Gene-based association studies report genetic links for clinical subtypes of frontotemporal dementia

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ABSTRACT

Genome-wide association studies in frontotemporal dementia showed limited success in identifying associated loci. This is possibly due to small sample size, allelic heterogeneity, small effect sizes of single genetic variants, and the necessity to statistically correct for testing millions of genetic variants. To overcome these issues, we performed gene-based association studies on 3348 clinically identified frontotemporal dementia cases and 9390 controls (discovery, replication and joint-cohort analyses). We report association of APOE and TOMM40 with behavioural variant frontotemporal dementia, and ARHGAP35 and SERPINA1 with progressive non-fluent aphasia. Further, we found the "2 and "4 alleles of APOE harbouring protective and risk increasing effects, respectively, in clinical subtypes of frontotemporal dementia against neurologically normal controls. The APOE-locus association with behavioural variant frontotemporal dementia indicates its potential risk-increasing role across different neurodegenerative diseases, whereas the novel genetic associations of ARHGAP35 and SERPINA1 with progressive non-fluent aphasia point towards a potential role of the stress-signalling pathway in its pathophysiology.

Keywords: gene-based association study; GWAS; FTD; MAGMA; stress-signalling pathway

Abbreviations: bvFTD = behavioural variant of frontotemporal dementia; GWAS = genome-wide association study; FTD = frontotemporal dementia; MND = motor neuron disease; LD = linkage disequilibrium; MAGMA = Multi-marker Analysis of GenoMic Annotation; PNFA = progressive non-fluent aphasia; SNP = single nucleotide polymorphism

Introduction

Frontotemporal dementia (FTD) is one of the leading causes of dementia in patients younger than 65 years of age (Rabinovici and Miller, 2010; Seelaar et al., 2011). It is characterized by degeneration of the frontal and anterior temporal lobes leading to a decline in behaviour and language. FTD is a heterogeneous condition clinically, pathologically and genetically (Cairns et al., 2007; Seelaar et al., 2011). Clinically, it is broadly categorized into the behavioural variant (bvFTD) and the language variant or primary progressive aphasia (PPA), which is further categorized into semantic dementia and progressive non-fluent aphasia (PNFA). There is frequent overlap between the presence of FTD and a number of motor diseases such as parkinsonian disorders, corticobasal syndrome, progressive supranuclear palsy and motor neuron disease (FTD-MND) (Rohrer et al., 2009). The underlying pathological spectrum of FTD, termed frontal temporal lobar degeneration (FTLD), is based on neuronal lesions and protein inclusions such as with tau or TAR-DNA binding protein (TDP)-43 pathology. Besides the Mendelian genes MAPT, GRN and C9orf72 that are causal in up to 30–50% of familial FTLD cases, rare variability in few other genes has been implicated in 55% of cases (Rohrer et al., 2009; Ferrari et al., 2013; Woollacott and Rohrer, 2016). To date, few large genome wide association studies (GWAS) have been performed for FTD (Van Deerlin et al., 2010; Ferrari et al., 2014, 2015) reporting an association with TMEM106B for FTLD with TDP-43 pathology (Van Deerlin et al., 2010), and with the locus comprising RAB38 and CTSC as well as the HLA-DRA/HLA-DRB5 locus for bvFTD and FTD, respectively (Ferrari et al., 2014).

In a typical GWAS, an association test on a single variant [single nucleotide polymorphisms (SNPs) or Indels] is performed to map genes associated with a phenotype; however, many independent risk alleles for a given phenotype can be localized within a gene (Yang et al., 2012; Tada et al., 2014; Zhang et al., 2014). Hence a classical GWAS approach will be less powered to detect genes containing many independent risk alleles (Hagg et al., 2015). A joint-variant gene-based test that combines independent association signals within a gene while accounting for the linkage disequilibrium (LD) between variants can overcome this limitation. A number of approaches have been reported to perform joint-SNP gene-based analysis: the permutation test—where empirical evidence of association of the combined test statistics is calculated by shuffling the samples while keeping markers intact—is currently considered the golden standard (Liu et al.,

2010). However, the requirement of genotype data and computational burden limits its use. Recently, our group developed a new approach called Multi-marker Analysis of GenoMic Annotation (MAGMA) that uses a multiple regression model to perform joint-SNP gene-based analysis using GWAS summary data (de Leeuw et al., 2015).

In this study, we performed a hypothesis free gene-wide association study on FTD subtypes (bvFTD, semantic dementia, PNFA and FTD-MND) using GWAS summary files obtained from the International FTD-Genomics consortium (IFGC) (Ferrari et al., 2014). We used the MAGMA software to perform the gene-based analysis. We report results of discovery, replication and combined cohort analyses for each FTD subtype; we also assessed individual risk variants for associated genes, which can be used for replication in the individual variant genotype setting.

Methods

Samples

The dataset used in the FTD-GWAS was described previously (Ferrari et al., 2014). Briefly, 44 international groups contributed clinical FTD samples. Patients were diagnosed according to the Neary criteria or the revised criteria for bvFTD and language variants of FTD (Neary et al., 1998; Gorno- Tempini et al., 2011; Rascovsky et al., 2011). Approximately 3% of cases were pathologically confirmed. To each individual case two ancestry and age-matched neurologically normal controls were assigned. For the current study we used the GWAS summary datasets of the discovery and replication cohorts of each FTD subtype, bvFTD (discovery: 1377 cases and 2754 controls; replication: 690 cases and 5092 controls), PNFA (discovery: 269 cases and 538 controls; replication: 221 cases and 5092 controls), semantic dementia (discovery: 308 cases and 616 controls; replication: 189 cases and 5092 controls) and FTD-MND (discovery: 200 cases and 400 controls; replication: 94 cases and 5092 controls). Overall bvFTD, PNFA, semantic dementia and FTD-MND constituted 61.74%, 14.64%, 14.85% and 8.78% of the total FTD cases, respectively.

