

## Genetic architecture of sporadic frontotemporal dementia and overlap with Alzheimer's and Parkinson's diseases

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## ABSTRACT

Clinical, pathological and genetic overlap between sporadic frontotemporal dementia (FTD), Alzheimer's disease (AD) and Parkinson's disease (PD) has been suggested; however the relationship between these disorders is still not well understood. Here we evaluated genetic overlap between FTD, AD and PD to assess shared pathobiology and identify novel genetic variants associated with increased risk for FTD.

Summary statistics were obtained from the International FTD Genomics Consortium, International PD Genetics Consortium, International Genomics of AD Project (n>75,000 cases and controls). We used conjunction false discovery rate (FDR) to evaluate genetic pleiotropy and conditional FDR to identify novel FTD associated SNPs. Relevant variants were further evaluated for expression quantitative loci.

We observed SNPs within the *HLA*, *MAPT* and *APOE* regions *jointly* contributing to increased risk for FTD and AD or PD. By conditioning on polymorphisms associated with PD and AD, we found 11 loci associated with increased risk for FTD. Meta-analysis across two independent FTD cohorts revealed a genome-wide signal within the *APOE* region (rs6857, 3'-UTR=*PVRL2*,  $p=2.21 \times 10^{-12}$ ), and a suggestive signal for rs1358071 within the *MAPT* region (intronic=*CRHR1*,  $p=4.91 \times 10^{-7}$ ) with the effect allele tagging the H1 haplotype. Pleiotropic SNPs at the *HLA* and *MAPT* loci associated with expression changes in *cis* genes supporting involvement of intracellular vesicular trafficking, immune response and endo/lysosomal processes.

Our findings demonstrate genetic pleiotropy in these neurodegenerative diseases and indicate that sporadic FTD is a polygenic disorder where multiple pleiotropic loci with small effects contribute to increased disease risk.

**Key words:** frontotemporal dementia, Parkinson's Disease, Alzheimer's Disease, genetics, clinical, pleiotropy, polygenicity

## INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder characterized by progressive impairment of behaviour, cognition and executive function or language.[1] Recent converging evidence suggests clinical, pathological and genetic overlap between FTD and other common neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD).

From a clinical perspective, FTD and AD can sometimes be difficult to distinguish at onset or during disease progression:[2] non-cognitive manifestations such as mood changes, psychosis or variable social conduct can characterize the initial phases of AD patients.[3] Similarly, cognitive dysfunctions such as changes in abstract thinking or poor judgment, planning and difficulty in completing tasks become evident in either condition as the disease progresses.[4] This might partially reflect the fact that FTD and AD are associated with progressive impairment of similar brain circuits (frontal, pre-frontal or temporal lobes and/or subcortical regions).[5] Of note, among the primary progressive aphasia (PPA) cases in FTD, logopenic progressive aphasia (LPA) has been suggested as an atypical early presentation of AD.[6] In addition, the subtype called frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) – linked to mutations in the microtubule-associated protein tau (*MAPT*)[7] and progranulin (*GRN*) genes[8] – shows parkinsonian-like syndrome,[9] whilst dementia features can be found in up to 30-80% of PD cases (PDD) in later stages of the disease.[10]

From a pathological perspective, abnormal intracellular accumulation of the tau protein is seen in both FTD and AD.[11] Additionally, TDP-43 pathology has been reported in both AD and FTD at different disease stages,[12] and in some rare PD cases associated with variability in *LRRK2* (leucine-rich repeat kinase 2).[13]

From a genetic perspective, distinct genetic and genome-wide scale studies have suggested potential genetic overlap between FTD, AD and PD at specific loci. The *MAPT* gene on chromosome 17 has been extensively investigated in FTD[11] and has been recently implicated in AD[14] and PD[15] suggesting that tau pathology might jointly contribute to FTD, AD and PD. In addition, genome-wide association studies (GWAS) have revealed that common genetic variants within the *HLA* region on chromosome 6 increase risk for FTD,[16] AD[17] and PD.[18]

Evaluating genetic overlap between complex traits is based on the concept that gene(s) or genetic variant(s) can influence more than one distinct phenotype (= genetic pleiotropy).[19] Availability of large-scale genetic datasets (e.g. genome-wide summary statistics) is a key to estimate the level of genetic overlap, or genetic pleiotropy, across diverse traits including groups of related disorders.[20]

We have recently developed methods to evaluate genetic pleiotropy across different disorders (identifying novel genetic variants associated with various conditions including multiple sclerosis and AD).[14, 21, 22]

In the current work we sought to apply these methods taking advantage of existing large-scale genetic data (i.e. summary statistics) for FTD,[16] AD[23] and PD[24] to identify genetic overlap, i.e. pleiotropic effects, across these neurodegenerative disorders.

## **MATERIALS AND METHODS**

### **Participant Samples**

We evaluated complete summary statistics (p-values and odds ratios) from GWAS data of clinically diagnosed FTD,[16] AD[23] and PD.[24] We used AD-GWAS summary statistic data from the International Genomics of AD Project (IGAP Stage 1), which consisted of 17,008 AD and 37,154 controls with genotyped or imputed data at 7,055,881 SNPs (Table 1, for additional details see).[23] We obtained PD-GWAS summary statistic data from the International Parkinson's Disease Genetics Consortium consisting of 5,333 cases and 12,019 controls with genotyped and imputed data at 7,689,524 SNPs (Table 1, for additional details see).[24]

We examined FTD summary statistic GWAS data (discovery + replication phase) from the International FTD Genomics Consortium (IFGC).[16] As our discovery cohort, we used the IFGC Phase 1 cohort (Table 1), consisting of 2,154 FTD cases and 4,308 controls with genotyped and imputed data at 6,026,384 SNPs.[16] To replicate our findings from the discovery analyses using IFGC Phase 1, we assessed the p-values of pleiotropic SNPs (conditional FDR < 0.05; see Statistical analysis below) within the IFGC Phase 2 sample. The IFGC Phase 2 sample consisted of 1,372 FTD cases and 5,094 controls genotyped using a partially custom-designed Illumina NeuroX chip (Table 1, for details see).[16] The IFGC Phase 1+2 multicenter GWAS has been described in detail elsewhere.[16] Briefly, 44 international

research groups contributed samples to this two-stage clinical FTD-GWAS. We evaluated genetic data from patients clinically diagnosed with behavioral variant FTD (bvFTD), semantic dementia (SD), progressive nonfluent aphasia (PNFA) and FTD with motor neuron disease (FTD-MND). As described in the original study we excluded any cases with clinically diagnosed logopenic progressive aphasia (LPA), progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD). In this study, *MAPT* and *GRN* mutation carriers were excluded whereas individuals with *C9orf72* expansions were not excluded because this locus was identified subsequent to original sample collection. 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.

