients with FTD. Building on prior work [6,7], our results suggest that immune dysfunction is central to the pathophysiology of a subset of FTD patients. These findings have important implications for future work focused on monitoring microglial activation as a marker of disease progression and on developing anti-inflammatory therapies to modify disease outcomes in patients with FTD.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

FINANCIAL DISCLOSURE

No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

ACKNOWLEDGEMENTS

Primary support for data analyses was provided by AG046374 (CMK), U24DA041123 (AMD, LPS, RSD), National Alzheimer's Coordinating Center (NACC) Junior Investigator (JI) Award (RSD), RSNA Resident/Fellow Grant (RSD), Foundation of ASNR Alzheimer's Imaging Grant (RSD), Alzheimer's Society Grant 284 (RF), ARRS/ASNR Scholar Award (LPS), and the Tau Consortium. Additional support was provided by the Larry L. Hillblom Foundation 2016-A-005-SUP (JSY), AFTD Susan Marcus Memorial Fund Clinical Research Grant (JSY), NIA K01 AG049152 (JSY), P01-AG-017586 (GDS), the Bluefield Project to Cure FTD (JSY), and the Tau Consortium (JSY, GDR). GUH was supported by the Deutsche Forschungsgemeinschaft (DFG, HO2402/6-2 & Munich Cluster for Systems Neurology SyNergy), the German Federal Ministry of Education and Research (BMBF, 01KU1403A), and the NOMIS Foundation (FTD project). The PSP-GWAS was funded by a grant from the CurePSP Foundation, the Peebler PSP Research Foundation.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

REFERENCES

1. Vieira RT, Caixeta L, Machado S, Silva AC, Nardi AE, Arias-Carrión O, Carta MG. Epidemiology of early-onset dementia: A review of the literature. Clinical Practice & Epidemiology in Mental Health 2013;9(1).

2. Arnold SE, Han L-Y, Clark CM, Grossman M, Trojanowski JQ. Quantitative neurohistological features of frontotemporal degeneration. Neurobiology of Aging 2000;21(6):913-9.

3. Lui H, Zhang J, Makinson S, Cahill M, Kelley K, Huang H, et al. Progranulin deficiency promotes circuit-specific synaptic pruning by microglia via complement activation. Cell 2016;165(4):921-35.

4. Yin F, Banerjee R, Thomas B, Zhou P, Qian L, Jia T, et al. Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. Journal of Experimental Medicine 2010;207(1):117-28.

5. Ferrari R, Hernandez DG, Nalls MA, Rohrer JD, Ramasamy A, Kwok JB, et al. Frontotemporal dementia and its subtypes: A genome-wide association study. The Lancet Neurology 2014;13(7):686-99.

6. Miller ZA, Rankin KP, Graff-Radford NR, Takada LT, Sturm VE, Cleveland CM, et al. TDP-43 frontotemporal lobar degeneration and autoimmune disease. Journal of Neurology, Neurosurgery & Psychiatry 2013;84(9):956-62.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

7. Miller ZA, Sturm VE, Camsari GB, Karydas A, Yokoyama JS, Grinberg LT, et al. Increased prevalence of autoimmune disease within C9 and FTD/MND cohorts completing the picture. Neurology-Neuroimmunology Neuroinflammation 2016;3(6):e301.

8. Stearns FW. One hundred years of pleiotropy: A retrospective. Genetics 2010;186(3):767-73.

9. Olney NT, Spina S, Miller BL. Frontotemporal dementia. Neurologic Clinics 2017;35(2):339-74.

10. Josephs KA. Frontotemporal dementia and related disorders: deciphering the enigma. Annals of neurology. 2008 Jul 1;64(1):4-14.

11. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, et al. Genome-wide meta-analysis increases to 71 the number of confirmed crohn's disease susceptibility loci. Nature Genetics 2010;42(12):1118-25.

12. Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nature Genetics 2011;43(3):246-52.

13. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. Nature Genetics 2010;42(6):508-14.

14. Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA, et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nature Genetics 2009;41(6):703-7.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

15. Dubois PC, Trynka G, Franke L, Hunt KA, Romanos J, Curtotti A, et al. Multiple common variants for celiac disease influencing immune gene expression. Nature Genetics 2010;42(4):295-302.

16. Ellinghaus D, Ellinghaus E, Nair RP, Stuart PE, Esko T, Metspalu A, et al. Combined analysis of genome-wide association studies for crohn disease and psoriasis identifies seven shared susceptibility loci. Am J Hum Genet 2012;90(4):636-47.

17. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black SA, et al. Frontotemporal lobar degeneration A consensus on clinical diagnostic criteria. Neurology 1998;51(6):1546-54.

