RESEARCH PAPER

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

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2016-314411).

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The IFGC and IPDGC members are listed in the supplementary acknowledgments.

Received 12 July 2016
Revised 24 October 2016
Accepted 1 November 2016
Published Online First 29 November 2016

ABSTRACT

Background 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.

Methods Summary statistics were obtained from the International FTD Genomics Consortium, International PD Genetics Consortium and 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.

Results 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*, $p=2.21\times10^{-12}$), and a suggestive signal for rs1358071 within the *MAPT* region (intronic=*CRHR1*, $p=4.91\times10^{-7}$) 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.

Conclusions 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.

To cite: Ferrari R, Wang Y, Vandrovcova J, *et al*. *J Neurol Neurosurg Psychiatry* 2017;**88**:152–164.

INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder characterised 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 and variable social conduct can characterise the initial phases of AD patients.[3] Similarly, cognitive dysfunctions such as changes in abstract thinking or poor judgement, 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, prefrontal 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 FTD 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] while dementia features can be found in up to 30–80% of PD cases (Parkinson's Disease Dementia (PDD)) in later stages of the disease.[10]

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

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

Disease/trait	Total N	# SNPs	Reference
Frontotemporal dementia (FTD)—IFGC phase I	6462	6 026 384	16
Frontotemporal dementia (FTD)—IFGC phase II	6466	Illumina NeuroX Chip	16
Alzheimer's disease (AD)—phase I	54 162	7 055 881	23
Parkinson's disease (PD)	17 352	7 689 524	24

GWAS, genome-wide association studies; IFGC, International FTD-Genomics Consortium.

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 data sets (eg, 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 (ie, summary statistics) for FTD,[16] AD[23] and PD[24] to identify genetic overlap, that is, pleiotropic effects, across these neurodegenerative disorders.

MATERIALS AND METHODS

Participant samples

We evaluated complete summary statistics (p values and ORs) 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 (see table 1 for additional details).[23] We obtained PD-GWAS summary statistic data from the International Parkinson's Disease Genomics Consortium (IPDGC) consisting of 5333 cases and 12 019 controls with genotyped and imputed data at 7 689 524 SNPs (see table 1 for additional details).[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 I cohort (table 1), consisting of 2154 FTD cases and 4308 controls with genotyped and imputed data at 6 026 384 SNPs.[16] To replicate our findings from the discovery analyses using IFGC phase I, we assessed the p values of pleiotropic SNPs (conditional FDR<0.05; see the 'Statistical analysis' section) within the IFGC phase II sample. The IFGC phase II sample consisted of 1372 FTD cases and 5094 controls genotyped using a partially custom-designed Illumina NeuroX chip (see table 1 for details).[16] The IFGC 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 behavioural variant FTD (bvFTD), semantic dementia (SD), progressive non-fluent aphasia (PNFA) and FTD with motor neuron disease (FTD-MND). As described in the original study, we excluded any cases with clinically diagnosed 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.

Statistical analysis

Using recently developed statistical methods to evaluate pleiotropic effects, we evaluated single nucleoide polymorphysms (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

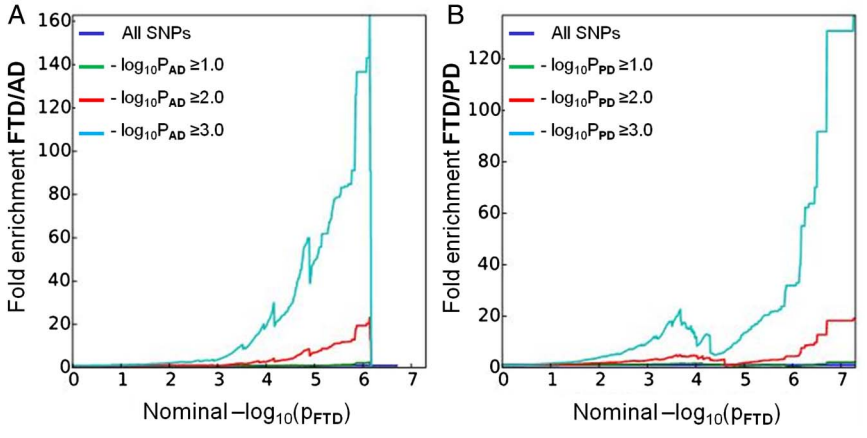

Figure 1 Fold-enrichment plots of enrichment versus nominal $-\log_{10}$ p values (corrected for inflation) in FTD below the standard GWAS threshold of $p<5\times10^{-8}$ as a function of significance of association with AD (A) and PD (B) and at the level of $-\log_{10}(p)\geq0$, $-\log_{10}(p)\geq1$, $-\log_{10}(p)\geq2$ corresponding to $p\leq1$, $p\leq0.1$ and $p\leq0.01$, respectively. Blue line indicates all SNPs. AD, Alzheimer's disease; FTD, frontotemporal dementia; GWAS, genome-wide association studies; PD, Parkinson's disease.