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

Disease/Trait	Total N	# SNPs	Reference
Frontotemporal Dementia (FTD) – IFGC phase 1	6,462	6,026,384	[16]
Frontotemporal Dementia (FTD) – IFGC phase 2	6,466	Illumina NeuroX Chip	[16]
Alzheimer’s disease (AD) – Phase 1	54,162	7,055,881	[23]
Parkinson’s disease (PD)	17,352	7,689,524	[24]

### Statistical analysis

Using recently developed statistical methods to evaluate pleiotropic effects, we evaluated SNPs associating with FTD, AD and PD. These methods have been described in extensive detail in a number of recent publications.[14, 17, 22] Briefly, for given associated phenotypes A and B, pleiotropic enrichment of phenotype A with phenotype B exists if the proportion of SNPs or genes associated with phenotype A increases as a function of increased association with phenotype B. To assess enrichment, we constructed fold-enrichment plots of nominal  $-\log_{10}(p)$  values for all FTD-SNPs and a subset of SNPs determined by the significance of their association with PD and AD. In fold-enrichment plots, the presence of enrichment is reflected by an upward deflection of the curve for phenotype A if the degree of deflection

from the expected null line is dependent on the degree of association with phenotype B. To assess for polygenic effects below the standard GWAS significance threshold, we focused the fold-enrichment plots on SNPs with nominal  $-\log_{10}(p) < 7.3$  (corresponding to p-value  $> 5 \times 10^{-8}$ ). The enrichment can be directly interpreted in terms of true discovery rate (TDR = 1 – False Discovery Rate [FDR]).[22]

To identify specific loci involved in both FTD and AD or FTD and PD, we computed conjunction FDR.[17] Conjunction FDR, denoted by  $FDR_{\text{trait1} \& \text{trait2}}$  is defined as the posterior probability that a SNP is null for either phenotype or both simultaneously, given the p-values for both traits are as small, or smaller, than the observed p-values. A conservative estimate of the conjunction FDR is given by the maximum statistic in taking the maximum of  $FDR_{\text{trait1}|\text{trait2}}$  and  $FDR_{\text{trait2}|\text{trait1}}$ . [17] We used an overall FDR threshold of  $< 0.05$ , which means 5 expected false discovery per hundred reported. Additionally, we constructed Manhattan plots based on the ranking of conjunction FDR to illustrate the genomic location of the pleiotropic loci.[17]

To identify specific FTD loci we computed conditional FDR.[14, 22] The standard FDR framework derives from a model that assumes the distribution of test statistics in a GWAS can be formulated as a mixture of null and non-null effects, with true associations (non-null effects) having more extreme test statistics, on average, than false associations (null effects). The conditional FDR is an extension of the standard FDR, which incorporates information from GWAS summary statistics of a second phenotype to adjust its significance level. The conditional FDR is defined as the probability that a SNP is null in the first phenotype given that the p-values in the first and second phenotypes are as small as, or smaller, than the observed ones. It is important to note that ranking SNPs by standard FDR or by p-values both give the same ordering of SNPs. In contrast, if the primary and secondary phenotypes are related genetically, conditional FDR re-orders SNPs, and results in a different ranking than that based on p-values alone. We used an overall FDR threshold of  $< 0.05$ , which means 5 expected false discovery per hundred reported. Additionally, we constructed Manhattan plots based on the ranking of conditional FDR to illustrate the genomic location of the pleiotropic loci. In all analyses, we controlled for the effects of genomic inflation by using intergenic SNPs.[14, 22] Detailed information on fold enrichment and conditional Q-Q plots, Manhattan plots, and conditional FDR can be found in prior reports.[14, 22]

For loci with conditional FDR < 0.05, we performed a fixed effects, inverse variance weighted meta-analysis across the discovery and replication FTD cohorts (IFGC Phases 1 and 2, total n = 3,526 FTD cases and 9,402 healthy controls) using the R package *meta* (<http://CRAN.R-project.org/package=meta>).[25] Briefly, the fixed effects, inverse variance weighted meta-analysis summarizes the combined statistical support across independent studies under the assumption of homogeneity of effects. Individual study  $\beta$  estimates (log odds ratios) are averaged, weighted by the estimated standard error.

### **Expression quantitative trait loci (QTL)**

For the expression quantitative trait loci (eQTL) analyses, we used data generated within the Braineac (<http://www.braineac.org>) and GTEx (<http://www.gtexportal.org/home/>) projects. Briefly, in braineac, eQTL data was generated from 101 neuropathologically defined controls in the following 10 brain regions: cerebellar cortex, frontal cortex, hippocampus, medulla (specifically inferior olivary nucleus), occipital cortex (specifically primary visual cortex), putamen, substantia nigra, thalamus, temporal cortex, and intralobular white matter. In GTEx eQTL data was available for the following 10 brain regions: anterior cingulate cortex (BA24; n=72), caudate (basal ganglia; n=100), cerebellar hemisphere (n=89), cerebellum (n=103), cortex (n=96), frontal cortex (BA9; n=92), hippocampus (n=81), hypothalamus (n=81), nucleus accumbens (basal ganglia; n=93) and putamen (basal ganglia; n=82).

Each eQTL was within +/- 1MB of each SNP and the significance threshold was  $p < 1 \times 10^{-5}$  as per website curators.

