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# Frontotemporal dementia and its subtypes: a genome-wide association study

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## Summary

**Background—**Frontotemporal dementia (FTD) is a complex disorder characterised by a broad range of clinical manifestations, differential pathological signatures, and genetic variability. Mutations in three genes—*MAPT*, *GRN*, and *C9orf72*—have been associated with FTD. We sought to identify novel genetic risk loci associated with the disorder.

**Methods—**We did a two-stage genome-wide association study on clinical FTD, analysing samples from 3526 patients with FTD and 9402 healthy controls. All participants had European ancestry. In the discovery phase (samples from 2154 patients with FTD and 4308 controls), we did separate association analyses for each FTD subtype (behavioural variant FTD, semantic dementia, progressive non-fluent aphasia, and FTD overlapping with motor neuron disease [FTD-MND]), followed by a meta-analysis of the entire dataset. We carried forward replication of the novel suggestive loci in an independent sample series (samples from 1372 patients and 5094 controls) and then did joint phase and brain expression and methylation quantitative trait loci analyses for the associated ($p<5 \times 10^{-8}$) and suggestive single-nucleotide polymorphisms.

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**Contributors**

JH, PM, ABS, MAN, RF, and JDR designed the study. JDR, RF and JH did the clinical quality checks. RF coordinated sample collection, received samples at UCL and TTUHSC, and did material quality control for discovery and replication phases. DGH received samples at NIH and coordinated material quality control at NIH. JDR, JBJK, CDS, PRS, WSB, JRH, GMH, OP, LB, ET, EH, IH, AR, MB BB, AP, LB, GB, RG, GF, DG, ES, CF, MS, JC, AL, RB, MLW, KN, CN, IRAM, GYRH, DMAM, JG, CMM, JA, TDG, IGM, AJT, PP, EDH, EMW, AB, EJ, MCT, PP, CR, SOC, EA, RP, JDS, PA, AK, IR, ER, LP, ER, PStGH, ER, GR, FT, GG, JBR, JCMS, JU, JC, SM, AD, VMVD, MG, JQT, JvdZ, TVL, CVB, WD, MC, SFC, ILB, AB, DH, VG, MV, BN, SS, SB, IP, JEN, LEH, MR, BI, MM, GG, SP, WG, MNR, NCF, JDW, MGS, HM, PR, PH, JSS, AG, AR, SR, ACB, RM, FF, CC, LB, MA, MG, MEC, NS, RR, MB, DWD, JEP, NRGR, RCP, DK, KAJ, BFB, WWS, BLM, AMK, HR, JCvS, EGPD, HS, YALP, PS, GL, RC, VN, AAP, MF, AP, GM, PS, HHC, CG, FP, AR, VD, FL, DK, LF, and SPB collected and characterised samples. MK was responsible for genotyping at ICH. JH, PM, ABS, and SPB provided funding for this study. JH, PM, and ABS supervised the study. MAN did statistical and association analyses. RF, MAN, and JH analysed and interpreted the data. AR helped in the interpretation of the e/mQTL data. RF, MAN, JH, and PM wrote the first draft of the paper. All other co-authors participated in preparation of the paper by reading and commenting on drafts before submission.

**Declaration of interests**

RF, DGH, MAN, JDR, AR, JBJK, CDS, WSB, GMH, JRH, OP, LB, ET, EH, IH, AR, MB, BB, AP, CC, NJC, LB, GB, RG, GF, DG, CF, MS, ES, JC, AL, RB, MLW, KN, CN, IRAM, GYRH, DMAM, JG, CMM, JA, TDG, IGM, AJT, PP, EDH, EMW, AB, EJ, MCT, PP, CR, SOC, EA, RP, JDS, PA, AK, IR, ER, LP, ER, PStGH, GR, FT, GG, JBR, JCMS, JU, JC, SM, AD, VMVD, MG, JQT, JvdZ, WD, TVL, SFC, ILB, DH, VG, MV, AB, BN, SS, SB, IP, JEN, LEH, MR, MM, BI, GG, SP, WG, MNR, NCF, JDW, MGS, HRM, PR, PH, JSS, SR, AR, AG, ACB, RM, FF, CC, LB, MA, MG, MEC, NS, MB, KAJ, JEP, WWS, AMK, HR, JCvS, EGPD, HS, YALP, PS, GL, RC, VN, AAP, MF, AP, GM, PS, MK, HHC, CG, FP, AR, VD, FL, DK, LF, SPB, JH, PM, and ABS declare no competing interests.

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**Findings—**We identified novel associations exceeding the genome-wide significance threshold ($p<5 \times 10^{-8}$) that encompassed the *HLA* locus at 6p21.3 in the entire cohort. We also identified a potential novel locus at 11q14, encompassing *RAB38/CTSC*, for the behavioural FTD subtype. Analysis of expression and methylation quantitative trait loci data suggested that these loci might affect expression and methylation *incis*.

**Interpretation—**Our findings suggest that immune system processes (link to 6p21.3) and possibly lysosomal and autophagy pathways (link to 11q14) are potentially involved in FTD. Our findings need to be replicated to better define the association of the newly identified loci with disease and possibly to shed light on the pathomechanisms contributing to FTD.

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## Introduction

Frontotemporal dementia (FTD) is the second most common form of young-onset dementia after Alzheimer's disease and comprises about 10–20% of all dementias worldwide.[1] FTD occurs in roughly three to 15 per 100 000 individuals aged between 55 years and 65 year[2] The disease has an insidious onset: it is familial in 30–50% of patients and affects men and women almost equally.[3] The main clinical syndromes are the behavioural variant[1,4] and the language variants (semantic dementia and progressive nonfluent aphasia).[1,5] FTD also overlap with motor neuron disease (FTD-MND), and atypical parkinsonian disorders.[3] The molecular pathology is heterogeneous and based on the type of neuronal lesions and protein inclusions: 40% or more of patients have frontotemporal lobar degeneration (FTLD) with tau pathology (FTLD-tau), about 50% have TDP-43 (TAR DNA-binding protein 43) pathology (FTLD-TDP),[6] and the remaining 10% have inclusions positive for fused in sarcoma (FUS; FTLD-FUS) or ubiquitin/p62 (FTLD-UPS [ubiquitin proteasome system]).[7] Mutations in three main genes are commonly associated with FTD: the microtubule-associated protein tau (*MAPT*),[8] granulin (*GRN*),[9,10] and *C9orf72*.[11–15] Mutations in the charged multivesicular body protein 2B (*CHMP2B*), the valosin-containing protein (*VCP*), and ubiquilin 2 (*UBQLN2*) genes are rare causes of disease.[13,16] Findings from a previous genome-wide association study (GWAS) of neuropathologically confirmed FTLD-TDP (515 patients *vs* 2509) showed *TMEM106B* to be a disease risk factor.[17]

We did a larger GWAS in samples from people with clinical FTD, and we report results for the discovery, replication, and joint phase analyses, as well as for assessment of the effect on expression and methylation quantitative trait loci (QTL) exerted by associated or suggestive SNPs. We aimed to identify novel genetic risk loci associated with FTD and its subtypes.