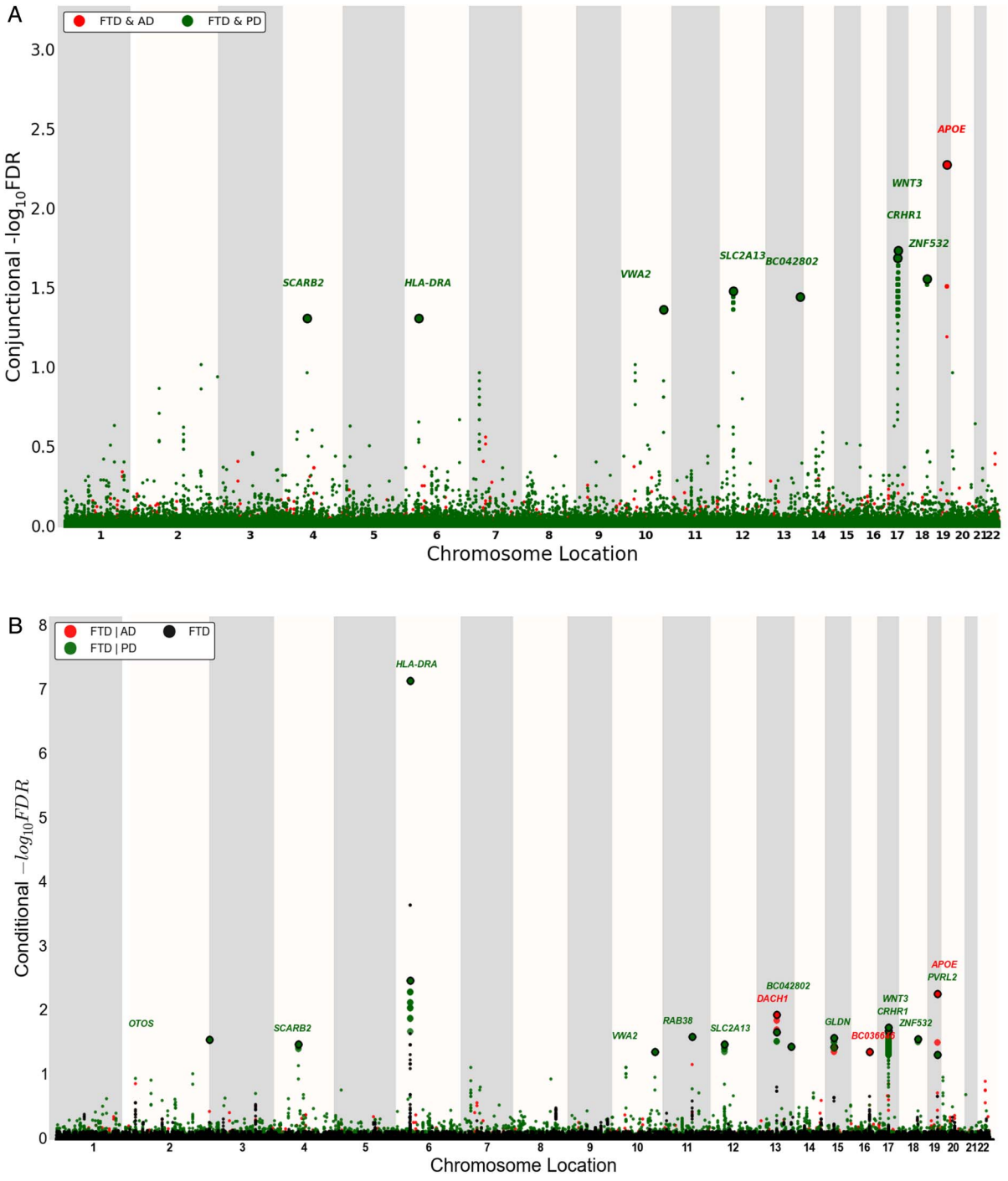

Figure 2 'Conjunction' (A) and 'conditional' (B) Manhattan plots of conjunction and conditional $-\log_{10}$ (FDR) values for FTD (black) and FTD given AD (FTD|AD, red) and PD (FTD|PD, green). SNPs with conditional and conjunction $-\log_{10}$ FDR>1.3 (ie, FDR<0.05) are shown with large points. A black 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 online supplementary information. AD, Alzheimer's disease; FTD, frontotemporal dementia; LD, linkage disequilibrium; PD, Parkinson's disease.

p value$>5\times10^{-8}$). 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 FTD and AD or FTD and PD, we computed conjunction FDR.[17] Conjunction FDR, denoted by $FDR_{trait1\&\ trait2}$, 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 $FDR_{trait1|trait2}$ and FDR $_{trait2|trait1}$.[17] We used an overall FDR threshold of<0.05, which means five 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