## **RESULTS**

### **Polygenic enrichment in FTD as a function of AD and PD**

We observed enrichment for FTD SNPs (IFGC Phase 1) across different levels of significance of association with AD and PD (Figure 1). For progressively stringent p-value thresholds of FTD-SNPs (i.e. increasing values of nominal  $-\log_{10}P_{\text{FTD}} \geq 6$ ), we found 140-fold and 120-fold pleiotropic enrichment as a function of AD ( $-\log_{10}P_{\text{AD}} \geq 3.0$ ) and PD ( $-\log_{10}P_{\text{PD}} \geq 3.0$ ) SNPs, respectively (Figure 1). Although decreased in magnitude, we observed a similar pattern of enrichment for AD- and PD-SNPs conditional



on FTD-SNPs suggesting symmetric genetic overlap between the three neurodegenerative diseases (Supplementary Figure 1).

### Conjunction FDR identifies shared FTD loci

At a conjunction FDR < 0.05, we identified 11 SNPs that were associated with FTD and AD or PD (Figure 2a, Table 2a). These included rs405509 (chromosome 19; intergenic; closest gene = *APOE*; conjunction trait = AD; min conjunction FDR = 0.0052) and rs9268877 (chromosome 6; intergenic; closest gene = *HLA-DRA*; conjunction trait = PD; min conjunction FDR = 0.048). We also found two pleiotropic loci in the *MAPT* haplotype-region, namely rs199528 (chromosome 17; intronic = *WNT3*; conjunction trait = PD; min conjunction FDR = 0.018) and rs1358071 (chromosome 17; intronic = *CRHR1*; conjunction trait = PD; min conjunction FDR = 0.02). We detected additional shared loci between FTD and PD on chromosomes 4 (rs7664889, intronic = *SCARB2*), 10 (rs676768, intronic = *VWA2*), 12 (rs10784359, intronic = *SLC2A13*), 13 (rs2893253; intergenic; closest gene = *EFNB2*) and 18 (rs12964543, intronic = *ZNF532*) (Table 2a).

**Table 2a.** Overlapping loci between FTD, PD and AD at a conjunction FDR < 0.05

SNP	Position	Chr	Location; Nearest Gene	Associated Phenotype	Min Conj FDR	FTD p-value	Associated Phenotype p-value	Direction of effect
rs7664889	77087704	4	Intronic; <i>SCARB2</i>	PD	4.84E-02	1.75E-04	8.88E-04	++++
rs9268877	32431147	6	Intergenic; <i>HLA-DRA</i>	PD	4.84E-02	1.04E-10	7.41E-04	++++
rs676768	116030773	10	Intronic; <i>VWA2</i>	PD	4.27E-02	3.12E-04	6.14E-04	++++
rs10784359	40445750	12	Intronic; <i>SLC2A13</i>	PD	3.26E-02	1.58E-04	7.47E-05	++++
rs2893253	107067203	13	Intergenic; <i>EFNB2</i>	PD	3.55E-02	2.02E-04	1.11E-04	++++

rs199528	44843136	17	Intronic; <i>WNT3</i>	PD	1.80E-02	4.09E-05	9.82E-16	++++
rs1358071	43803189	17	Intronic; <i>CRHR1</i>	PD	2.02E-02	4.96E-05	7.76E-15	++++
rs12964543	56543095	18	Intronic; <i>ZNF532</i>	PD	2.73E-02	1.12E-04	3.08E-04	++++
rs405509	45408836	19	Intergenic; <i>APOE</i>	AD	5.22E-03	1.25E-05	6.16E-70	++++

### Conditional FDR identifies novel FTD loci

To identify novel SNPs associated with FTD we ranked IFGC Phase 1 FTD-SNPs conditional on their genetic association with AD and PD (conditional FDR), particularly focusing on those SNPs that did not reach genome-wide significant levels in the previous FTD-GWAS. At a conditional FDR < 0.05, we found 13 novel FTD susceptibility loci: 11/13 polymorphisms were available for replication purposes within the IFGC2 cohort (7 actual SNPs and 4 proxies with linkage disequilibrium [LD]  $r^2 \geq 0.7$  and within 500KB distance from the reference SNP [based on HapMap 22/21]) (Figure 2b, Table 2b). Then, meta-analysis across IFGC Phase 1 and 2 cohorts revealed one genome-wide significant locus ( $p < 5 \times 10^{-8}$ ): rs6857 on chromosome 19 (3'-UTR = *PVRL2*; conditioning trait = PD; reference allele = T; OR = 1.34; 95% CI = 1.23-1.45;  $p = 2.21 \times 10^{-12}$ ) (Table 2b, Figures 3a and 4a). We also found one suggestive locus (at  $p < 5 \times 10^{-7}$ ) on rs1358071 within the *MAPT* region on chromosome 17 (intronic = *CRHR1*; conditioning trait = PD; reference allele = A; OR = 1.19; 95% CI = 1.11-1.27;  $p = 4.91 \times 10^{-7}$ ) (Table 2b, Figures 3b and 4b).

**Table 2b.** Novel SNPs showing association with FTD at conditional FDR < 0.05. Odds ratios provided for the reference allele