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# Methods

## Study population

44 international research groups ([appendix]) contributed samples to this two-stage (discovery phase and replication phase) GWAS of clinical FTD. Investigators at every site obtained appropriate written informed consent from patients and control individuals. Every participating group provided consent for the use of these samples for the purposes of this study. The patients included in the discovery phase were diagnosed according to the Neary criteria[1] for FTD, whereas those included in replication phase were diagnosed according to the Neary criteria,[1] or the revised criteria for behavioural FTD[4] and the language variants of FTD[5] at every collaborative site. For each patient, the diagnosis was made by a neurologist with an interest in FTD or (the minority: <5%) by pathological diagnosis. To cover the most relevant FTD clinical signatures, we included patients diagnosed with behavioural FTD, semantic dementia, progressive nonfluent aphasia, or FTD-MND.[18] We reviewed all patients with a diagnosis of language impairment to exclude cases of the logopenic variant of primary progressive aphasia,[5] most of which are associated with Alzheimer's disease pathology. Samples were obtained from North America (USA and Canada), UK, France, the Netherlands, Belgium, Germany, Denmark, Sweden, Spain, and Italy and all patients were of confirmed European ancestry.

DNA was collected at the three institutions leading this project: the Department of Molecular Neuroscience at University College London (UCL), UK; the Laboratory of Neurogenetics of the National Institute on Aging at the National Institutes of Health (NIH), MD, USA; and the Laboratory of Neurogenetics at the Texas Tech University Health Sciences Center (TTUHSC); TX, USA. All samples were anonymous and stored with a patientspecific coded identification number. Each DNA sample was assessed for quality with gel electrophoresis and DNA concentrations were assessed via spectrophotometer (Nanodrop; Wilmington, DE, USA) or fluorometer (Qubit; Life Technologies, Grand Island, NY, USA). Samples from non-overlapping patients were genotyped at the Laboratory of Neurogenetics of the National Institute on Aging, NIH (40%) or at the core facility at the Institute of Child Health, UCL (60%). We obtained standardised clinical, pathological, and genetic data for each patient from all the collaborating groups ([appendix]). Sporadic cases along with probands from FTD families were included in the study.. We excluded carriers of mutations in *MAPT* and *GRN*. We did not exclude individuals with *C9orf72* expansions because this locus was identified subsequent to sample collection. After quality control of genotyping data and detailed assessment of the clinical diagnosis, we used 2154 and 1372 samples in the discovery phase and replication phase, respectively, for association analysis (table 1). In total, after quality control, we analysed 3526 FTD samples (table 1). Further details about cases included in the study are provided in the [appendix].

Control samples for the discovery phase were taken from studies previously done at the Laboratory of Neurogenetics of the National Institute on Aging at the NIH or at UCL. Control individuals were matched to patients on the basis of population ancestry and

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genotyping platform. Aggregate data for control samples were merged based on overlapping single-nucleotide polymorphisms (SNPs). The selected 7444 control samples were from the USA, UK, Italy, Germany, France, Sweden, and the Netherlands, and were used as controls in previous GWAS;[19] all individuals had given consent for their samples to be used as controls. All were free of neurological illness at the time of sampling, but most had not been screened for the absence of a family history of FTD. For each patient, at least two controls were matched based on compatibility of genetic ancestry estimates by principal components analysis to accommodate the lack of precisely matched clinical controls. After quality control, we included 4308 control samples in this study. The genotyping of controls for the replication phase was done at the Laboratory of Neurogenetics of the National Institute on Aging, NIH (90%) and at the core facility at the Institute of Child Health, UCL (10%). All control samples used in the replication phase were collected from the groups participating in the study (5094 samples passed quality control) and were of European ancestry from the following countries: USA (European American), UK, Italy, France, Germany, Sweden, Spain, and the Netherlands.

## Procedures

For every sample, 2 μg of DNA extracted from either blood or the brain at each collaborative site was collected (whole genome amplified DNA samples were excluded). Samples were securely stored at −20°C. Every sample was first screened for integrity and purity by means of gel electrophoresis on 1% agarose gel, and concentrations were analysed by spectrophotometric (Nanodrop) or fluorometric (Qubit) quantification. The same procedure was implemented at NIH, UCL, and TTUHSC.

Samples from patients and control individuals included in the discovery phase were genotyped using Illumina human 370K, 550K, and 660K Quad Beadchips and Omni Express chips (Illumina Inc, CA, USA). We used Illumina NeuroX custom chips for all samples included in replication phase genotyping. The NeuroX chip is a partially custom-designed chip that specifically targets the main loci associated with several different neurological disorders obtained from GWAS or whole-exome sequencing data. The NeuroX chip holds about 267K SNPs, of which 3759 were FTD-specific, being selected from SNPs that had p values of less than $1 \times 10^{-4}$ during the discovery phase of the study. These SNPs were tag SNPs based on European ancestry linkage-disequilibrium patterns from the most up-to-date data for samples of European ancestry from the 1000 Genomes project.[20] For all GWAS significant hits and candidate SNPs, five linkage-disequilibrium-based proxies or technical replicates were included on the array per locus, tagging associations within +/−250 kb and $r^2$ >0·5 from the most strongly associated proximal SNP. To replicate each locus, we picked the tag SNP most significant in the discovery phase before beginning. If no linkage-disequilibrium-based proxies were available, technical replicates were included. All genotyping arrays (discovery phase and replication phase) were assayed on the Illumina Infinium platform (Illumina, San Diego, CA, USA) at the Laboratory of Neurogenetics of the National Institute on Aging, NIH and at the core facility at the Institute of Child Health, UCL. All genotypes for this project were called centrally using Illumina Genome Studio and all 3759 SNPs of interest for FTD were manually examined to ensure high-quality genotype clusters before data export.

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For the purpose of assessing possible biological relevance for any associated SNPs we used quantitative trait loci (QTL) data generated by the UK Brain Expression Consortium (UKBEC) and the North American Brain Expression Consortium (NABEC) for brain tissues assayed for genome-wide expression and methylation. Details about sample collection, RNA/DNA extraction, and genotyping are provided in the appendix.