Table 2 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	77 087 704	4	Intronic; *SCARB2*	PD	4.84E−02	1.75E−04	8.88E−04	++++
rs9268877	32 431 147	6	Intergenic; *HLA-DRA*	PD	4.84E−02	1.04E−10	7.41E−04	++++
rs676768	116 030 773	10	Intronic; *VWA2*	PD	4.27E−02	3.12E−04	6.14E−04	++++
rs10784359	40 445 750	12	Intronic; *SLC2A13*	PD	3.26E−02	1.58E−04	7.47E−05	++++
rs2893253	107 067 203	13	Intergenic; *EFNB2*	PD	3.55E−02	2.02E−04	1.11E−04	++++
rs199528	44 843 136	17	Intronic; *WNT3*	PD	1.80E−02	4.09E−05	9.82E−16	++++
rs1358071	43 803 189	17	Intronic; *CRHR1*	PD	2.02E−02	4.96E−05	7.76E−15	++++
rs12964543	56 543 095	18	Intronic; *ZNF532*	PD	2.73E−02	1.12E−04	3.08E−04	++++
rs405509	45 408 836	19	Intergenic; *APOE*	AD	5.22E−03	1.25E−05	6.16E−70	++++

AD, Alzheimer's disease; FDR, false discovery rate; FTD, frontotemporal dementia; PD, Parkinson's disease.

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 five 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 I and II, total n=3526 FTD cases and 9402 healthy controls) using the R package *meta* (http://CRAN.R-project.org/package=meta).[25] Briefly, the fixed effects, inverse variance weighted meta-analysis summarises the combined statistical support across independent studies under the assumption of homogeneity of effects. Individual study β estimates (log ORs) are averaged, weighted by the estimated SE.

Expression quantitative trait loci

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 were 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 were 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 ± 1 MB of each SNP, and the significance threshold was $p<1\times10^{-5}$ as per website curators.

RESULTS

Polygenic enrichment in FTD as a function of AD and PD

We observed enrichment for FTD-SNPs (IFGC phase I) across different levels of significance of association with AD and PD (figure 1). For progressively stringent p value thresholds of FTD-SNPs (ie, increasing values of nominal $-\log_{10}P_{FTD}\geq6$), we found 140-fold and 120-fold pleiotropic enrichment as a function of AD ($-\log_{10}P_{AD}\geq3.0$) and PD ($-\log_{10}P_{PD}\geq3.0$) SNPs, respectively (figure 1). Although decreased in magnitude, we observed a similar pattern of enrichment for AD-SNPs and PD-SNPs conditional on FTD-SNPs suggesting symmetric genetic overlap between the three neurodegenerative diseases (see online supplementary figure S1).

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 and table 2). 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 2).

Conditional FDR identifies novel FTD loci

To identify novel SNPs associated with FTD, we ranked IFGC phase I 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) $r^2\geq0.7$ and within 500 kb distance from the reference SNP (based on HapMap 22/21)) (figure 2b, table 3). Then,

Table 3 Novel SNPs showing association with FTD at conditional FDR<0.05

SNP	Position	Chr	Nearest gene	Reference allele	Associated phenotype	Min Cond FDR	IFGC phase I p-value	IFGC phase I OR (95% CI)	IFGC phase II p-value	IFGC phase II OR (95% CI)	Meta-analysis p-value	Meta-analysis OR (95% CI)
rs4417745	241 225 364	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	77 087 704	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	116 030 773	10	Intronic; *VWA2*#	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	71 420 424	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	51 679 783	15	Intronic; *GLDN*#	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	73 737 373	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	44 843 136	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)
rs1358071	43 803 189	17	Intronic; *CRHR1*	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	56 543 095	18	Intronic; *ZNF532*#	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	45 392 254	19	3'-UTR; *PVRL2*#	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	45 408 836	19	Intergenic; *APOE*	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)

ORs provided for the reference allele.
rs676768 not available, proxy SNP rs12782946 from IFGC phase II.
rs2446406 not available, proxy SNP rs2445742 from IFGC phase II.
rs12964543 not available, proxy SNP exm2272683 from IFGC phase II.
rs6857 not available, proxy SNP rs2075650 from IFGC phase II.
AD, Alzheimer's disease; FDR, false discovery rate; FTD, frontotemporal dementia; IFGC, International FTD-Genomics Consortium; PD, Parkinson's disease.

meta-analysis across IFGC phase I and II cohorts revealed one genome-wide significant locus ($p<5\times10^{-8}$): rs6857 on chromosome 19 (3'-UTR=*PVRL2*; conditioning trait=PD; reference allele=T; OR=1.34; 95% CI 1.23 to 1.45; $p=2.21\times10^{-12}$) (table 3, figures 3A and 4B). We also found one suggestive locus (at $p<5\times10^{-7}$) on rs1358071 within the *MAPT* region on chromosome 17 (intronic=*CRHR1*; conditioning trait=PD; reference allele=A; OR=1.19; 95% CI 1.11 to 1.27; $p=4.91\times10^{-7}$) (table 3, figures 3B and 4B).

Expression quantitative trait loci

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 data set, while data extracted from GTEx indicated up to 144 significant eQTLs (table 4). 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 were 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 4).