SNP	Position	Chr	Nearest Gene	Reference Allele	Associated phenotype	Min Cond FDR	IFGC Phase1 p-value	IFGC Phase1 OR (95%CI)	IFGC Phase 2 p-value	IFGC Phase 2 OR (95% CI)	Meta-analysis p-value	Meta-analysis OR (95% CI)
rs4417745	241225364	2	Intergenic; OTOS	A	PD	2.73E-02	2.52E-05	1.36 (1.18-1.57)	0.47	1.06 (0.90-1.25)	3.20E-04	1.22 (1.09-1.36)
rs7664889	77087704	4	Intronic; SCARB2	T	PD	3.23E-02	1.75E-04	0.73 (0.62-0.86)	0.82	0.98 (0.81-1.18)	3.18E-03	0.83 (0.73-0.94)
rs676768	116030773	10	Intronic; VWA2 <sup>#</sup>	T	PD	4.25E-02	3.12E-04	0.78 (0.68-0.90)	0.55	0.96 (0.82-1.11)	2.40E-03	0.86 (0.78-0.95)
rs1328032	71420424	13	Intergenic; DACH1	A	AD	1.38E-02	1.93E-07	0.67 (0.57-0.78)	0.34	0.94 (0.83-1.06)	7.39E-05	0.80 (0.72-0.88)
rs2446406	51679783	15	Intronic; GLDN <sup>#</sup>	A	PD	2.59E-02	7.18E-07	0.81 (0.74-0.88)	0.40	0.96 (0.87-1.06)	2.24E-05	0.87 (0.82-0.93)
rs7184882	73737373	16	In orf; LOC101927998	T	AD	4.24E-02	6.64E-07	0.71 (0.62-0.81)	0.08	0.89 (0.78-1.02)	3.08E-06	0.78 (0.71-0.86)
rs199528	44843136	17	Intronic; WNT3	T	PD	1.79E-02	4.09E-05	0.82 (0.74-0.90)	0.03	0.89 (0.80-0.99)	9.59E-06	0.85 (0.79-0.91)

**Table 2b.** Novel SNPs showing association with FTD at conditional FDR < 0.05. Odds ratios provided for the reference allele (continued)

rs1358071	43803189	17	Intronic; <i>CRHR1</i>	A	PD	2.01E-02	4.96E-05	1.22 (1.12-1.31)	0.001	1.16 (1.07-1.26)	4.91E-07	1.19 (1.11-1.27)
rs12964543	56543095	18	Intronic; <i>ZNF532</i> <sup>#</sup>	A	PD	2.71E-02	1.12E-04	1.24 (1.11-1.38)	0.24	1.05 (0.96-1.15)	9.10E-04	1.12 (1.05-1.2)
rs6857	45392254	19	3'-UTR; <i>PVRL2</i> <sup>#</sup>	T	PD	4.69E-02	7.03E-07	1.31 (1.18-1.46)	4.46E-07	1.37 (1.21-1.55)	2.21E-12	1.34 (1.23-1.45)
rs405509	45408836	19	Intergenic; <i>APOE</i>	T	AD	5.26E-03	1.25E-05	1.18 (1.09-1.27)	0.93	1.0 (0.92-1.09)	5.98E-05	1.15 (1.08-1.24)

# rs676768 not available, proxy SNP rs12782946 from IFGC Phase 2

# rs2446406 not available, proxy SNP rs2445742 from IFGC Phase 2

# rs12964543 not available, proxy SNP exm2272683 from IFGC Phase 2

# rs6857 not available, proxy SNP rs2075650 from IFGC Phase 2

### Expression quantitative trait loci (eQTL)

We evaluated potential biological relevance for each of the identified conjunction and conditional FDR SNPs (rs7664889, rs9268877, rs676768, rs10784359, rs2893253, rs199528, rs1358071, rs12964543, rs405509, rs4417745, rs1328032, rs2446406, rs7184882, rs6857, rs302665 and rs10507789) in human brain tissues assayed for genome-wide gene expression. There were 20 eQTLs in the Braineac dataset, whilst data extracted from GTEx indicated up to 144 significant eQTLs (Table 3). These were driven by rs199528 and rs1358071 (chr 17; *MAPT*-haplotype locus), and by rs9268877 (chr 6; *HLA* locus). No eQTLs were found for rs405509 and rs6857 (chr19; *APOE* locus).

The eQTL data from Braineac and GTEx was cross-supportive in different brain regions, including frontal and temporal cortices, jointly indicating influence on expression levels of *LRRC37A2*, *KANSL1*, *LRRC37A4* and *CRHR1* for rs199528 and rs1358071; conversely, changes in expression of *HLA-DPA1* (from Braineac in frontal cortex), and *HLA-DRB1* and *HLA-DQA2* (from GTEx in subcortical regions and cerebellum) were evident for rs9268877 (Table 3).

**Table 3.** Summary of eQTL in brain from Braineac and GTEx

SNP	bp	Risk allele	Chr	Location	Nearest gene	eQTL							
						Braineac				GTEx			
						gene	brain region	p-value	Effect of risk allele	gene	brain region	p-value	Effect of risk allele
rs7664889	77087704	/	4	Intronic	SCARB2	no eQTL				no eQTL			
rs9268877	32431147	A	6	Intergenic	HLA-DRA	HLA-DPA1	Frontal cortex	3.1x10 <sup>-5</sup>	increased expression	HLA-DRB1	Cerebellum	5.2x10 <sup>-8</sup>	increased expression
											Anterior cingulate cortex	8.8x10 <sup>-8</sup>	
										Putamen	8.9x10 <sup>-7</sup>		
HLA-DQA2	Cerebellum	1.3x10 <sup>-6</sup>	decreased expression										
rs676768	116030773	/	10	Intronic	VWA2	no eQTL				no eQTL			
rs10784359	40445750	/	12	Intronic	SLC2A13	no eQTL				no eQTL			
rs2893253	107067203	/	13	Intergenic	EFNB2	no eQTL				no eQTL			
rs199528	44843136	C	17	Intronic	WNT3	LRRC37A2	Temporal cortex	3x10 <sup>-6</sup>	decreased expression	RP11-259G18.2	Anterior cingulate cortex	4x10 <sup>-14</sup>	decreased expression
										LRRC37A2		1.7x10 <sup>-12</sup>	
										KANSL1-AS1		4.5x10 <sup>-12</sup>	
										RP11-259G18.3		1.6x10 <sup>-11</sup>	
										LRRC37A2	Caudate (basal ganglia)	4.5x10 <sup>-20</sup>	
										KANSL1-AS1		6.6x10 <sup>-20</sup>	
										RP11-259G18.2		1.9x10 <sup>-19</sup>	
										RP11-259G18.3		3.5x10 <sup>-19</sup>	
										LRRC37A	5.4x10 <sup>-7</sup>		
										RP11-259G18.3	Cerebellar Hemisphere	1.1x10 <sup>-18</sup>	
										LRRC37A2		5.7x10 <sup>-17</sup>	
										KANSL1-AS1		2.3x10 <sup>-16</sup>	
										RP11-259G18.2		2x10 <sup>-13</sup>	
LRRC37A	2x10 <sup>-10</sup>												