## Statistical analysis

We did standard quality control for GWAS data before association analyses. Briefly, for the discovery phase, we extracted overlapping SNPs across all Illumina arrays used. This was done as a means of dealing with the low numbers of matched cases and controls per study site or chip type to facilitate the FTD subtype analyses. We maximised sample size for the subtype analyses by pooling as many possible samples while sacrificing some array content, leaving 228 189 autosomal SNPs as a basis for imputation after the quality control was completed. We excluded samples possibly mismatched for sex by assessing X chromosome heterozygosity. Samples with a call rate of greater than 95% and SNPs with a minor allele frequency greater than 1% were filtered and included in the analyses. We calculated Hardy-Weinberg equilibrium p values (exclusion at p values $<1 \times 10^{-5}$). We assessed non-random missingness per SNP by case-control status with exclusion at p values of less than $1 \times 10^{-5}$ and non-random missingness per SNP by haplotype at p values for exclusion $<1 \times 10^{-5}$. We assessed the presence of relatedness by identifying and excluding first-degree relatives (through identity by descent for any pairwise with an estimate of less than 0·125) and verified European ancestry by principal components analysis compared with HapMap3 populations, with European ancestry ascertained at values for the first two eigenvectors less than six SDs from the population mean for the combined Europeans from Utah and Tuscans from Italy reference samples.[21] After preliminary quality assessment, principal components analysis as implemented in EIGENSTRAT[22] was used to assess matching between cases and controls based on all available cases and controls. Custom coding in R was used to match cases to controls. We treated each subtype (behavioural FTD, semantic dementia, progressive nonfluent aphasia, and FTD-MND) as a separate group in which the two most genetically similar unique controls per case were selected based on eigenvectors 1 and 2 in order to compensate for a lack of precisely matched controls at recruitment. In this respect, matched controls were unique per case and non-redundant across subtype datasets. Thus, cases and controls were matched for each subtype (behavioural FTD, semantic dementia, progressive nonfluent aphasia, and FTD-MND) based on similarity of the first two eigenvectors from principal components analysis and did not overlap across subtypes. We used logistic regression based on imputed dosages to assess the association between each SNP and any of the FTD subtypes, adjusting for eigenvectors 1 and 2 from principal components analysis as covariates. Eigenvectors were generated separately for each subtype, as in the overall sample pool, parameter estimates for the first two were associated with case status at p values of less than 0·05. We did fixed-effects meta-analyses to combine results across subtypes and quantify heterogeneity across subtypes. Genomic inflation was minimal across subtypes and in the meta analysis across subtypes ($\lambda<1{\cdot}05$), therefore we did not use genomic control (see appendix for quantile-quantile plots and $\lambda$ values per discovery phase analysis). SNPs were imputed to August, 2010 release of the 1000 Genomes haplotypes using default settings of minimac and were excluded if their minor allele frequency was less

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than 0·01 or imputation quality (Rsq) was less than 0·30 across all samples, leaving 6 026 385 SNPs for analyses.

For the replication phase, we did standard quality control as for the discovery phase with slight adjustments to account for the bias in NeuroX array content (candidate neurological or neurodegenerative disease SNPs and exonic content). Standard content variants included on the NeuroX array that were used for sample quality control were called using a publicly available cluster file based on more than 60 000 samples.[23] For quality control, variants with GenTrain scores greater than 0·70 (indicative of high-quality genotype clusters) were extracted first to calculate call rates. Samples with call rates greater than 95% were excluded, as were samples whose genetically determined sex conflicted with that from the clinical data and samples exhibiting excess heterozygosity. Next, SNPs overlapping with HapMap phase 3 samples were extracted from the previous subset and pruned for linkage disequilibrium (SNPs excluded if $r^2$ >0·50 within a 50 SNP sliding window), and SNPs with minor allele frequency less than 5%, Hardy-Weinberg equilibrium p values less than $1 \times 10^{-5}$, and per SNP missingness rates greater than 5%. At this stage, we used pairwise identity-by-descent filtering to remove samples that were cryptically related and principal components analysis to identify samples to be excluded when genetic ancestry was not consistent with European descent based on comparisons with HapMap phase 3 reference populations. For replication analyses and due to an effort to maximise the restricted power of this phase compared to the discovery phase, analyses of each subtype included all control samples available, adjusting for the first five eigenvectors only from principal components analysis as covariates in the logistic regression model. No other adjustments were implemented. Additionally, we pooled the individual genotypes from different subsets in the replication phase to help increase statistical power. For details about QTL statistical analysis, see [appendix].

### Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. No pharmaceutical company or other agency paid to write this article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

In the discovery phase, we analysed samples from 2154 patients (table 1) and 4308 controls. We first did separate association analyses for each subtype (behavioural FTD, semantic dementia, progressive nonfluent aphasia, and FTD-MND; table 2) and then undertook a meta-analysis of the entire dataset. Findings from the meta-analysis showed 29 SNPs ([appendix]) exceeding genome-wide significance (p value $<5\times10^{-8}$) at the *HLA* locus (6p21.3), encompassing the butyrophilinlike 2 (MHC class II associated) gene (*BTNL2*) and the major histocompatibility complex, class II, DR alpha (*HLA-DRA*), and DR beta 5 (*HLA-DRB5*; figure, table 3). To identify susceptibility loci for the behavioural FTD subtype we analysed 1377 patient samples (table 2) and 2754 control samples. Two non-coding SNPs at 11q14, locating to intron 1 of the gene *RAB38*, member RAS oncogene family (*RAB38*;

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rs302652) and encompassing *RAB38* and cathepsin C (*CTSC*; rs74977128), passed the genome-wide significance threshold (figure, table 3). Similarly, we did analyses on the other subtypes (table 1): 308 semantic dementia versus 616 controls, 269 progressive nonfluent aphasia versus 538 controls, and 200 FTD-MND versus 400 controls. No SNP reached genome-wide significance in either subtype, probably due to the small sample size. However, several SNPs ([appendix]) showed suggestive associations (p values between $1 \times 10^{-6}$ and $1 \times 10^{-7}$; figure) and warrant further investigation in future screenings.

In the replication phase, we analysed samples from 1372 patients (table 1) and 5094 controls. We assessed the associated SNPs at 6p21.3 (rs9268877, rs9268856, and rs1980493) in the whole replication cohort (table 3). Table 3 shows findings from the surrogate or proxy SNPs assessed for replication at 11q14 in 690 behavioural FTD cases: rs302668 and rs16913634. Combined analyses of discovery and replication phases showed genome-wide significant association at 6p21.3 for all SNPs (table 3). Joint p values of the SNPs at 11q14 only revealed suggestive association for rs302668 (table 3) possibly because of decreased power due to proxy-based replication ($r^2$ of rs302652 to rs302668=0·65).

We then assessed biological relevance for the novel potential loci in human brain cortex tissues assayed for genome-wide expression and methylation. There was no eQTL in our dataset, but assessment of Zeller and colleagues' dataset[38] showed a *cis*-eQTL ($p=5{\cdot}05 \times 10^{-32}$; [appendix]) at 11q14 for rs302652 (chr11:87894881, risk allele T) causing a decreased expression of *RAB38* (Illumina ILMN_2134974 located on chr11:87846656-87846705) in monocytes. These data suggest a role in transcriptional processes *in cis* for this SNP. Furthermore, we identified significant *cis*-mQTL at 6p21.3 after multiple test correction for rs1980493 (risk allele T) that associated with changes in the methylation levels related to *HLADRA* in the frontal cortex (table 4).