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 eight polymorphisms specific to FTD-PD and one to FTD-AD; through the conditional FDR (which leverages secondary phenotypes, eg, AD and PD, to improve statistical power for gene discovery) we identified 13 novel FTD associated loci. Of note, all nine 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 α 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

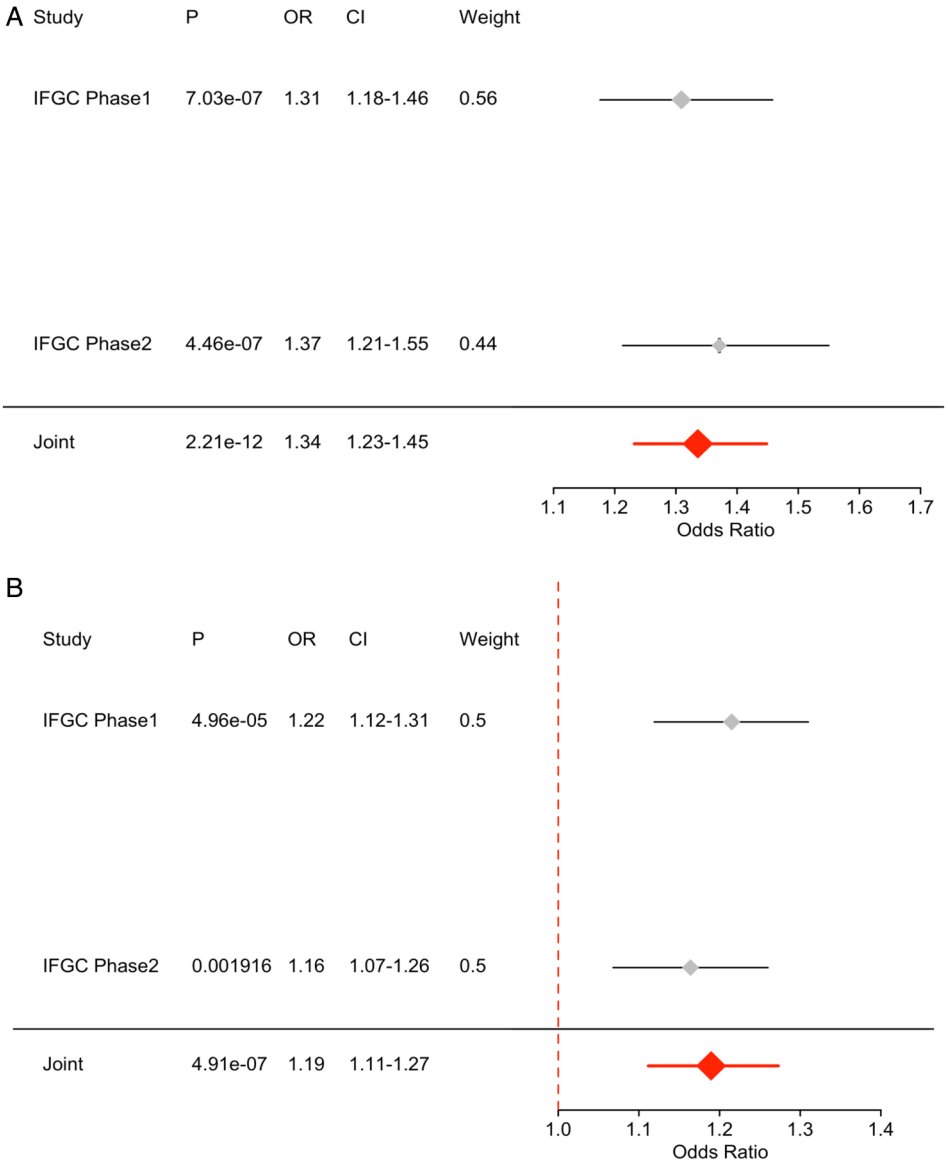

Figure 3 Forest plots for (A) rs6857 on chromosome 19 and (B) rs1358071 on chromosome 17.

condition,[28] including FTD and PD. While *HLA-DRB1* has functions similar to *HLA-DPA1*, *HLA-DQA2* belongs to the HLA class II α 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 localisation within the endolysosome.[29] Taken together, these data support and further elucidate details about the role of immune system and endolysosomal processes in 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, these data strongly suggest that the H1 *MAPT*-haplotype contributes to increased risk for 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=2.21×10^{-12}) and identified rs405509, intergenic between *TOMM40* (translocase of outer mitochondrial membrane 40) and *APOE* (apolipoprotein E), as jointly associated with FTD and AD. Rs6857 and rs405509 are in linkage equilibrium (LE; $r^2=0.1$) and are part of two separate haplotypes