18. Kouri N, Ross OA, Dombroski B, Younkin CS, Serie DJ, Soto-Ortolaza A, et al. Genome-wide association study of corticobasal degeneration identifies risk variants shared with progressive supranuclear palsy. Nature Communications 2015;6.

19. Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K, et al. Office of rare diseases neuropathologic criteria for corticobasal degeneration. Journal of Neuropathology & Experimental Neurology 2002;61(11):935-46.

20. Höglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang L-S, Klei L, et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nature Genetics 2011;43(7):699-705.

21. van Rheenen W, Shatunov A, Dekker AM, McLaughlin RL, Diekstra FP, Pulit SL, et al. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. Nature Genetics 2016;48(9):1043-8.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

22. Andreassen OA, Djurovic S, Thompson WK, Schork AJ, Kendler KS, ODonovan MC, et al. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. The American Journal of Human Genetics 2013;92(2):197-209.

23. Andreassen OA, Thompson WK, Schork AJ, Ripke S, Mattingsdal M, Kelsoe JR, et al. Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. PLoS Genet 2013;9(4):e1003455.

24. Desikan RS, Schork AJ, Wang Y, Witoelar A, Sharma M, McEvoy LK, et al. Genetic overlap between alzheimers disease and parkinsons disease at the MAPT locus. Molecular Psychiatry 2015;20(12):1588-95.

25. Yokoyama JS, Wang Y, Schork AJ, Thompson WK, Karch CM, Cruchaga C, et al. Association between genetic traits for immune-mediated diseases and alzheimer disease. JAMA Neurology 2016.

26. Yokoyama JS, Karch CM, Fan CC, Bonham LW, Kouri N, Ross OA, et al. Shared genetic risk between corticobasal degeneration, progressive supranuclear palsy, and frontotemporal dementia. Acta Neuropathologica 2017;1-13.

27. Ramasamy A, Trabzuni D, Guelfi S, Varghese V, Smith C, Walker R, et al. Genetic variability in the regulation of gene expression in ten regions of the human brain. Nat Neurosci 2014;17(10):1418-28.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

28. Westra HJ, Peters MJ, Esko T, Yaghootkar H, Schurmann C, Kettunen J, et al. Systematic identification of trans eqtls as putative drivers of known disease associations. Nat Genet 2013;45(10):1238-43.

29. Warde-Farley D, Donaldson SL, Comes O, Zuberi K, Badrawi R, Chao P, et al. The genemania prediction server: Biological network integration for gene prioritization and predicting gene function. Nucleic Acids Res 2010, Jul;38(Web Server issue):W214-20.

30. Mostafavi S, Ray D, Warde-Farley D, Grouios C, Morris Q. GeneMANIA: A real-time multiple association network integration algorithm for predicting gene function. Genome Biol 2008;9 Suppl 1:S4.

31. Chen-Plotkin AS, Geser F, Plotkin JB, Clark CM, Kwong LK, Yuan W, et al. Variations in the progranulin gene affect global gene expression in frontotemporal lobar degeneration. Hum Mol Genet 2008;17(10):1349-62.

32. Zhang Y, Chen K, Sloan SA, Bennett ML, Scholze AR, O'Keeffe S, et al. An rna-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. Journal of Neuroscience 2014;34(36):11929-47.

33. Karch CM, Ezerskiy LA, Bertelsen S, Goate AM. Alzheimers disease risk polymorphisms regulate gene expression in the ZCWPW1 and the CELF1 loci. PLoS One 2016;11(2):e0148717.

34. Ishizawa K, Dickson DW. Microglial activation parallels system degeneration in progressive supranuclear palsy and corticobasal degeneration. Journal of Neuropathology & Experimental Neurology 2001;60(6):647-57.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

35. Toh H, Chitramuthu BP, Bennett HPJ, Bateman A. Structure, function, and mechanism of progranulin; the brain and beyond. Journal of Molecular Neuroscience 2011;45(3):538.

36. Dattola V, Famà F, Russo M, Calabrò RS, Logiudice AL, Grasso MG, et al. Multiple sclerosis and amyotrophic lateral sclerosis: A human leukocyte antigen challenge. Neurol Sci 2017, Apr 18.

37. Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, et al. Phenotype, genotype, and worldwide genetic penetrance of lrrk2-associated parkinson's disease: A case-control study. The Lancet Neurology 2008;7(7):583-90.

38. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, et al. Genome-wide association defines more than 30 distinct susceptibility loci for crohn's disease. Nature Genetics 2008;40(8):955-62.