To assess potential genetic overlap between FTD and closely related forms of neurodegenerative diseases we selected relevant SNPs for candidate loci and analysed them in our dataset. This analysis included published association studies for amyotrophic lateral sclerosis,[39] progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD),[40] Alzheimer's disease,[41] and FTLD-TDP.[17] We also assessed whether the two loci identified through this study had also been reported previously in other studies of neurological disorders.

For the *C9orf72* locus (for amyotrophic lateral sclerosis), the SNP rs3849942 (effect allele A) was associated with the FTD-MND subtype, which was consistent with our post-hoc analyses (about 23% of expansion carriers in this subtype; table 5; [appendix]). Association was modest in behavioural FTD ($p=7{\cdot}38\times10^{-3}$, OR=1·155) as well as in the entire discovery cohort, but we saw no evidence for association in the semantic dementia or progressive nonfluent aphasia subtypes (table 5). These results confirm that the *C9orf72* locus associates mainly with FTD-MND and to a lesser extent with behavioural FTD ([appendix]).

For the *MAPT* locus (PSP/CBD), the SNPs rs242557 (effect allele G) and rs8070723 (effect allele A)[40] were significantly associated only within the entire cohort and in the behavioural FTD and progressive nonfluent aphasia subtypes (rs8070723 only; table 5). The effect was

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small in our study although in the same direction as in the GWAS for progressive supranuclear palsy (5·46[40] *vs* about 1·2–1·4 in our study; table 5). These results might have arisen because we excluded all known chromosome 17 mutation carriers and because tau pathology is a less common feature of sporadic FTD.

For the *TOMM40/APOE* locus (Alzheimer's disease), the SNP rs2075650 (effect allele G) (table 5). Several Alzheimer's disease GWASs reported association with the minor allele of this SNP with ORs greater than 2·5,[41] but in our study the OR was about 1·3 (table 5). This suggestive association might be indicative of clinical overlap between patients with clinically diagnosed FTD and those with Alzheimer's disease.[42]

For the *TMEM106B* locus (FTLD-TDP), we assessed the three associated SNPs reported by Van Deerlin and colleagues (rs1990622, effect allele A; rs6966915, effect allele C; rs1020004, effect allele T).[17] All achieved modest p values in the entire dataset with lowest p values in the range of $10^{-2}$–$10^{-3}$ only in the behavioural FTD subtype (table 5). Van Deerlin and colleagues' study[17] was done on samples from patients with autopsy-confirmed FTLD-TDP, whereas our cohort is mainly clinically defined. Additionally, the previous study included many *GRN* mutation carriers, who frequently present with behavioural FTD;[17] in our study, *GRN* mutation carriers were excluded. Biochemical evidence has suggested that *TMEM106B* is directly related to *GRN* metabolism,[13] thus we regard our data as a limited replication of the original finding.

Finally, the *RAB38* locus previously showed suggestive association in multiple sclerosis,[43] but the *HLA* locus was reported to associate with multiple sclerosis,[44,45] Parkinson's disease,[19,46] and Alzheimer's disease.[47] None of the SNPs reported in these studies, and which were assessed in our dataset (table 5),[43–46] showed association with FTD, probably suggesting that different risk haplotype sub-structures at the same loci associate with distinctive phenotypes.

## Discussion

FTD is characterised by a broad range of clinical manifestations, differential pathological signatures, and substantial genetic variability, which imply a complex disease mechanisms.[15] In the search for novel disease risk loci associated with FTD we have done an extensive GWAS on a large cohort of mainly clinically diagnosed FTD samples from patients of European ancestry. Several limitations might apply to this study. In view of the phenotype heterogeneity of FTD, and considering that it is a rare neurodegenerative disorder,[2] testing the hypothesis "common variant – common disease" for diseases of this kind is challenging and clearly benefits from large sample sizes. Additionally, our findings might indicate association with specific loci without necessarily implying causality; low heritability due to common variability can also apply. However, the QQ plots and associated λ values ([appendix]) conformed to GWAS standards, lending support to our findings.

We included samples from more than 3500 patients and, thus, we know of no larger GWAS for FTD. We have identified two novel potential loci for FTD: 11q14, encompassing

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*RAB38/CTSC*, was suggestive for the behavioural FTD subtype, and 6p21.3, encompassing the *HLA* locus was statistically significant for the entire cohort.

*RAB38*[48] encodes the transmembrane protein RAB38, which is expressed in the thyroid, in elements of the immune system, and in the brain. From a functional perspective, RAB38 has been shown to mediate protein trafficking to lysosomal-related organelles and maturation of phagosomes (panel).[49,50] *CTSC* is a lysosomal cysteine-proteinase that participates in the activation of serine proteinases in immune and inflammatory cells that are involved in immune and inflammatory processes including phagocytosis of pathogens and local activation and deactivation of inflammatory factors (*Online Mendelian Inheritance in Man* [OMIM] number 602365). The SNP rs302652 at the *RAB38/CTSC* locus shows an eQTL in monocytes[38] associated with decreased expression of *RAB38*, possibly indicating that a decreased function of RAB38 might be the mechanism by which the association at this locus is mediated. Both *RAB38* and *CTSC* are implicated in lysosomal biology and an association with lysosomal and autophagic processes in FTD was previously suggested in two studies of *GRN*[51] and *TMEM106B*.[52] A role for autophagy has also been shown in Parkinson's disease.[53] Our findings will need to be replicated in other FTD cohorts in follow-up studies (eg, fine-mapping studies) to lend support to the proposal that lysosomal biology and autophagy might be involved in the aetiology of FTD.[54]

The genetic association that we identified with the *HLA* locus supports the idea of a link between FTD and the immune system. Our mQTL data showed that risk at this locus is associated with *cis*-changes in methylation levels of *HLA-DRA* in the frontal cortex. *HLA* associations have been previously reported in Alzheimer's disease,[47] Parkinson's disease,[19,46] and multiple sclerosis.[44,45] Additionally, a general involvement of the innate and the adaptive immune responses has been suggested in the pathogenesis of neurodegenerative diseases,[55,56] lending supporting to the idea that the immune system plays an important part within the spectrum of neurological disorders.

Future studies should aim to replicate our findings and, in so doing, elucidate the functional basis of FTD. Additionally, our data indicate that common pathways and processes might underlie different forms of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and FTD. Exploring the possibility of developing therapeutic measures targeting general damage responses could hold promise—after replication and validation of our findings—for the development and implementation of treatment options for these neurological disorders, including FTD.