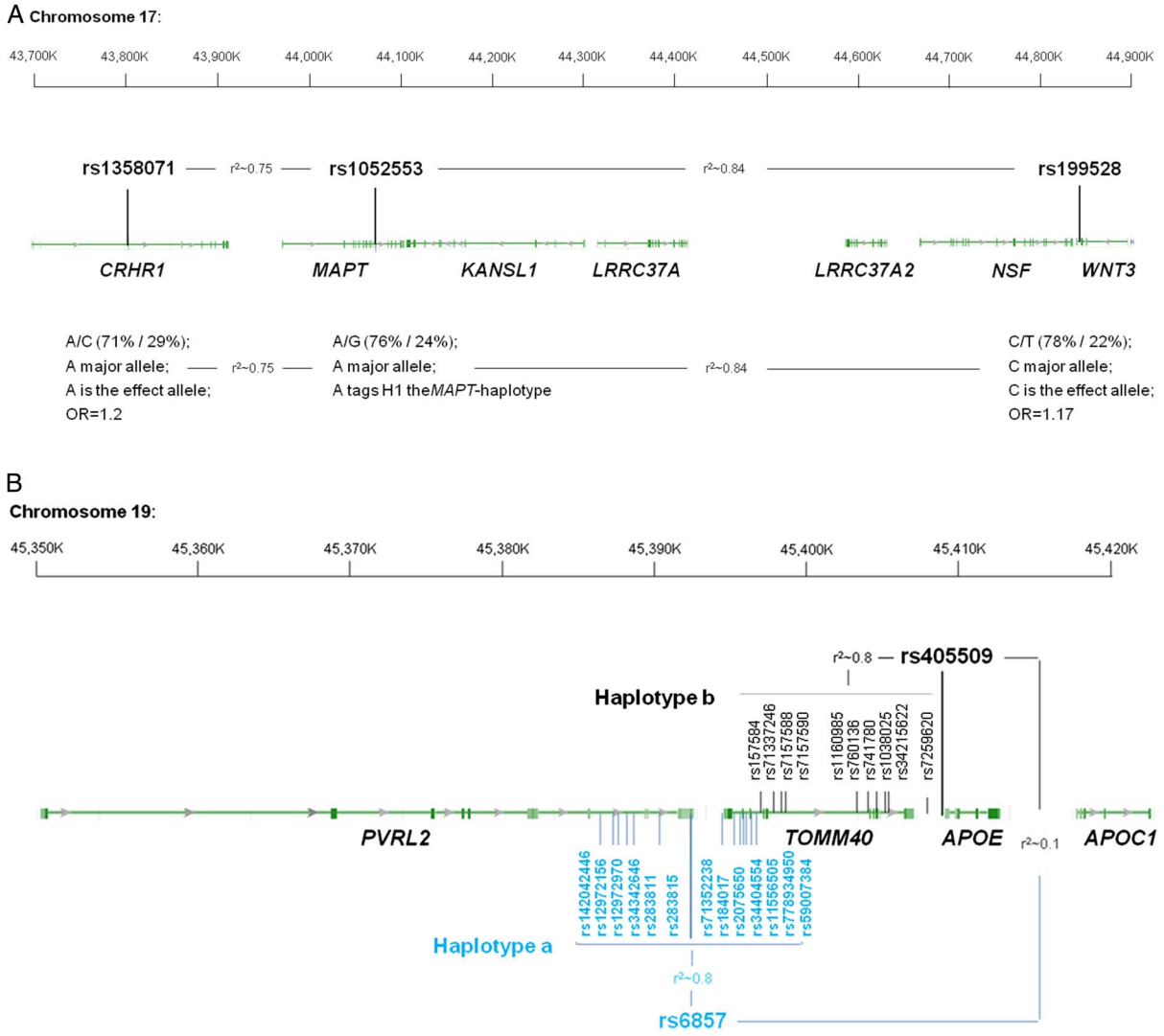

Figure 4 (A) *MAPT*-locus on chromosome 17. The two SNPs, rs1358071 and rs199528, are shared between FTD and PD. Either SNP is in LD with rs1052553 whose major allele (A) tags the H1 *MAPT*-haplotype. The major alleles of rs1358071 and rs199528 are also the effect alleles, and they are in LD with rs1052553 (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^2~0.8; font color: blue). Haplotype b is the one driven by rs405509 with 10 SNPs in LD (r^2~0.8; font color: black). Rs6857 and rs405509, and the respective haplotypes a and b, are in LE (r^2~0.1). FTD, frontotemporal dementia; LD, linkage disequilibrium; LE, linkage equilibrium; PD, Parkinson's disease.