**Table 3.** Summary of eQTL in brain from Braineac and GTEx (continued)

rs199528	44843136	C	17	Intronic	WNT3	LRRC37A2	Temporal cortex	$3 \times 10^{-6}$	RP11-259G18.1	Cerebellar Hemisphere	$4.6 \times 10^{-10}$	decreased expression
									MAPT-AS1		$1.6 \times 10^{-8}$	
									MAPT		$1.3 \times 10^{-7}$	increased expression
									RP11-259G18.3	Cerebellum	$2 \times 10^{-25}$	decreased expression
									KANSL1-AS1		$3.9 \times 10^{-20}$	
									LRRC37A2		$6.2 \times 10^{-19}$	
									RP11-259G18.2		$1.6 \times 10^{-17}$	
									LRRC37A		$4 \times 10^{-13}$	
									RP11-259G18.1		$1.3 \times 10^{-12}$	
									MAPT		$8.7 \times 10^{-12}$	increased expression
						MAPT-AS1	$3.6 \times 10^{-8}$	decreased expression				
						SPPL2C	$1.3 \times 10^{-7}$					
						KANSL1-AS1	Cortex		$2.4 \times 10^{-18}$			
						RP11-259G18.3			$5.1 \times 10^{-18}$			
						RP11-259G18.2			$1.3 \times 10^{-17}$			
						LRRC37A2			$2.5 \times 10^{-14}$			
						KANSL1-AS1	Frontal Cortex		$1.3 \times 10^{-20}$			
						RP11-259G18.2			$1.5 \times 10^{-16}$			
						LRRC37A2			$2.3 \times 10^{-16}$			
						RP11-259G18.3			$8.4 \times 10^{-16}$			
MAPT		$1.3 \times 10^{-7}$	increased expression									
KANSL1-AS1	Hippocampus	$2.4 \times 10^{-16}$										
RP11-259G18.3		$3.1 \times 10^{-13}$										
RP11-259G18.2		$7 \times 10^{-13}$										
LRRC37A2		$3.7 \times 10^{-12}$										
KANSL1-AS1	Hypothalamus	$1.3 \times 10^{-15}$										



**Table 3.** Summary of eQTL in brain from Braineac and GTEx (continued)

rs199528	44843136	C	17	Intronic	WNT3	KANSL1	Hippocampus	1x10 <sup>-5</sup>	decreased expression	LRRC37A2	Hypothalamus	7.6x10 <sup>-15</sup>	decreased expression
										RP11-259G18.3		1.6x10 <sup>-13</sup>	
										RP11-259G18.2		5.8x10 <sup>-13</sup>	
										LRRC37A		5.6x10 <sup>-8</sup>	
										KANSL1-AS1	Nucleus accumbens (basal ganglia)	1.8x10 <sup>-20</sup>	
										RP11-259G18.3		1.4x10 <sup>-18</sup>	
										LRRC37A2		4.9x10 <sup>-17</sup>	
										RP11-259G18.2		3.4x10 <sup>-16</sup>	
										RP11-259G18.1	7.3x10 <sup>-7</sup>		
										KANSL1-AS1	Putamen (basal ganglia)	2.5x10 <sup>-19</sup>	
										RP11-259G18.3		6.9x10 <sup>-15</sup>	
										LRRC37A2		3.1x10 <sup>-14</sup>	
										RP11-259G18.2		9.6x10 <sup>-11</sup>	
										LRRC37A		1x10 <sup>-6</sup>	
										RP11-259G18.1		1.6x10 <sup>-6</sup>	
										rs1358071	43803189	A	
1.8x10 <sup>-16</sup>	RP11-259G18.2	1.6x10 <sup>-9</sup>											
Frontal cortex	3.6x10 <sup>-10</sup>	RP11-707O23.5	4.3x10 <sup>-9</sup>	decreased expression									
Hippocampus	4.7x10 <sup>-10</sup>	LRRC37A2	5.3x10 <sup>-8</sup>										
	5.3x10 <sup>-7</sup>	RP11-259G18.3	7.5x10 <sup>-7</sup>										
Medulla	2.7x10 <sup>-8</sup>	KANSL1-AS1	9.7x10 <sup>-7</sup>										
Occipital cortex	1.9x10 <sup>-11</sup>	LRRC37A4P	7.3x10 <sup>-15</sup>	increased expression									
	5.5x10 <sup>-11</sup>	LRRC37A2	1.7x10 <sup>-14</sup>	decreased expression									
Putamen	2.2x10 <sup>-6</sup>	RP11-707O23.5	4.5x10 <sup>-13</sup>										
	7.3x10 <sup>-11</sup>	RP11-259G18.2	3.1x10 <sup>-12</sup>										
Substantia nigra	2.4x10 <sup>-7</sup>	KANSL1-AS1	2.8x10 <sup>-11</sup>										