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## *Panel*: Research in context

### Systematic review

We searched PubMed for the most relevant research articles and review articles on frontotemporal dementia using the following terms: “FTD” and “genetics”, and “FTD” and “review”.[1,4,5,8–17,54] We compared our results to several previously published genome-wide association studies. We identified only one directly relevant study that investigated a pathologically defined subtype of frontotemporal dementia (frontotemporal lobar degeneration with TDP43-positive inclusions; FTLD-TDP).[17] The other studies were of related diseases such as amyotrophic lateral sclerosis,[39] Alzheimer’s disease,[41,47] progressive supranuclear palsy and corticobasal degeneration,[40] multiple sclerosis,[43–45] and Parkinson’s disease.[19,46]

### Interpretation

To the best of our knowledge, ours is the first genome-wide association study in samples from patients with clinical frontotemporal dementia. In view of the complexity and heterogeneity of the disease, mutations in only three main genes—*MAPT*, *GRN*, and *C9orf72*—have been associated with frontotemporal dementia, and these explain only a small proportion of cases. Most importantly, little is known about the mechanisms involved in the development of this disorder. Our findings suggest that common variability in loci that point to immune processes, and possibly to lysosomal biology and autophagy, are involved in the pathobiology of the disease. These findings provide a basis for future replication and functional studies.

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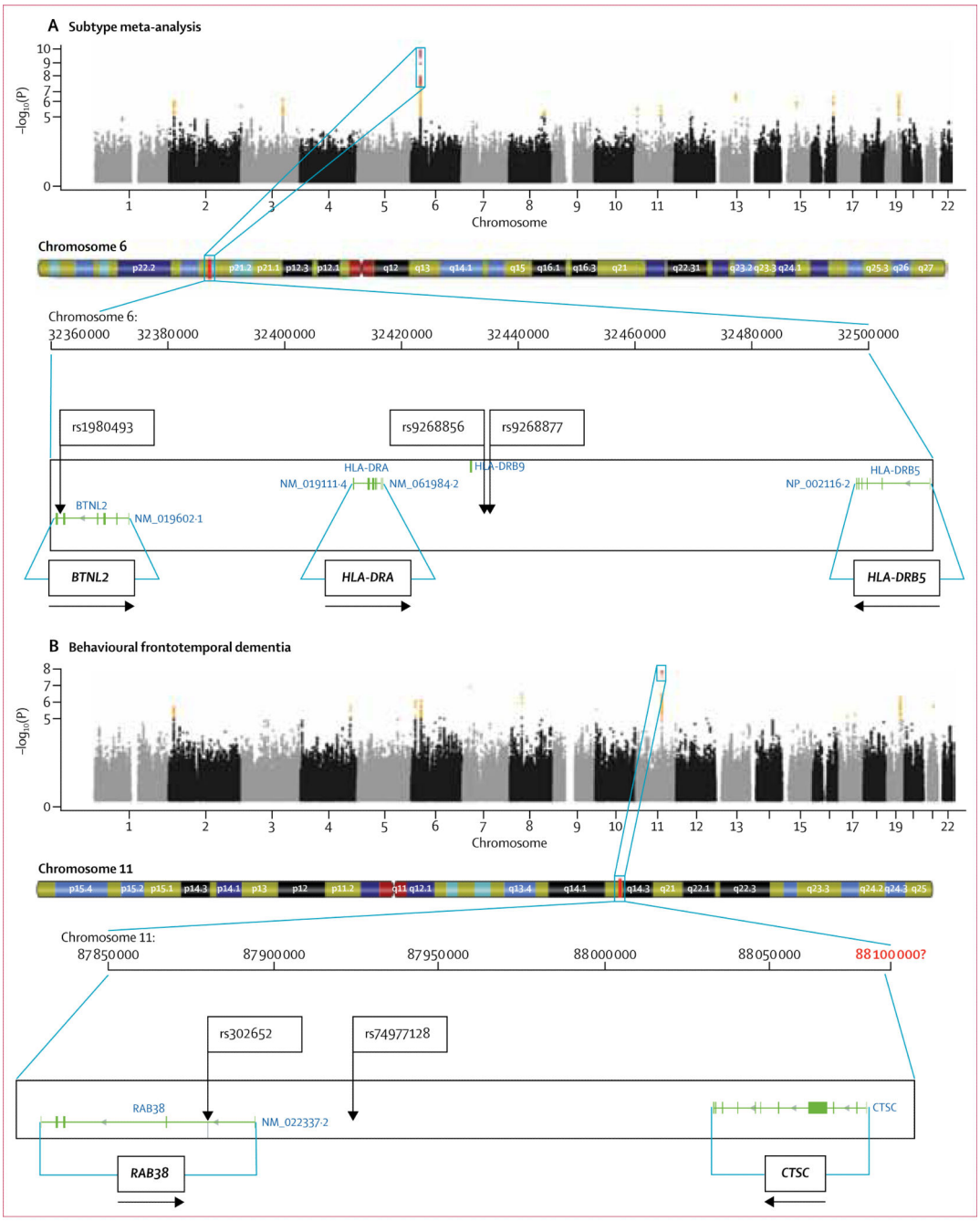


**Figure 1. Manhattan plots identifying regions with genome–wide significant associations**

(A) Manhattan plot for the entire dataset of the discovery phase depicts the associated regionat 6p21.3. Single–nucleotide polymorphisms (SNPs) with smallest p values and their location within or in proximity of the nearest genes are shown. (B) Manhattan plot for the behavioural frontotemporal dementia set in the discovery phase depicts the associated region at 11q14.