39. Ferrari R, Wang Y, Vandrovcova J, Guelfi S, Witeolar A, Karch CM, Schork AJ, Fan CC, Brewer JB, Momeni P, Schellenberg GS. Genetic architecture of sporadic frontotemporal dementia and overlap with Alzheimer9s and Parkinson9s diseases. J Neurol Neurosurg Psychiatry. 2016 Dec 20:jnnp-2016.

40. Dächsel JC, Ross OA, Mata IF, Kachergus J, Toft M, Cannon A, et al. Lrrk2 G2019S substitution in frontotemporal lobar degeneration with ubiquitin-immunoreactive neuronal inclusions. Acta Neuropathologica 2007;113(5):601-6.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

41. Moehle MS, Webber PJ, Tse T, Sukar N, Standaert DG, DeSilva TM, et al. LRRK2 inhibition attenuates microglial inflammatory responses. J Neurosci 2012, Feb;32(5):1602-11.

42. Bouwmeester T, Bauch A, Ruffner H, Angrand PO, Bergamini G, Croughton K, et al. A physical and functional map of the human tnf-alpha/nf-kappa B signal transduction pathway. Nat Cell Biol 2004;6(2):97-105.

43. Cirulli ET, Lasseigne BN, Petrovski S, Sapp PC, Dion PA, Leblond CS, Couthouis J, Lu YF, Wang Q, Krueger BJ, Ren Z. Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. Science. 2015 Mar 27;347(6229):1436-41.

44. Freischmidt A, Wieland T, Richter B, Ruf W, Schaeffer V, Müller K, Marroquin N, Nordin F, Hübers A, Weydt P, Pinto S. Haploinsufficiency of TBK1 causes familial ALS and fronto-temporal dementia. Nature neuroscience. 2015 May 1;18(5):631-6.

45. Pottier C, Bieniek KF, Finch N, van de Vorst M, Baker M, Perkersen R, Brown P, Ravenscroft T, van Blitterswijk M, Nicholson AM, DeTure M. Whole-genome sequencing reveals important role for TBK1 and OPTN mutations in frontotemporal lobar degeneration without motor neuron disease. Acta neuropathologica. 2015 Jul 1;130(1):77-92.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

46. Sjögren M, Folkesson S, Blennow K, Tarkowski E. Increased intrathecal inflammatory activity in frontotemporal dementia: Pathophysiological implications. Journal of Neurology, Neurosurgery & Psychiatry 2004;75(8):1107-11.

47. Maphis N, Xu G, Kokiko-Cochran ON, Jiang S, Cardona A, Ransohoff RM, et al. Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. Brain 2015;138(6):081.

48. Funk KE, Mirbaha H, Jiang H. Holtzman DM, Diamond MI. Distinct therapeutic mechanisms of tau antibodies. Journal of Biological Chemistry 2015; 290(35): 21652-62.

49. Rizzu P, Van Swieten JC, Joosse M, Hasegawa M, Stevens M, Tibben A, et al. High prevalence of mutations in the microtubule-associated protein tau in a population study of frontotemporal dementia in the Netherlands. The American Journal of Human Genetics 1999;64(2):414-21

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Table 1. Summary data from all GWAS used in the current study

Disease/Trait		**Total N**	**#**	**Reference**
Frontotemporal Dementia	FTD	6,462	6,026,384	[5]
Corticobasal degeneration	CBD	3,463	533,898	[18]
Progressive Supranuclear Palsy	PSP	4,361	531,451	[20]
Amyotropic Lateral Sclerosis	ALS	36,052	18,741,501	[21]
Crohn Disease	CD	51,109	942,858	[11]
Ulcerative colitis	UC	26,405	1,273,589	[12]
Rheumatoid arthritis	RA	25,708	2,554,714	[13]
Type 1 diabetes	T1D	16,559	841,622	[14]
Celiac disease	CeD	15,283	528,969	[15]
Psoriasis	PSOR	7,484	1,121,166	[16]

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Table 2. Overlapping loci between FTD and immune-mediated disease at a conjunction FDR < 0.05.