(figure 4b): (1) one spanning 12 kb (including 13 SNPs [rs142042446, rs12972156, rs12972970, rs34342646, rs283811, rs283815, rs71352238, rs184017, rs2075650, rs34404554, rs11556505, rs778934950 and rs59007384] with r^2~0.8) and encompassing *PVRL2* and *TOMM40* for rs6857 (haplotype a), and (2) one spanning 14 kb (including 10 SNPs [rs157584, rs71337246, rs7157588, rs7157590, rs1160985, rs760136, rs741780, rs1038025, rs34215622 and rs7259620] with r^2 ~0.8) and encompassing *TOMM40* and *APOE* for rs405509 (haplotype b). Our data indicate that rs6857 increases risk of FTD, while 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, these data raise the question whether the detected *PVRL2* SNP tags an FTD-specific risk disease haplotype: future work will be required to further characterise 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 FTD and PD. The marker on chromosome 12, rs10784359 maps to the

Table 4 Summary of eQTL in brain from Braineac and GTEx

						eQTL							
						Braineac				GTEx			
SNP	bp	Risk allele	Chr	Location	Nearest gene	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	3.1×10^{-5}	increased expression	HLA-DRB1	Cerebellum	5.2×10^{-8}	Increased expression
											Anterior cingulate cortex	8.8×10^{-8}	
											Putamen	8.9×10^{-7}	
										HLA-DQA2	Cerebellum	1.3×10^{-6}	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	3×10^{-6}	Decreased expression	RP11–259G18.2	Anterior cingulate cortex	4×10^{-14}	Decreased expression
										LRRC37A2		1.7×10^{-12}	
										KANSL1-AS1		4.5×10^{-12}	
										RP11–259G18.3		1.6×10^{-11}	
										LRRC37A2	Caudate (basal ganglia)	4.5×10^{-20}	
										KANSL1-AS1		6.6×10^{-20}	
										RP11–259G18.2		1.9×10^{-19}	
										RP11–259G18.3		3.5×10^{-19}	
										LRRC37A		5.4×10^{-7}	
										RP11–259G18.3	Cerebellar hemisphere	1.1×10^{-18}	
										LRRC37A2		5.7×10^{-17}	
										KANSL1-AS1		2.3×10^{-16}	
										RP11–259G18.2		2×10^{-13}	
										LRRC37A		2×10^{-10}	
rs199528	44843136	C	17	Intronic	*WNT3*	LRRC37A2	Temporal cortex	3×10^{-6}	Decreased expression	RP11–259G18.1	Cerebellar hemisphere	4.6×10^{-10}	Decreased expression
										MAPT-AS1		1.6×10^{-8}	
										MAPT		1.3×10^{-7}	Increased expression
										RP11–259G18.3	Cerebellum	2×10^{-25}	Decreased expression
										KANSL1-AS1		3.9×10^{-20}	
										LRRC37A2		6.2×10^{-19}	
										RP11–259G18.2		1.6×10^{-17}	
										LRRC37A		4×10^{-13}	
										RP11–259G18.1		1.3×10^{-12}	
										MAPT		8.7×10^{-12}	Increased expression
										MAPT-AS1		3.6×10^{-8}	Decreased expression
										SPPL2C		1.3×10^{-7}	
						KANSL1	Hippocampus	1×10^{-5}		KANSL1-AS1	Cortex	2.4×10^{-18}	
										RP11–259G18.3		5.1×10^{-18}	
										RP11–259G18.2		1.3×10^{-17}	
										LRRC37A2		2.5×10^{-14}	
										KANSL1-AS1	Frontal cortex	1.3×10^{-20}	
										RP11–259G18.2		1.5×10^{-16}	
										LRRC37A2		2.3×10^{-16}	
										RP11–259G18.3		8.4×10^{-16}	