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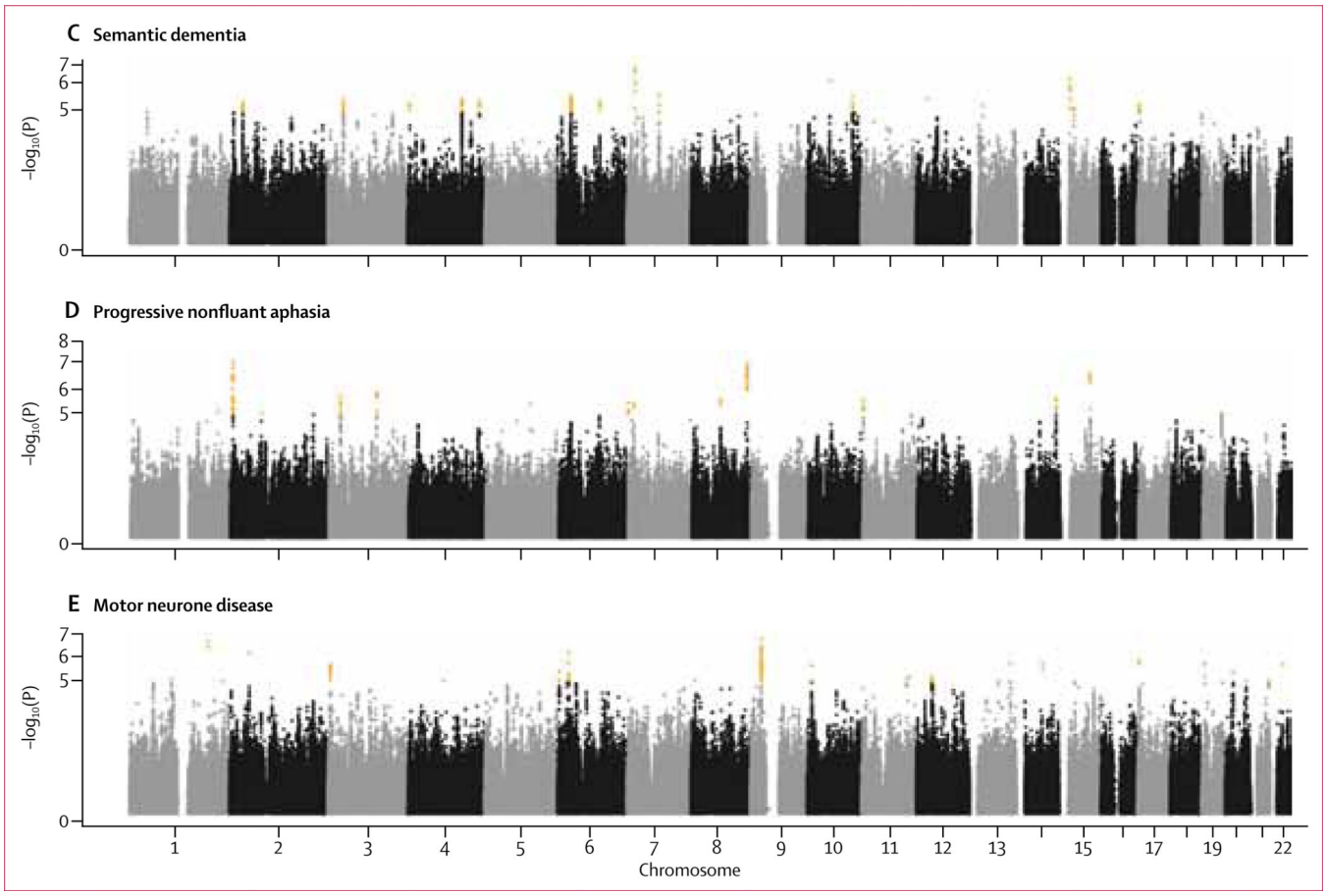


**Figure 2. Manhattan plots identifying regions with genome–wide significant associations**

SNPs with smallest p values and their location within or in proximity of the nearest genes are shown.Manhattan plots for semantic dementia (C), progressive nonfluent aphasia (D), and motor neurone disease (E) frontotemporal dementia sets.

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**Table 1**

Sample characteristics

| | Samples collected (n) | | | Samples included in analysis (n) | | | Samples from women (% [n/N]) | | Mean age at onset | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Discovery phase | Replication phase | Total | Discovery phase | Replication phase | Total | Discovery phase | Replication phase | Discovery phase | Replication phase |
| USA | 706 | 209 | 915 | 579 | 175 | 754 | 44% (257/579) | 49% (85/174) | 60 (23–85); 520 | 63 (24–93); 120 |
| Canada | 25 | 37 | 62 | 24 | 29 | 53 | 52% (12/23) | 57% (8/14) | 64 (43–85); 15 | 59 (43–75); 9 |
| UK | 494 | 372 | 866 | 401 | 284 | 685 | 43% (171/400) | 40% (108/272) | 60 (23–83); 372 | 61 (35–86); 167 |
| Spain | 100 | 330 | 430 | 0 | 309 | 309 | NA | 43% (133/309) | NA | 65 (32–89); 308 |
| France | 238 | 54 | 292 | 205 | 42 | 247 | 44% (91/205) | 48% (20/42) | 62 (39–79); 190 | NA |
| Belgium | 240 | 51 | 291 | 191 | 42 | 233 | 46% (88/191) | 29% (12/42) | 63 (29–90); 191 | 64 (43–84); 42 |
| Netherlands | 333 | 93 | 426 | 250 | 77 | 327 | 52 (129/250) | 40% (31/77) | 58 (29–76); 250 | 61 (51–69); 59 |
| Denmark | 35 | 0 | 35 | 7 | 0 | 7 | 71% (5/7) | NA | 57 (40–62); 7 | NA |
| Germany | 349 | 34 | 383 | 320 | 33 | 353 | NA | 50% (15/30) | 61 (36–83); 243 | 57 (29–72); 30 |
| Sweden | 26 | 112 | 138 | 18 | 98 | 116 | 56% (10/18) | 61% (60/98) | 57 (38–75); 16 | 62 (28–78); 93 |
| Italy | 1035 | 563 | 1598 | 564 | 371 | 935 | 53% (297/561) | 45% (168/371) | 64 (31–83); 429 | 65 (31–87); 353 |
| Australia | 0 | 138 | 138 | 0 | 121 | 121 | NA | 36% (44/121) | NA | 59 (32–77); 112 |
| Meta-analysis | 3581 | 1993 | 5574 | 2559 (2154*) | 1581 (1372*) | 4140 (3526*) | 47% (1186/2552) | 44% (684/1550) | 61 (23–90); 2233 | 62 (24–93); 1293 |

NA=.

*The number of the samples that passed genotyping data quality control and were used for association analyses.

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**Table 2**

Sample characteristics, by subtype

| | Behavioural frontotemporal dementia | | | Semantic dementia | | | Progressive nonfluent aphasia | | | Frontotemporal dementia/ myotrophic lateral sclerosis | | | FTLD-U | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Discovery phase | Replication phase | Total | Discovery phase | Replication phase | Total | Discovery phase | Replication phase | Total | Discovery phase | Replication phase | Total | Discovery phase | Replication phase | Total |
| USA | 315 | 25 | 340 | 147 | 12 | 159 | 81 | 15 | 96 | 36 | 21 | 57 | 0 | 102 | 102 |
| Canada | 22 | 5 | 27 | 1 | 1 | 2 | 0 | 5 | 5 | 1 | 7 | 8 | 0 | 11 | 11 |
| UK* | 207 | 152 | 359 | 75 | 53 | 128 | 69 | 44 | 113 | 50 | 16 | 66 | 0 | 19 | 19 |
| Spain | NA | 194 | 194 | NA | 41 | 41 | NA | 51 | 51 | NA | 13 | 13 | NA | 10 | 10 |
| France | 135 | 30 | 165 | 3 | 0 | 3 | 8 | 3 | 11 | 59 | 8 | 67 | 0 | 1 | 1 |
| Belgium | 135 | 27 | 162 | 13 | 1 | 14 | 22 | 2 | 24 | 21 | 2 | 23 | 0 | 10 | 10 |
| Netherlands | 159 | 37 | 196 | 47 | 31 | 78 | 24 | 6 | 30 | 20 | 3 | 23 | 0 | 0 | 0 |
| Denmark | 2 | NA | 2 | 0 | NA | 0 | 1 | NA | 1 | 4 | NA | 4 | 0 | NA | 0 |
| Germany | 209 | 18 | 227 | 45 | 8 | 53 | 55 | 6 | 61 | 11 | 1 | 12 | 0 | 0 | 0 |
| Sweden | 7 | 53 | 60 | 2 | 20 | 22 | 6 | 10 | 16 | 3 | 8 | 11 | 0 | 7 | 7 |
| Italy | 443 | 186 | 629 | 28 | 22 | 50 | 69 | 86 | 155 | 24 | 16 | 40 | 0 | 61 | 61 |
| Australia* | NA | 56 | 56 | NA | 26 | 26 | NA | 19 | 19 | NA | 20 | 20 | NA | 0 | 0 |
| Meta-analysis | 1634 (1377†) | 783 (690†) | 2417 (2061†) | 361 (308†) | 215 (190†) | 576 (495†) | 335 (269†) | 247 (221†) | 582 (486†) | 229 (200†) | 115 (94†) | 344 (294†) | 0 | 221 (177†) | 221 (177†) |

NA=.