SNP	Chr	Nearest Gene	Associated Phenotype	Associated Phenotype *p*-value	Min Conj FDR	FTD *p*-value	Direction of Allelic Effect
rs2269423	6	*AGPAT1*	Ced	4.63E-02	4.63E-02	6.28E-01	+/-
rs3117097	6	*BTNL2*	RA	8.21E-05	8.21E-05	7.19E-03	+/+
rs204989	6	*GPSM3*	UC	2.90E-02	9.02E-03	2.58E-01	+/+
rs204991	6	*GPSM3*	T1D	1.00E-02	9.02E-03	2.58E-01	+/+
rs17427887	6	*HLA-DQA2*	RA	3.70E-02	3.70E-02	6.02E-01	-/-
rs10484561	6	*HLA-DQB1*	T1D	1.86E-02	1.71E-02	4.17E-01	-/+
rs3135353	6	*HLA-DRA*	CD	2.29E-02	3.58E-03	1.35E-01	+/+
rs9268852	6	*HLA-DRA*	UC	1.25E-07	1.25E-07	1.03E-04	+/+
rs3129890	6	*HLA-DRA*	T1D	5.54E-05	5.54E-05	7.19E-03	+/+
rs6457590	6	*HLA-DRA*	RA	1.52E-02	1.52E-02	3.80E-01	+/+
rs9268877	6	*HLA-DRA*	RA	3.64E-07	1.25E-07	1.03E-04	+/-
rs875142	6	*PAQR8*	CD	4.62E-02	4.62E-02	5.51E-01	-/-
rs9261536	6	*TRIM15*	T1D	4.31E-02	4.31E-02	6.98E-01	-/+

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

rs3094138	6	*TRIM26*	T1D	4.63E-02	2.87E-02	6.28E-01	-/+
rs7778450	7	*TNS3*	CeD	4.26E-02	4.26E-02	6.17E-01	-/-
rs2192493	7	*TWISTNB*	T1D	4.17E-02	4.17E-02	6.09E-01	+/+
rs10216900	8	*CR590356*	T1D	3.09E-02	3.09E-02	6.40E-01	+/+
rs10784359	12	*SLC2A13*	RA	3.33E-02	3.33E-02	5.90E-01	+/+
rs17572851	17	*MAPT*	T1D	2.47E-02	2.47E-02	5.90E-01	+/+
rs199533	17	*NSF*	CD	3.90E-02	1.95E-02	4.56E-01	+/+
rs2134297	18	*DCC*	CeD	3.11E-02	3.11E-02	5.73E-01	+/+

Abbreviations: CeD, Celiac disease; Chr, Chromosome location; CD, Crohn disease; FTD, Frontotemporal dementia; Min Conj FDR, minimum conjunction false discovery rate; PSOR, Psoriasis; RA, Rheumatoid arthritis; SNP, Single-nucleotide polymorphism; T1D, Type 1 diabetes; UC, Ulcerative colitis; –, negative effect estimate; +, positive effect estimates.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Table 3. Genes associated with FTD and immune-mediated disease differentially altered in FTD-U patients versus controls.

Gene	**Ctrl v. FTD-U *p*-value**	**Ctrl v. *GRN* *p*-value**
AOAH	0.631	**0.013**
HLA-A	0.622	**0.004**
HLA-C	0.372	**0.002**
HLA-F	0.592	**0.001**
HLA-DRA (LOC101060835)	**0.017**	**0.008**
HLA-DRQ (HLA-DQB1)	**0.009**	**0.001**
MAPT	0.376	0.090
TBKBP1	**0.005**	0.108
PGBD5	0.528	**0.016**
LRRK2	N/A	N/A

P values ≤ 0.05 are in bold.

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

FIGURES

Figure 1A. Fold enrichment plots of enrichment versus nominal -$\log_{10}$ *p*-values (corrected for inflation) in frontotemporal dementia (FTD) below the standard GWAS threshold of $p < 5\text{x}10^{-8}$ as a function of significance of association with 6 immune-mediated diseases, namely Crohn's disease (CD), ulcerative colitis (UC), type 1 diabetes (T1D), rheumatoid arthritis (RA), celiac disease (CeD), and psoriasis (PSOR) and at the level of $-\log_{10}(p) \geq 0$, $-\log_{10}(p) \geq 1$, $-\log_{10}(p) \geq 2$ corresponding to $p \leq 1$, $p \leq 0.1$, $p \leq 0.01$, respectively. Teal line indicates all SNPs.

Figure 1B. 'Conjunction' Manhattan plot of conjunction $-\log_{10}$ (FDR) values for frontotemporal dementia (FTD) given Crohn's disease (CD; FTD|CD, red), ulcerative colitis (UC, FTD|UC, orange), type 1 diabetes (T1D, FTD|T1D, teal), rheumatoid arthritis (RA, FTD|RA, green), celiac disease (CeD, FTD|CeD, magenta), and psoriasis (PSOR, FTD|PSOR, blue). SNPs with conjunction $-\log_{10}$ FDR > 1.3 (i.e. FDR < 0.05) are shown with large points. A black line around the large points indicates the most significant SNP in each LD block and this SNP was annotated with the closest gene, which is listed above the symbols in each locus.