**Table 3.** Summary of eQTL in brain from Braineac and GTEx (continued)

rs1358071	43803189	A	17	Intronic	CRHR1	LRRC37A4	Temporal cortex	3.1x10 <sup>-12</sup>	increased expression	RP11-259G18.3	Caudate (basal ganglia)	1.1x10 <sup>-10</sup>	decreased expression
								1.1x10 <sup>-7</sup>		LRRC37A		6.3x10 <sup>-6</sup>	
							Thalamus	5.7x10 <sup>-12</sup>		LRRC37A4P	1.3x10 <sup>-15</sup>	increased expression	
								5.2x10 <sup>-10</sup>		PLEKHM1	4.0x10 <sup>-13</sup>		
						White matter	7.7x10 <sup>-6</sup>	LRRC37A2	2.6x10 <sup>-12</sup>	decreased expression			
						KANSL1	Hippocampus	6.1x10 <sup>-7</sup>	decreased expression		RP11-259G18.2	1.5x10 <sup>-9</sup>	
											RP11-259G18.3	1.9x10 <sup>-9</sup>	
											RP11-259G18.1	2.6x10 <sup>-9</sup>	
											KANSL1-AS1	6.1x10 <sup>-9</sup>	
											LRRC37A	2.5x10 <sup>-8</sup>	
											RP11-798G7.5	5.9x10 <sup>-8</sup>	increased expression
											RP11-707O23.5	2.8x10 <sup>-7</sup>	decreased expression
											FMNL1	4.2x10 <sup>-7</sup>	increased expression
											CTD-2020K17.1	5.2x10 <sup>-6</sup>	
										MAPT	6.6x10 <sup>-6</sup>		
						LRRC37A4P	5.3x10 <sup>-18</sup>	Cerebellum	decreased expression				
						PLEKHM1	4.2x10 <sup>-17</sup>						
						RP11-259G18.3	5.6x10 <sup>-16</sup>						
						LRRC37A2	3.3x10 <sup>-15</sup>						
						RP11-259G18.2	6.6x10 <sup>-15</sup>						
						RP11-707O23.5	2.6x10 <sup>-13</sup>						
						RP11-259G18.1	1.5x10 <sup>-10</sup>						
						LRRC37A	1.7x10 <sup>-10</sup>						
KANSL1-AS1	7.1x10 <sup>-10</sup>												
RP11-798G7.5	1.4x10 <sup>-9</sup>	increased expression											
MAPT	5.4x10 <sup>-9</sup>												

**Table 3.** Summary of eQTL in brain from Braineac and GTEx (continued)

rs1358071	43803189	A	17	Intronic	CRHR1	KANSL1	Hippocampus	6.1x10 <sup>-7</sup>	decreased expression	MAPT-AS1	Cerebellum	6.2x10 <sup>-8</sup>	decreased expression
										FMNL1		2.7x10 <sup>-6</sup>	increased expression
										KANSL1-AS1	Cortex	1.5x10 <sup>-14</sup>	decreased expression
										LRRC37A2		1.6x10 <sup>-11</sup>	
										RP11-707O23.5		2.7x10 <sup>-11</sup>	
										LRRC37A4P	3.2x10 <sup>-11</sup>	increased expression	
										RP11-259G18.3	Cortex	5.7x10 <sup>-11</sup>	decreased expression
										RP11-259G18.2		1.3x10 <sup>-10</sup>	
										CRHR1-IT1		1.3x10 <sup>-8</sup>	
										PLEKHM1		9.4x10 <sup>-7</sup>	
										RP11-259G18.1		7.8x10 <sup>-6</sup>	
						LRRC37A2	2.5x10 <sup>-11</sup>						
						LRRC37A4P	9.3x10 <sup>-11</sup>	increased expression					
						RP11-259G18.2	Frontal Cortex	2.2x10 <sup>-10</sup>		decreased expression			
						KANSL1-AS1		8.2x10 <sup>-10</sup>					
						RP11-707O23.5		9.8x10 <sup>-10</sup>					
						RP11-259G18.3		1.7x10 <sup>-9</sup>					
						DND1P1		1.6x10 <sup>-6</sup>					
						CRHR1-IT1		2.7x10 <sup>-6</sup>					
						MAPT	4.1x10 <sup>-6</sup>	increased expression					
						LRRC37A4P	Hippocampus	2.0x10 <sup>-12</sup>		decreased expression			
						LRRC37A2		1.6x10 <sup>-11</sup>					
						RP11-259G18.2		2.7x10 <sup>-11</sup>					
KANSL1-AS1	4.1x10 <sup>-11</sup>												
RP11-707O23.5	5.8x10 <sup>-11</sup>												
RP11-259G18.3	2.5x10 <sup>-8</sup>												
CRHR1	Medulla	2.9x10 <sup>-6</sup>	decreased expression	LRRC37A2	2.5x10 <sup>-11</sup>	increased expression							
				LRRC37A4P	9.3x10 <sup>-11</sup>	increased expression							
				RP11-259G18.2	2.2x10 <sup>-10</sup>	decreased expression							
				KANSL1-AS1	8.2x10 <sup>-10</sup>								
				RP11-707O23.5	9.8x10 <sup>-10</sup>								
				RP11-259G18.3	1.7x10 <sup>-9</sup>								
				DND1P1	1.6x10 <sup>-6</sup>								
				CRHR1-IT1	2.7x10 <sup>-6</sup>								
				MAPT	4.1x10 <sup>-6</sup>	increased expression							
				LRRC37A4P	Hippocampus	2.0x10 <sup>-12</sup>	decreased expression						
				LRRC37A2		1.6x10 <sup>-11</sup>							
				RP11-259G18.2		2.7x10 <sup>-11</sup>							
KANSL1-AS1	4.1x10 <sup>-11</sup>												
RP11-707O23.5	5.8x10 <sup>-11</sup>												
RP11-259G18.3	2.5x10 <sup>-8</sup>												