*Used the same control samples.

†The number of the samples that passed genotyping data quality control and were used for association analyses.

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**Table 3**

Characteristics of single-nucleotide polymorphisms exceeding genome-wide significance in the discovery phase

| | Chromosome | Base pair | Candidate gene | Minor allele | Major allele | Frequency of minor allele ($r^2$ when applicable) | Imputation quality | Odds ratio (95% CI) | Standard error | p value |
|---|---|---|---|---|---|---|---|---|---|---|
| **Discovery phase** | | | | | | | | | | |
| Behavioural frontotemporal dementia | | | | | | | | | | |
| rs302652 | 11 | 87894831 | *RAB38* | A | T | 0·259 | 0·9296 | 0·730 (0·65–0·82) | 0·057 | $2{\cdot}02\times10^{-8}$ |
| rs74977128 | 11 | 87936874 | *RAB38/CTSC* | C | T | 0·118 | 0·4182 | 1·815 (1·48–2·24) | 0·107 | $3{\cdot}06\times10^{-8}$ |
| All frontotemporal dementia* | | | | | | | | | | |
| rs9268877 | 6 | 32431147 | *HLA-DRA/HLA-DRB5* | A | G | 0·440 | 0·7783 | 1·331 (1·22–1·45) | 0·045 | $1{\cdot}65\times10^{-10}$ |
| rs9268856 | 6 | 32429719 | *HLA-DRA/HLA-DRB5* | A | C | 0·251 | 0·8563 | 0·752 (0·68–0·83) | 0·050 | $1{\cdot}30\times10^{-8}$ |
| rs1980493 | 6 | 32363215 | *BTNL2* | C | T | 0·147 | 0·9642 | 0·720 (0·69–0·81) | 0·060 | $4{\cdot}94\times10^{-8}$ |
| **Replication phase** | | | | | | | | | | |
| Behavioural frontotemporal dementia | | | | | | | | | | |
| rs302668 (proxy) | 11 | 87876911 | *RAB38* | C | T | 0·325 (0·65) | NA | 0·877 (0.77–0.99) | 0·064 | 0·041 |
| rs16913634 (proxy) | 11 | 87934068 | *RAB38/CTSC* | A | G | 0·104 (0·54) | NA | 0·964 (0.79–1.17) | 0·098 | 0·710 |
| All frontotemporal dementia* | | | | | | | | | | |
| rs9268877 | 6 | 32431147 | *HLA-DRA/HLA-DRB5* | A | G | 0·449 | NA | 1·080 (0·98–1·18) | 0·047 | 0·104 |
| rs9268856 | 6 | 32429719 | *HLA-DRA/HLA-DRB5* | A | C | 0·253 | NA | 0·878 (0·79–0·97) | 0·053 | 0·014 |
| rs1980493 | 6 | 32363215 | *BTNL2* | C | T | 0·145 | NA | 0.85 (0·75–0·97) | 0·068 | 0·020 |
| **Discovery and replication combined** | | | | | | | | | | |
| Behavioural frontotemporal dementia | | | | | | | | | | |
| rs302668 (proxy) | 11 | 87876911 | *RAB38* | C | T | 0·292 (0·65) | NA | 0·814 (0·71–0·92) | 0·064 | $2{\cdot}44\times10^{-7}$ |
| rs16913634 (proxy)† | 11 | 87934068 | *RAB38/CTSC* | A | G | 0·111 (0·54) | NA | 1·248 (1·14–1·37) | 0·049 | $8{\cdot}15\times10^{-4}$ |
| All frontotemporal dementia* | | | | | | | | | | |
| rs9268877† | 6 | 32431147 | *HLA-DRA/HLA-DRB5* | A | G | 0·4445 | NA | 1·204 (1·11–1·30) | 0·039 | $1{\cdot}05\times10^{-8}$ |
| rs9268856 | 6 | 32429719 | *HLA-DRA/HLA-DRB5* | A | C | 0·252 | NA | 0·809 (0·76–0·86) | 0·029 | $5{\cdot}51\times10^{-9}$ |

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| | Chromosome | Base pair | Candidate gene | Minor allele | Major allele | Frequency of minor allele ($r^2$ when applicable) | Imputation quality | Odds ratio (95% CI) | Standard error | p value |
|---|---|---|---|---|---|---|---|---|---|---|
| rs1980493 | 6 | 32363215 | *BTNL2* | C | T | 0·146 | NA | 0·775 (0·69–0·86) | 0·058 | $1{\cdot}57\times10^{-8}$ |

Replication and joint analyses were assessed for the same single-nucleotide polymorphisms (SNPs) at 6p21.3, whereas proxy SNPs were used to assess the association at 11q14 (for which $r^2$ values are included). The odds ratio is shown for the minor allele.

[†]NA=.

[*]Denotes only minimal cross-subtype heterogeneity, with heterogeneity p values ranging from 0·793 to 0·944 based on Cochran's Q test.

[†]Heterogeneity p value <0·01 in the meta-analyses of the discovery and replication phases combined.

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**Table 4**

Summary of association of top hits with *cis*-methylation levels at 6p21.3

| | CpG probe | Single-nucleotide polymorphism | Chromosome | Position (base pair) | Reference allele | Alternate allele | Frequency of reference allele | Imputation quality | Effect estimate of alternate allele (in *Z* units) | Standard error | p value | FDR adjsuted p value | Probe start (base pair) | Probe end (base pair) | Symbol |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Frontal cortex (CpG methylation) | cg21415604 | rs1980493 | 6 | 32363215 | T | C | 0·8361 | 0·9888 | −0·463 | 0·116 | 0·0000701 | 0·00834666 | 31948433 | 31948483 | C4B |
| Frontal cortex (CpG methylation) | cg25764570 | rs1980493 | 6 | 32363215 | T | C | 0·8361 | 0·9888 | −0·652 | 0·116 | $2{\cdot}17\times10^{-8}$ | 0·00000773 | 32407239 | 32407289 | HLA-DRA |
| Frontal cortex (CpG methylation) | cg25764570 | rs9268856 | 6 | 32429719 | C | A | 0·748 | 0·9687 | −0·484 | 0·1 | $1{\cdot}16\times10^{-6}$ | 0·000207417 | 32407239 | 32407289 | HLA-DRA |

Association is shown for rs1980493 and rs9268877, which indicates an involvement of methylation processes and patterns in relation to *HLA-DRA*.