Figure 2. Fold enrichment plots of enrichment (after removing all regions in LD with *HLA* on chr 6) versus nominal -$\log_{10}$ *p*-values (corrected for inflation) in frontotemporal dementia (FTDnoMHC) below the standard GWAS threshold of $p < 5\text{x}10^{-8}$ as a function of significance of association with 6 immune-mediated diseases, namely Crohn's disease (CD), ulcerative colitis (UC), type 1 diabetes (T1D), rheumatoid arthritis (RA), celiac disease (CeD), and psoriasis (PSOR) and at the level of $-\log_{10}(p) \geq 0$, $-\log_{10}(p) \geq 1$, -

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

$\log_{10}(p) \geq 2$ corresponding to $p \leq 1, p \leq 0.1, p \leq 0.01$, respectively. Teal line indicates all SNPs.

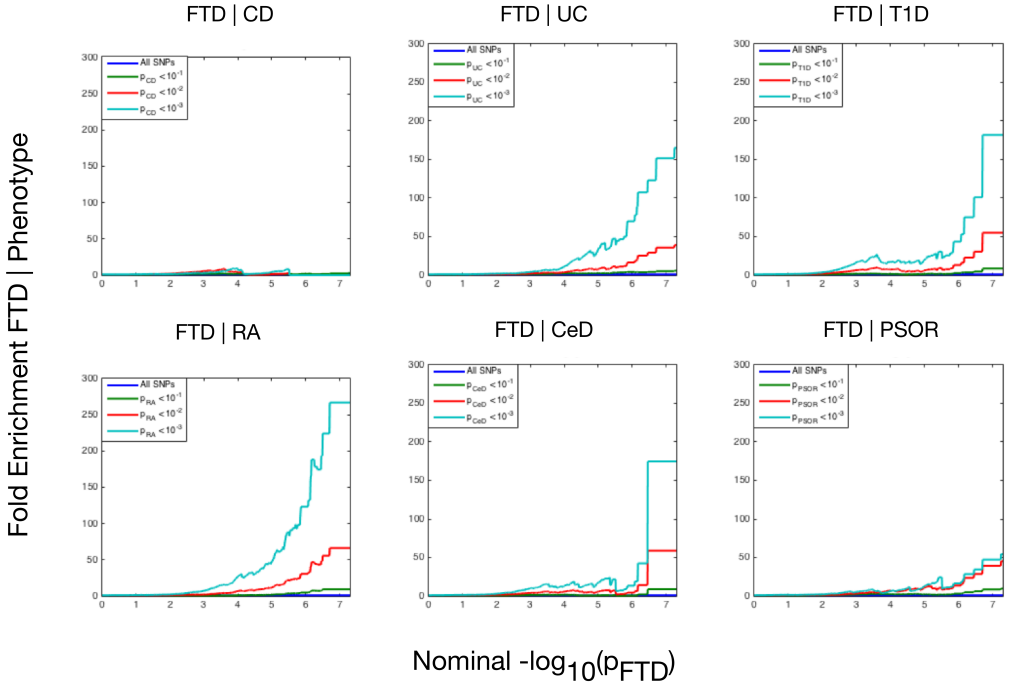
Figure 3. Network interaction graph predominantly illustrating co-expression and shared protein domains for functionally expressed FTD-immune pleiotropic genes.

Figure 4. FTD-Immune genes are elevated in FTD-*GRN* brains. Expression for the genes with the largest effect sizes are plotted: A) *HLA-A*, B) *HLA-C*, C) *HLA-DRA*, and D) *HLA-DRQ*. Expression values were obtained from GSE13162 for FTD-U brains with and without *GRN* mutations and neuropathology-free controls. Horizontal bar represents mean ± SEM.

Figure 5. Microglia enrichment in FTD-Immune genes. FTD-Immune genes were analyzed to determine the cell-type in which each gene is most highly expressed [32]. A) Pie chart plotting the relative number of genes most highly expressed in in each cell type. No genes were most highly expressed in endothelial cells or oligodendrocytes. B) Individual bar plots showing cell-type specific expression for genes with the largest effect size.