Continued

Table 4 Continued

						eQTL							
						Braineac				GTEx			
SNP	bp	Risk allele	Chr	Location	Nearest gene	Gene	Brain region	p-value	Effect of risk allele	Gene	Brain region	p-value	Effect of risk allele
										MAPT		1.3×10^{-7}	Increased expression
										KANSL1-AS1	Hippocampus	2.4×10^{-16}	Decreased expression
										RP11–259G18.3		3.1×10^{-13}	
										RP11–259G18.2		7×10^{-13}	
										LRRC37A2		3.7×10^{-12}	
										KANSL1-AS1	Hypothalamus	1.3×10^{-15}	
rs199528	44843136	C	17	Intronic	*WNT3*	KANSL1	Hippocampus	1×10^{-5}	Decreased expression	LRRC37A2	Hypothalamus	7.6×10^{-15}	Decreased expression
										RP11–259G18.3		1.6×10^{-13}	
										RP11–259G18.2		5.8×10^{-13}	
										LRRC37A		5.6×10^{-8}	
										KANSL1-AS1	Nucleus accumbens (basal ganglia)	1.8×10^{-20}	
										RP11–259G18.3		1.4×10^{-18}	
										LRRC37A2		4.9×10^{-17}	
										RP11–259G18.2		3.4×10^{-16}	
										RP11–259G18.1		7.3×10^{-7}	
										KANSL1-AS1	Putamen (basal ganglia)	2.5×10^{-19}	
										RP11–259G18.3		6.9×10^{-15}	
										LRRC37A2		3.1×10^{-14}	
										RP11–259G18.2		9.6×10^{-11}	
										LRRC37A		1×10^{-6}	
										RP11–259G18.1		1.6×10^{-6}	
rs1358071	43803189	A	17	Intronic	*CRHR1*	LRRC37A4	Cerebellum	7.4×10^{-22}	Increased expression	LRRC37A4P	Anterior cingulate cortex	1.9×10^{-11}	Increased expression
								1.8×10^{-16}		RP11–259G18.2		1.6×10^{-9}	Decreased expression
							Frontal cortex	3.6×10^{-10}		RP11–707O23.5		4.3×10^{-9}	
							Hippocampus	4.7×10^{-10}		LRRC37A2		5.3×10^{-8}	
								5.3×10^{-7}		RP11–259G18.3		7.5×10^{-7}	
							Medulla	2.7×10^{-8}		KANSL1-AS1		9.7×10^{-7}	
							Occipital cortex	1.9×10^{-11}		LRRC37A4P	Caudate (basal ganglia)	7.3×10^{-15}	Increased expression
								5.5×10^{-11}		LRRC37A2		1.7×10^{-14}	Decreased expression
							Putamen	2.2×10^{-6}		RP11–707O23.5		4.5×10^{-13}	
							Substantia nigra	7.3×10^{-11}		RP11–259G18.2		3.1×10^{-12}	
								2.4×10^{-7}		KANSL1-AS1		2.8×10^{-11}	
rs1358071	43803189	A	17	Intronic	*CRHR1*	LRRC37A4	Temporal cortex	3.1×10^{-12}	Increased expression	RP11–259G18.3	Caudate (basal ganglia)	1.1×10^{-10}	Decreased expression
								1.1×10^{-7}		LRRC37A		6.3×10^{-6}	
							Thalamus	5.7×10^{-12}		LRRC37A4P	Cerebellar hemisphere	1.3×10^{-15}	Increased expression
								5.2×10^{-10}		PLEKHM1		4.0×10^{-13}	
							White matter	7.7×10^{-6}		LRRC37A2		2.6×10^{-12}	Decreased expression
						KANSL1	Hippocampus	6.1×10^{-7}	Decreased expression	RP11–259G18.2		1.5×10^{-9}	
										RP11–259G18.3		1.9×10^{-9}	
										RP11–259G18.1		2.6×10^{-9}	
										KANSL1-AS1		6.1×10^{-9}	
										LRRC37A		2.5×10^{-8}	

Continued

Table 4 Continued

						eQTL							
						Braineac				GTEx			
SNP	bp	Risk allele	Chr	Location	Nearest gene	Gene	Brain region	p-value	Effect of risk allele	Gene	Brain region	p-value	Effect of risk allele
										RP11–798G7.5		5.9×10^{-8}	Increased expression
										RP11–707O23.5		2.8×10^{-7}	Decreased expression
										FMNL1		4.2×10^{-7}	Increased
										CTD-2020K17.1		5.2×10^{-6}	expression
										MAPT		6.6×10^{-6}	
										LRRC37A4P	Cerebellum	5.3×10^{-18}	
										PLEKHM1		4.2×10^{-17}	
										RP11–259G18.3		5.6×10^{-16}	Decreased
										LRRC37A2		3.3×10^{-15}	expression
										RP11–259G18.2		6.6×10^{-15}	
										RP11–707O23.5		2.6×10^{-13}	
										RP11–259G18.1		1.5×10^{-10}	
										LRRC37A		1.7×10^{-10}	
										KANSL1-AS1		7.1×10^{-10}	
										RP11–798G7.5		1.4×10^{-9}	Increased
										MAPT		5.4×10^{-9}	expression
rs1358071	43803189	A	17	Intronic	*CRHR1*	KANSL1	Hippocampus	6.1×10^{-7}	Decreased expression	MAPT-AS1	Cerebellum	6.2×10^{-8}	Decreased expression
										FMNL1		2.7×10^{-6}	Increased expression
										KANSL1-AS1	Cortex	1.5×10^{-14}	Decreased
										LRRC37A2		1.6×10^{-11}	expression
										RP11–707O23.5		2.7×10^{-11}	
										LRRC37A4P		3.2×10^{-11}	Increased expression
										RP11–259G18.3		5.7×10^{-11}	Decreased
										RP11–259G18.2		1.3×10^{-10}	expression
										CRHR1-IT1		1.3×10^{-8}	
										PLEKHM1		9.4×10^{-7}	
										RP11–259G18.1		7.8×10^{-6}	
						CRHR1	Medulla	2.9×10^{-6}		LRRC37A2	Frontal cortex	2.5×10^{-11}	
										LRRC37A4P		9.3×10^{-11}	Increased expression
										RP11–259G18.2		2.2×10^{-10}	Decreased
										KANSL1-AS1		8.2×10^{-10}	expression
										RP11–707O23.5		9.8×10^{-10}	
										RP11–259G18.3		1.7×10^{-9}	
										DND1P1		1.6×10^{-6}	
										CRHR1-IT1		2.7×10^{-6}	
										MAPT		4.1×10^{-6}	Increased
										LRRC37A4P	Hippocampus	2.0×10^{-12}	expression
										LRRC37A2		1.6×10^{-11}	Decreased
										RP11–259G18.2		2.7×10^{-11}	expression