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**Table 5**

rphisms and loci associated with other disorders

| Previous studies | | | This study (discovery phase) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Frequency of reference allele | Reported association | | Frequency of reference allele | Imputation quality (RSQ) | Meta-analysis (all frontotemporal dementia) | | Behavioural frontotemporal dementia | | Semantic dementia | | Progressive nonfluent aphasia | | Frontotemporal dementia/motor neuron disease | |
| | p value (joint) | Odds ratio | | | p value | Odds ratio (95% CI) | p value | Odds ratio (95% CI) | p value | Odds ratio (95% CI) | p value | Odds ratio (95% CI) | p value | Odds ratio (95% CI) |
| ion[40] | | | | | | | | | | | | | | |
| 0·950 (stage 1); 0·940 (stage 2) | $1·50\times10^{-11}$ | 5·46 | 0·765 | 0·8400 | $2·80\times10^{-4}$ | 1·201 (1·09–1·32) | $3·14\times10^{-3}$ | 1·201 (1·06–1·36) | $4·34\times10^{-1}$ | 1·103 (0·86–1·41) | $8·72\times10^{-3}$ | 1·471 (1·10–1·97) | $5·82\times10^{-1}$ | 1·091 (0·80–1·49) |
| 0·470 (stage 1); 0·500 (stage 2) | $4·20\times10^{-70}$ | 0·51 | 0·634 | 0·5246 | $4·82\times10^{-3}$ | 0·853 (1·05–1·31) | $1·27\times10^{-2}$ | 0·841 (0·73–0·96) | $3·20\times10^{-1}$ | 0·867 (0·65–1·15) | $2·02\times10^{-1}$ | 0·815 (0·59–1·11) | $8·23\times10^{-1}$ | 0·961 (0·68–1·36) |
| 0·150 | $1·80\times10^{-157}$ | 2·53 | 0·141 | 0·9978 | $8·81\times10^{-7}$ | 1·304 (0·69–0·85) | $1·37\times10^{-6}$ | 1·383 (0·63–0·82) | 3·64×10− | 1·326 (0·58–0·98) | $8·69\times10^{-1}$ | 0·976 (0·76–1·38) | $2·06\times10^{-1}$ | 1·252 (0·56–1·13) |
| | | | | | | | | | | | | | | |
| 0·260 | $1·01\times10^{-8}$ | 1·20 | 0·253 | 0·9996 | $4·38\times10^{-4}$ | 1·166 (1·07–1·27) | $7·38\times10^{-3}$ | 1·155 (0·78–0·96) | $9·89\times10^{-1}$ | 1·010 (0·80–1·25) | $9·03\times10^{-1}$ | 0·990 (0·79–1·31) | $2·12\times10^{-6}$ | 1·957 (0·39–0·68) |
| | | | | | | | | | | | | | | |
| 0·679 | $1·08\times10^{-11}$ | 1·64 | 0·600 | 0·9588 | $7·88\times10^{-2}$ | 1·080 (0·99–1·16) | $5·85\times10^{-3}$ | 1·144 (1·04–1·26) | $8·36\times10^{-1}$ | 0·978 (0·80–1·20) | $8·98\times10^{-1}$ | 0·985 (0·79–1·23) | $3·11\times10^{-1}$ | 0·876 (0·68–1·13) |
| 0·679 | $1·63\times10^{-11}$ | 1·64 | 0·596 | 0·9675 | $1·21\times10^{-1}$ | 1·070 (0·87–1·02) | $5·74\times10^{-3}$ | 1·144 (1·04–1·26) | $5·27\times10^{-1}$ | 0·936 (0·76–1·15) | $7·26\times10^{-1}$ | 0·961 (0·77–1·20) | $3·62\times10^{-1}$ | 0·888 (0·69–1·14) |

| | Reference allele | Alternate allele | Previous studies | | | This study (discovery phase) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Frequency of reference allele | Reported association | | Frequency of reference allele | Imputation quality (RSQ) | Meta-analysis (all frontotemporal dementia) | | Behavioural frontotemporal dementia | | Semantic dementia | |
| | | | | p value (joint) | Odds ratio | | | p value | Odds ratio (95% CI) | p value | Odds ratio (95% CI) | p value | Odds ratio (95% CI) |
| rs1020004 (12255778) | T | C | 0·767 | $5·00×10^{-11}$ | 1·66 | 0·693 | 0·9538 | $4·59×10^{-1}$ | 1·030 (0·95–1·12) | $5·71×10^{-2}$ | 1·104 (1·00–1·22) | $8·53×10^{-1}$ | 0·980 (0·79– |
| **Chromosome 6** | | | | | | | | | | | | | |
| Multiple sclerosis[43,44] | | | | | | | | | | | | | |
| *RAB38* | | | | | | | | | | | | | |
| rs1386330 (87819427) | C | T | 0·130 | $2·00×10^{-6}$ | NA | 0·141 | 0·9694 | $3·35×10^{-1}$ | 1·050 (0·85–1·06) | $6·09×10^{-1}$ | 1·040 (0·84–1·10) | $7·60×10^{-1}$ | 1·040 (0·72– |
| *HLA-DRA* | | | | | | | | | | | | | |
| rs3129871 (32406342) | A | G | 0·230 | $8·94×10^{-81}$ | 1·99 | 0·131 | 0·9734 | $4·80×10^{-2}$ | 1·122 (1·00–1·26) | $2·10×10^{-1}$ | 1·095 (0·79–1·05) | $1·25×10^{-1}$ | 1·254 (0·60– |
| Parkinson's disease[45,46] | | | | | | | | | | | | | |
| *HLA-DRA* | | | | | | | | | | | | | |
| rs3129871 (32406342) | A | C | 0·504 | $5·70×10^{-15}$ | 1·72 | 0·337 | 0·9379 | $3·43×10^{-1}$ | 0·961 (0·88–1·04) | $3·15×10^{-1}$ | 0·949 (0·95–1·16) | $4·94×10^{-1}$ | 1·078 (0·75– |
| rs3129882 (32409530) | G | A | 0·450 | $1·90×10^{-10}$ | 1·26 | 0·456 | 0·9992 | $3·36×10^{-2}$ | 1·086 (0·85–0·99) | $3·27×10^{-2}$ | 1·106 (0·82–0·99) | $7·52×10^{-1}$ | 1·033 (0·79– |

NA=. FLTD-TDP=frontotemporal lobar degeneration with TDP43-positive inclusions. RSQ=



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