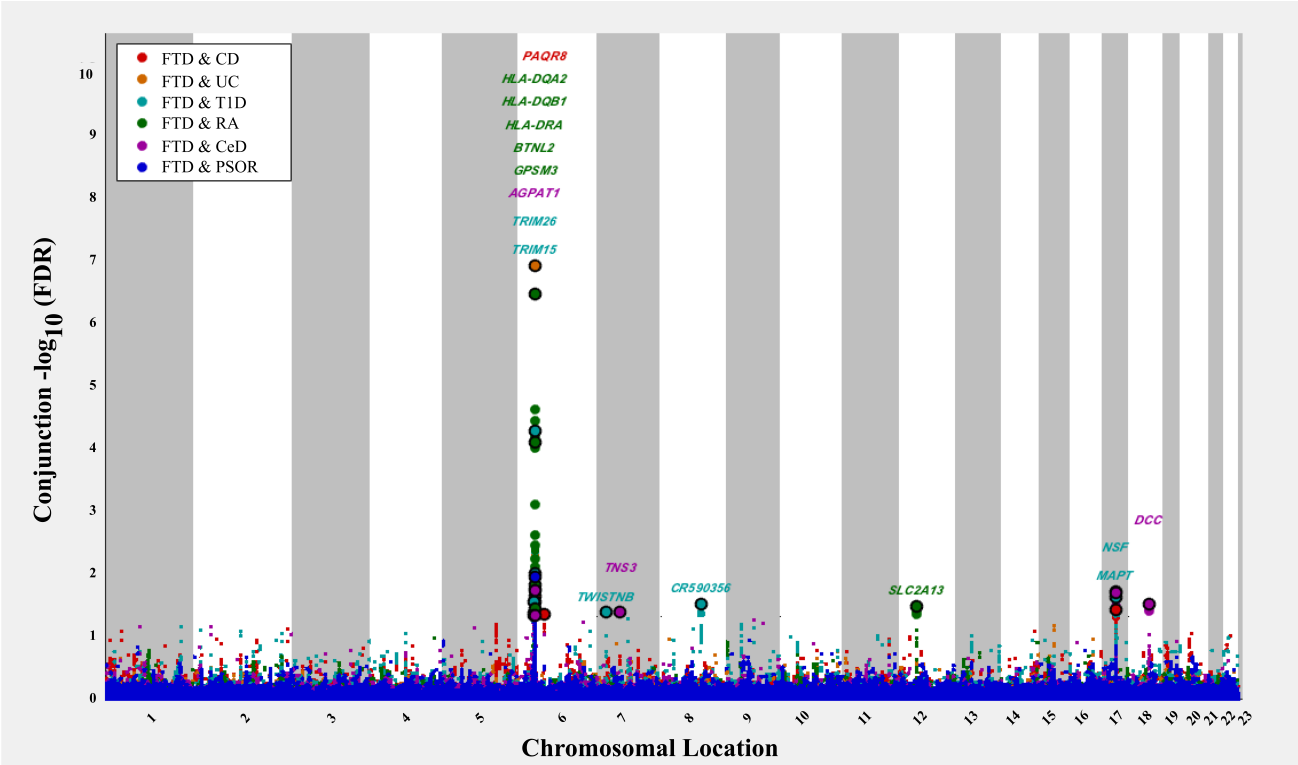
bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Figure 1A.



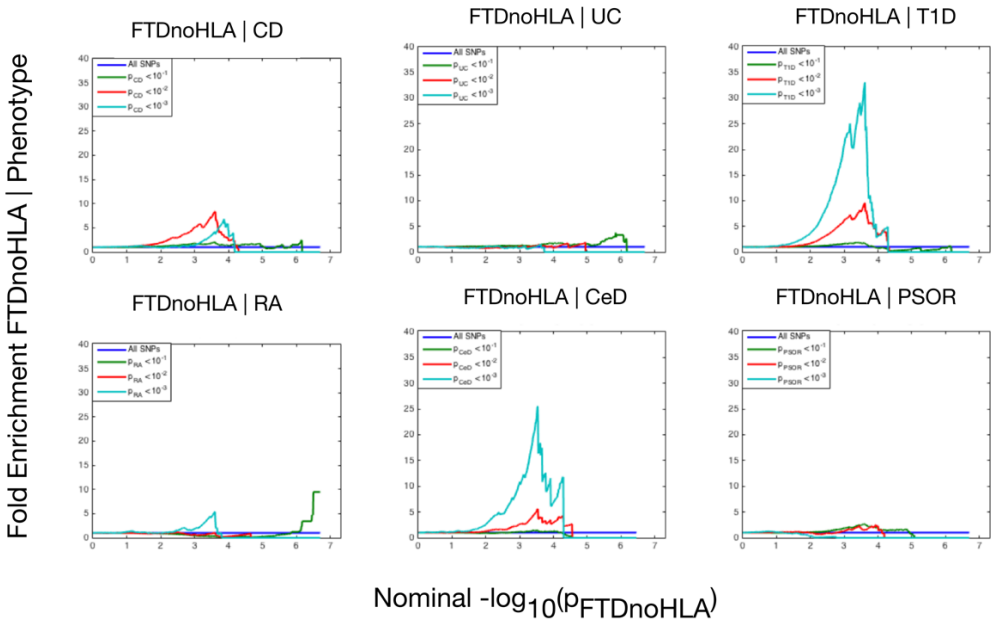
bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Figure 1B.