**Table 3.** Summary of eQTL in brain from Braineac and GTEx (continued)

rs1358071	43803189	A	17	Intronic	<i>CRHR1</i>	CRHR1	Medulla	$2.9 \times 10^{-6}$	decreased expression	CRHR1-IT1	Hippocampus	$4.8 \times 10^{-8}$	decreased expression
										DND1P1	Hippocampus	$2.4 \times 10^{-6}$	
										LRRC37A2	Hypothalamus	$1.1 \times 10^{-12}$	increased expression
										RP11-707O23.5		$3.2 \times 10^{-11}$	
										KANSL1-AS1		$8.7 \times 10^{-10}$	
										LRRC37A4P		$1.8 \times 10^{-9}$	
										RP11-259G18.2	decreased expression	$2.1 \times 10^{-8}$	
										RP11-259G18.3		$2.3 \times 10^{-8}$	
										LRRC37A4P	Nucleus accumbens (basal ganglia)	$2.2 \times 10^{-16}$	increased expression
										KANSL1-AS1		$2.3 \times 10^{-13}$	decreased expression
										RP11-707O23.5		$1.2 \times 10^{-11}$	
										RP11-259G18.3		$4.2 \times 10^{-11}$	
										LRRC37A2		$5.8 \times 10^{-11}$	
										RP11-259G18.2		$8.6 \times 10^{-9}$	
										CRHR1-IT1		$1.0 \times 10^{-7}$	
										LRRC37A4P		Putamen (basal ganglia)	$2.9 \times 10^{-12}$
										LRRC37A2	$1.5 \times 10^{-10}$		decreased expression
										KANSL1-AS1	$2.9 \times 10^{-10}$		
										RP11-707O23.5	$1.6 \times 10^{-9}$		
RP11-259G18.3	$4.1 \times 10^{-9}$												
RP11-259G18.2	$1.7 \times 10^{-8}$												
CRHR1-IT1	$5.8 \times 10^{-7}$												
rs12964543	56543095	/	18	Intronic	<i>ZNF532</i>	no eQTL			no eQTL				
rs405509	45408836	/	19	Intergenic	<i>APOE</i>	no eQTL			no eQTL				
rs4417745	241225364	/	2	Intergenic	<i>OTOS</i>	no eQTL			no eQTL				
rs1328032	71420424	/	13	Intergenic	<i>DACH1</i>	no eQTL			no eQTL				

**Table 3.** Summary of eQTL in brain from Braineac and GTEx (continued)

rs2446406	51679783	/	15	Intronic	<i>GLDN</i>	no eQTL	no eQTL
rs7184882	73737373	C	16	In orf	<i>LOC101927998</i>	no eQTL	no eQTL
rs6857	45392254	T	19	3'-UTR	<i>PVRL2</i>	no eQTL	no eQTL
rs302665	87879627	/	11	Intronic	<i>RAB38</i>	no eQTL	no eQTL
rs10507789	71409940	/	13	Intergenic	<i>DACH1</i>	no eQTL	no eQTL

## DISCUSSION

The current work shows that several genetic markers are jointly associated with increased risk for FTD, AD and PD. By leveraging recently developed and validated genetic methods, our findings indicate potential shared genetic architecture among these neurodegenerative diseases and suggest the polygenic nature of sporadic FTD where multiple pleiotropic loci with small effect size contribute to increased disease risk. To the best of our knowledge this is the first large-scale study assessing genetic overlap between sporadic FTD and AD, and sporadic FTD and PD.

Using the *conjunction FDR* (which identifies loci jointly associated with two traits) we found 8 polymorphisms specific to FTD-PD and 1 to FTD-AD; through the *conditional FDR* (which leverages secondary phenotypes, e.g. AD and PD, to improve statistical power for gene discovery) we identified 13 novel FTD associated loci. Of note, all 9 *conjunction FDR* loci were also detected in the *conditional FDR* analyses supporting the notion that the shared polymorphisms increase risk for developing sporadic FTD. Across all analyses, we found notable relevance for the *HLA*, *MAPT* and *APOE* regions.

Building on prior work implicating the involvement of the immune system in PD[26] and AD,[17] we found that rs9268877, on chromosome 6, intergenic between *HLA-DRA* and *HLA-DRB5*, is a shared marker between FTD and PD. The risk allele of this SNP was robustly associated with changes in expression of *HLA-DPA1* (increased expression), *HLA-DRB1* (increased expression) and *HLA-DQA2* (decreased expression) in brain tissues. *HLA-DPA1* is an HLA class II alpha chain paralogue presenting peptides derived from extracellular proteins;[27] this is of particular relevance as impairment of clearance of extracellular debris might increase risk of developing a neurodegenerative condition,[28] including FTD and PD. While *HLA-DRB1* has functions similar to *HLA-DPA1*, *HLA-DQA2* belongs to the HLA class II alpha chain family located in intracellular vesicles: it plays a central role in the peptide loading of MHC class II molecules and releasing the class II-associated invariant chain peptide (CLIP) molecule from the peptide binding site. This prevents the binding of self-peptide fragments prior to MHC II localization within the endolysosome.[29] Taken together, this data supports and further elucidates details about the role of immune system and endolysosomal processes in both FTD and PD.

Our results also point to the *MAPT* region as jointly involved in PD and FTD through two SNPs on chromosome 17 mapping to *WNT3* (wingless-type MMTV integration site family member 3; rs199528) and *CRHR1* (corticotropin releasing hormone receptor 1; rs1358071). The risk alleles of both markers, which tag the H1 *MAPT*-haplotype (Figure 4a), are associated with robust expression changes of *LRRC37A2* (decreased expression), *KANSL1* (decreased expression), *LRRC37A4* (increased expression) and *CRHR1* (decreased expression). The *LRRC37A* (leucine-rich repeat containing 37 member) genes encode plasma membrane proteins that pass from the Golgi to the endoplasmic reticulum (ER) and extracellular areas through vesicle transport[30] reiterating that intracellular vesicle trafficking is a sensitive and potentially vulnerable process in the brain. The *KANSL1* (KAT8 regulatory NSL complex subunit 1) gene encodes a nuclear protein targeting the DNA and involved in histone acetylation with the MLL1 and NSL1 complexes: disruption, mutations or haploinsufficiency of this gene have been associated with the 17q21.31 microdeletion syndrome.[31] *CRHR1* encodes a G-protein coupled receptor for neuropeptides involved in diverse physiological processes including stress and immune responses.[32] Overall, this data strongly suggests that the H1 *MAPT*-haplotype contributes to increased risk for both FTD and PD and its effect is likely mediated by modulating changes in the expression profiles of functionally important *cis*-genes.