Continued

Table 4 Continued

						eQTL							
						Braineac				GTEx			
SNP	bp	Risk allele	Chr	Location	Nearest gene	Gene	Brain region	p-value	Effect of risk allele	Gene	Brain region	p-value	Effect of risk allele
										KANSL1-AS1		4.1×10^{-11}	
										RP11–707O23.5		5.8×10^{-11}	
										RP11–259G18.3		2.5×10^{-8}	
rs1358071	43803189	A	17	Intronic	*CRHR1*	CRHR1	Medulla	2.9×10^{-6}	Decreased expression	CRHR1-IT1	Hippocampus	4.8×10^{-8}	Decreased expression
										DND1P1		2.4×10^{-6}	
										LRRC37A2	Hypothalamus	1.1×10^{-12}	
										RP11–707O23.5		3.2×10^{-11}	
										KANSL1-AS1		8.7×10^{-10}	
										LRRC37A4P		1.8×10^{-9}	Increased expression
										RP11–259G18.2		2.1×10^{-8}	Decreased expression
										RP11–259G18.3		2.3×10^{-8}	
										LRRC37A4P	Nucleus accumbens (basal ganglia)	2.2×10^{-16}	Increased expression
										KANSL1-AS1		2.3×10^{-13}	Decreased expression
										RP11–707O23.5		1.2×10^{-11}	
										RP11–259G18.3		4.2×10^{-11}	
										LRRC37A2		5.8×10^{-11}	
										RP11–259G18.2		8.6×10^{-9}	
										CRHR1-IT1		1.0×10^{-7}	
										LRRC37A4P	Putamen (basal ganglia)	2.9×10^{-12}	Increased expression
										LRRC37A2		1.5×10^{-10}	Decreased expression
										KANSL1-AS1		2.9×10^{-10}	
										RP11–707O23.5		1.6×10^{-9}	
										RP11–259G18.3		4.1×10^{-9}	
										RP11–259G18.2		1.7×10^{-8}	
										CRHR1-IT1		5.8×10^{-7}	
rs12964543	56543095	/	18	Intronic	*ZNF532*	no eQTL				no eQTL			
rs405509	45408836	/	19	Intergenic	*APOE*	no eQTL				no eQTL			
rs4417745	241225364	/	2	Intergenic	*OTOS*	no eQTL				no eQTL			
rs1328032	71420424	/	13	Intergenic	*DACH1*	no eQTL				no eQTL			
rs2446406	51679783	/	15	Intronic	*GLDN*	no eQTL				no eQTL			
rs7184882	73737373	C	16	In orf	*LOC101927998*	no eQTL				no eQTL			
rs6857	45392254	T	19	3′-UTR	*PVRL2*	no eQTL				no eQTL			
rs302665	87879627	/	11	Intronic	*RAB38*	no eQTL				no eQTL			
rs10507789	71409940	/	13	Intergenic	*DACH1*	no eQTL				no eQTL			

eQTL, expression quantitative trait loci.

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 characterise 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 (1) genetic overlap between FTD and AD and FTD and PD and (2) novel loci influencing FTD pathobiology with small effect size illustrating that a substantial polygenic component contributes to FTD risk.

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Acknowledgements The authors thank the International FTD-Genomics Consortium (IFGC), the International Parkinson's Disease Genomic Consortium (IPDGC) and the International Genomics of Alzheimer's Project (IGAP) for providing summary statistics data for these analyses. Further acknowledgments for IFGC, IPDGC and IGAP are found in the online supplementary material.

Contributors 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 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

Contributors RF and RSD analysed and interpreted data and wrote the manuscript. YW, JV, SG, AW, CMK, AJS, CCF, JBB, PM, GSS, WPD, LPS, CPH, JSY, LWB, GDR, BLM, OAA, AMD and JH contributed to the conception or design of the work or the acquisition or analysis of data and critically reviewed the drafted manuscript at multiple stages.

Funding This research was supported by grants from the National Institutes of Health (NIH-AG046374, K01 AG049152), Larry J Hilbom Foundation, the Research Council of Norway (#213837, #225989, #223273, #237250/EU JPND), the South East Norway Health Authority (2013–123), Norwegian Health Association and the KG Jebsen Foundation. RSD was supported by the National Alzheimer's Coordinating Center Junior Investigator Award, ASNR Foundation Alzheimer's Imaging Research Grant Program and NIH/NIDA grant U24DA041123. RF is supported by Alzheimer's Society (grant number 284). For IFGC, IPDGC and IGAP funding sources, see online supplemental acknowledgements.

Disclaimer The funding organisations had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests None declared.

Ethics approval 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.

Provenance and peer review Not commissioned; externally peer reviewed.

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

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J Neurol Neurosurg Psychiatry 2017 88: 152-164 originally published online November 29, 2016
doi: 10.1136/jnnp-2016-314411