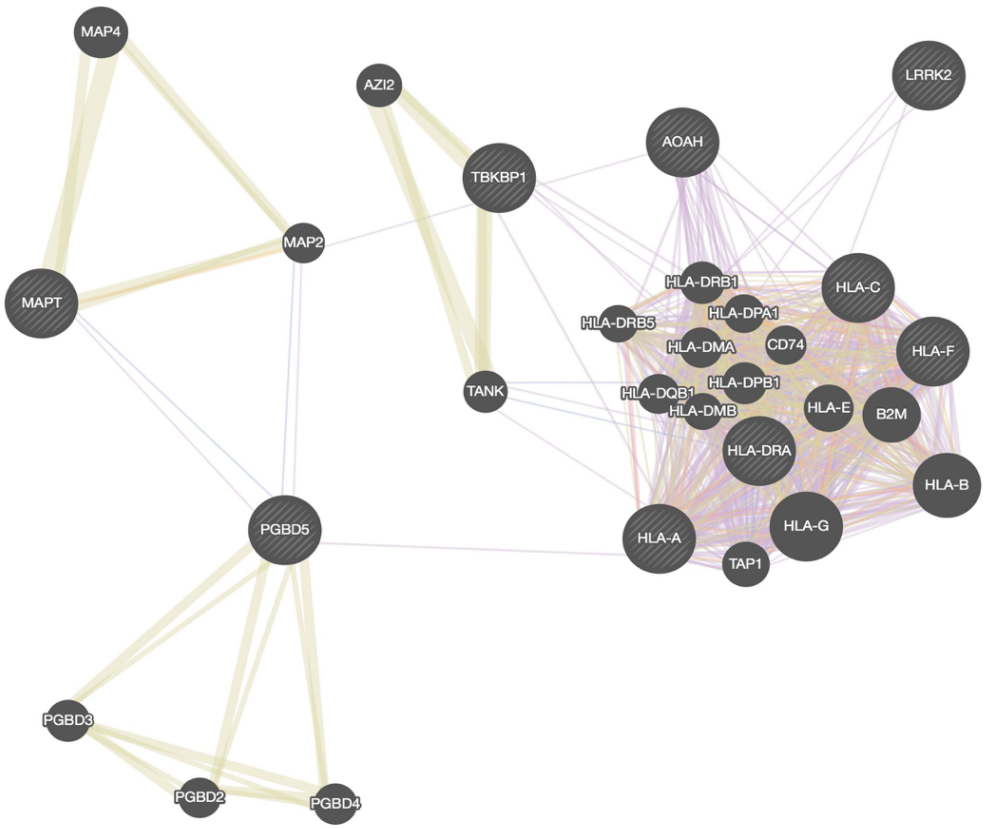
bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Figure 2.



bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Figure 3.