We found evidence for involvement of the *APOE* region in FTD. We detected a genome-wide significant association signal in sporadic FTD for rs6857 (3'UTR in *PVRL2*; p-value =  $2.21 \times 10^{-12}$ ) and identified rs405509, intergenic between *TOMM40* (translocase of outer mitochondrial membrane 40) and *APOE* (apolipoprotein E), as jointly associated with both FTD and AD. Rs6857 and rs405509 are in linkage equilibrium (LE;  $r^2=0.1$ ) and are part of two separate haplotypes (Figure 4b): (i) one spanning 12 Kbp (including 13 SNPs [rs142042446, rs12972156, rs12972970, rs34342646, rs283811, rs283815, rs71352238, rs184017, rs2075650, rs34404554, rs11556505, rs778934950 and rs59007384] with  $r^2 \sim 0.8$ ) and encompassing *PVRL2* and *TOMM40* for rs6857 (haplotype a), and; (ii) one spanning 14 Kbp (including 10 SNPs [rs157584, rs71337246, rs7157588, rs7157590, rs1160985, rs760136, rs741780, rs1038025, rs34215622 and rs7259620] with  $r^2 \sim 0.8$ ) and encompassing *TOMM40* and *APOE* for rs405509 (haplotype b). Our data indicate that rs6857 increases risk of FTD, whilst this was not the case for rs405509. No SNP within either haplotype (a or b) was functionally associated with *cis*-regulatory

effects. A large body of evidence implicates *APOE* as a strong genetic risk factor for AD. Whether it is a genetic modifier of disease risk with non-AD neurodegenerative diseases is still unclear. In this respect, several studies in the literature have highlighted this locus as a potential risk factor, with variable effect size, for a variety of conditions including vascular dementia (VD), amyotrophic lateral sclerosis (ALS), PD and dementia with Lewy bodies (DLB).[33] Although early work did not find a clear association between the *APOE* locus and FTD,[34] more recent studies suggest that it might associate with FTD risk[35-37] and accelerate frontotemporal brain atrophy.[38] Given potential overlap between patients diagnosed with clinical FTD and AD,[39] it is unclear whether the current findings reflect a genuine association with FTD or might be inflated by subtle presence of AD or FTD cases in either original study cohort. Nonetheless, this data raises the question whether the detected *PVRL2* SNP tags an FTD-specific risk disease haplotype: future work will be required to further characterize the potential role of this locus – in particular, haplotype a – in FTD.

We also detected several pleiotropic loci between FTD and PD, in addition to *HLA*, *MAPT* and *APOE*. The marker on chr 4, rs7664889, is intronic to the *SCARB2* (scavenger receptor class B member 2) gene that encodes a glycoprotein locating to the membrane of lysosomes and endosomes further supporting the notion of impacted endolysosomal tracts in both FTD and PD. The marker on chromosome 12, rs10784359 maps to the intronic region of *SLC2A13* (solute carrier family 2 member 13) a gene, which is part of the extended locus that includes *LRRK2* indicating that this region may also mediate FTD risk.[40]

Some limitations might apply to studies of this kind. Particularly, in the original works, the diagnoses of FTD, AD and PD were established clinically. This has the potential to introduce subtle clinical overlap across cohorts, thus assessments in large pathology confirmed cohorts is the next valuable and warranted step to take. However, it must be acknowledged that such *ad hoc* cohorts are currently not yet available.

Considered together with prior work, our results overall are a first step in the process of decrypting common underpinnings of FTD, AD and PD: they suggest that a subset of genetic markers in the *HLA* and *MAPT*-H1 regions (and potentially the *APOE* cluster) might be jointly involved in these neurodegenerative disorders. In the case of the *HLA* and *MAPT* loci, differentially expressed genes in



distinct brain regions might account for the clinical and phenotypic differences observed across these disorders.[41] Of note, the relevant pleiotropic SNPs that we found in the *HLA* and *MAPT* regions do appear to exert their effect by influencing expression changes in *cis*-genes involved in immune response, endolysosomal processes, intracellular vesicular trafficking and DNA/chromatin-associated metabolism, further supporting the notion of involvement of these processes in neurodegenerative disease, including FTD.[42] More work will be needed to further characterize our pleiotropic signals, which might hold promise in the future for developing global preventive and therapeutic strategies for FTD, AD and PD.

In summary, we here identified (i) genetic overlap between FTD and AD and FTD and PD, and (ii) novel loci influencing FTD pathobiology with small effect size illustrating that a substantial polygenic component contributes to FTD risk.

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## FIGURE LEGENDS

**Figure 1.** Fold enrichment plots of enrichment versus nominal  $-\log_{10}$  p-values (corrected for inflation) in frontotemporal dementia (FTD) below the standard GWAS threshold of  $p < 5 \times 10^{-8}$  as a function of significance of association with Alzheimer's disease (AD, panel A) and Parkinson's disease (PD, panel B) 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. Blue line indicates all SNPs.

**Figure 2.** 'Conjunction' (a) and 'conditional' (b) Manhattan plots of conjunction and conditional  $-\log_{10}$  (FDR) values for frontotemporal dementia (FTD) (black) and FTD given Alzheimer's disease (AD; FTD|AD, red) and Parkinson's disease (PD; FTD|PD, green). SNPs with conditional and 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. For additional details, see Supplemental Information.

**Figure 3.** Forest plots for (a) rs6857 on chromosome 19 and (b) rs1358071 on chromosome 17.

**Figure 4.** (a) *MAPT*-locus on chromosome 17. The two SNPs, rs1358071 and rs199528 are shared between FTD and PD. Either SNP is in LD with rs1052553 whose major allele (A) tags the H1 *MAPT*-haplotype. The major alleles of rs1358071 and rs199528 are also the effect alleles and they are in LD with rs1052553 ( $r^2=0.75$  and  $0.84$ , respectively). Thus the effect at this locus is H1 driven. (b) *APOE*-locus. The two haplotypes a and b are depicted. Haplotype a is the one driven by rs6857 with 13 SNPs in LD ( $r^2 \sim 0.8$ ; font color: blue). Haplotype b is the one driven by rs405509 with 10 SNPs in LD ( $r^2 \sim 0.8$ ; font color: black). Rs6857 and rs405509, and the respective haplotypes a and b, are in LE ( $r^2 \sim 0.1$ ).