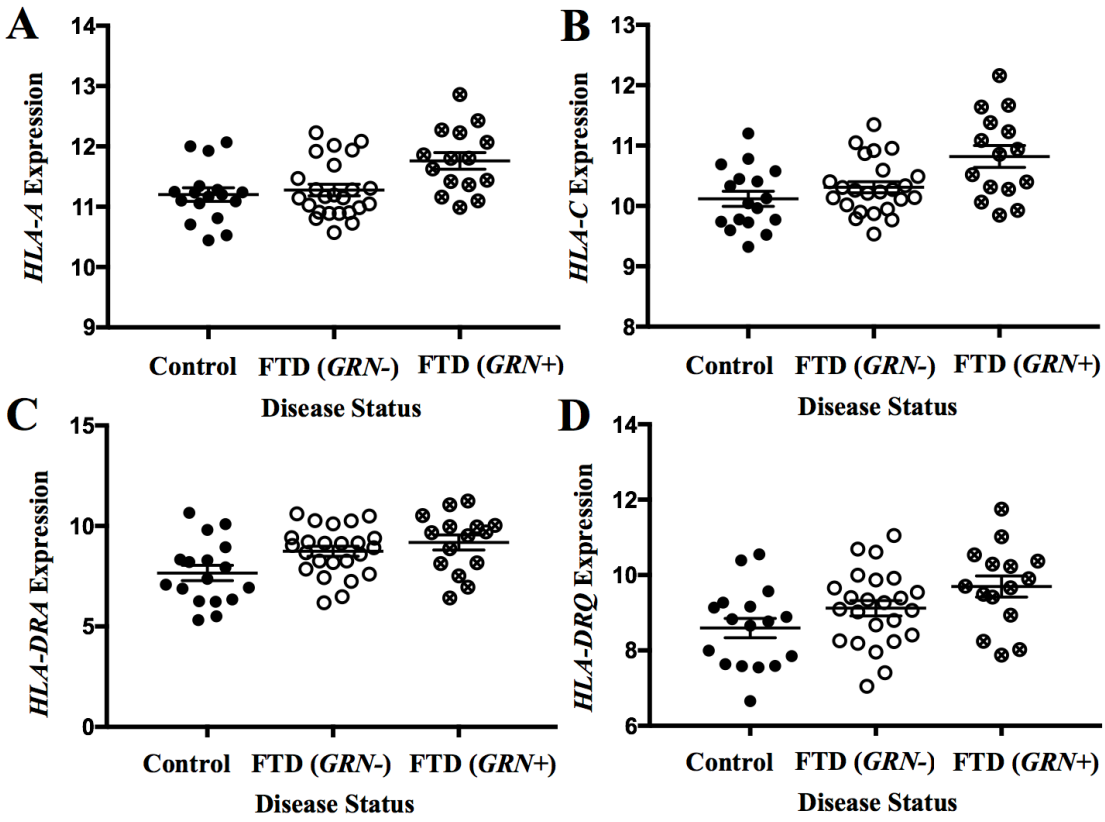


Networks

- Co-expression (90.93%)
- Shared protein domains (4.79%)
- Physical Interactions (2.03%)
- Predicted (1.82%)
- Co-localization (0.44%)

bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

Figure 4.



bioRxiv preprint doi: https://doi.org/10.1101/157875; this version posted July 4, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-ND 4.0 International license.

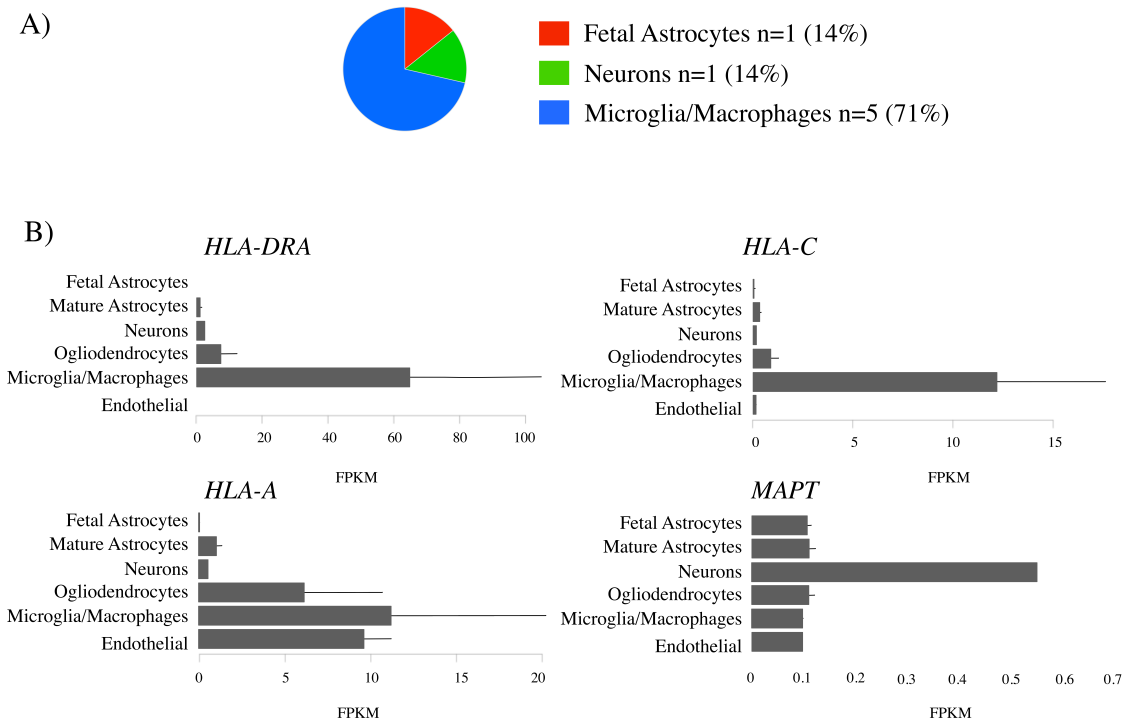



Figure 5.