Statistical analysis

We performed the joint-SNP gene-based analysis using MAGMA (de Leeuw et al., 2015). The MAGMA approach is based on a multiple linear principal components regression model. By projecting the multivariate LD matrix of SNPs in a gene it first extracts principal components that explain genetic variation. These principal components are further used as predictors of a phenotype under a linear regression framework. MAGMA then uses Fisher's test to compute P-values to test association between a gene and the phenotype.

We used 19 418 hg19 annotated protein-coding genes to perform the analysis. As all the samples involved were of European descent, we used the 1000 Genomes phase 1 European reference population to estimate LD between variants (1000 Genomes Project Consortium et al., 2012). We only considered SNPs in the 5'- and 3'-untranslated region (UTR) and the open reading frame for the joint-SNP gene-based tests. This strategy resulted in loss of cis- regulatory variants, but was more stringent and open reading framespecific. The schematic representation of the strategy for multi-stage gene-wide association analysis for FTD and subtypes is described in Supplementary Fig. 1. We performed separate gene-based tests using discovery and replication datasets for each FTD subtype reported previously by the IFGC (Ferrari et al., 2014). We performed gene-based tests using only those variants that were either genotyped or imputed with imputation score 40.50. Moreover, we only considered common variants with minor allele frequency 40.01. For individual

FTD subtypes, 4 303 460 and 55 375 variants were available for the gene-based analysis in the discovery and replication cohorts, respectively. Further, 16 313 and 10 349 genes that contained at least one variant within the 5'-, 3'-UTR and open reading frame, were tested for association with a given FTD subtype in the discovery and replication cohorts, respectively. To identify additional genes associated with individual FTD subtypes, we meta-analysed the gene-based P-values obtained in the discovery and replication cohorts using the Stouffer's combination approach for the sample size weighted combination of P-values. For each FTD subtype we tested association of total 16 920 genes either in the discovery or replication cohorts.

To correct for multiple association tests performed for 16 920 genes with one of the four subtypes of

FTD, we applied the conservative Bonferroni correction method establishing a gene-wide significance threshold at 7.388 □ 10□7 [= 0.05 / (4 □ 16 920)]. To identify genes associated with any FTD subtype, we combined the gene-based test statistics for either subtype (bvFTD, semantic dementia, PNFA and FTD-MND) using the sample size weighted Stouffer's combination method.

Functional characterization of associated genes

We downloaded the gene expression profiles of the associated genes across 13 human brain tissues (in alphabetical order: amygdala, anterior cingulate cortex, caudate, cerebral hemisphere, cerebellum, cortex, frontal cortex, hippocampus, nucleus accumbens, putamen, spinal cord, substantia nigra) using the GTEx portal (Mele et al., 2015) (GTEx Analysis V6 dbGaP Accession phs000424.v6.p1). We also investigated the functional annotations of variants that are in LD (r240.8 in the 1000 Genomes phase 1 European panel) with SNPs used in deriving gene-based P-values of the associated genes using software HaploReg (Ward and Kellis, 2012) (version 4.1) and RegulomeDB (Boyle et al., 2012) (version 1.1).

Results

Associations with frontotemporal dementia and its subtypes

Behavioural variant frontotemporal dementia

In the discovery cohort, two genes passed the gene-wide significant P-value threshold 7.39 □ 10□7: TOMM40 (P = 5.79 □ 10□8) and APOE (P = 1.37 □ 10□7). In the replication cohort the P-values were 6.40 □ 10□5 for TOMM40 and 1.69 □ 10□3 for APOE suggesting consistency of associations across independent bvFTD samples. No other genes passed the significance threshold for the bvFTD subtype (Supplementary Fig. 2A).

Interestingly, in the discovery cohort the SNPs rs7412 and rs429358, which determine three epsilon (") alleles "2, "3 and "4 of the APOE gene, were among the SNPs driving its association with bvFTD, with P-values 0.023 (rs7412) and 5.04 □ 10□6 (rs429358). In the replication cohort rs429358 was not genotyped, whereas information on rs769449, an intronic variant in high LD (r2 = 0.82, 1000 Genomes phase 1 European population) with rs429358, was available; here the P-values were 0.222 for rs7412 and 1.95 □ 10□4 for rs769449.

To check whether the association of TOMM40 with bvFTD was independent of the epsilon variants, we reperformed the gene-based test on TOMM40 gene using only those variants in negligible LD (r250.2) with rs7412 and rs429358 in 1000 Genomes phase 1 European panel. This analysis showed moderate association of TOMM40 with bvFTD (P = 7.51 □ 10□6; Table 1) suggesting that the TOMM40 gene harbours signals for the risk of bvFTD that are independent of the epsilon alleles of APOE gene.

The summary statistics of variants used for deriving gene- based P-values for TOMM40 and APOE are given in Supplementary Tables 1A and B, respectively, and the regional plots are shown in Fig. 1A and B. The regional plots show many variants in TOMM40 with P-values50.05 that are in negligible LD (r250.2) with rs769449, a proxy of epsilon variant rs429358. Furthermore we did not find significant gene-based association of RAB38 gene, which was identified as associated with bvFTD using the SNP-based GWAS. The association P-value of RAB38 gene in our joint-SNP gene-based analysis might be diluted due to inclusion of many non-risk variants, refer to Supplementary Fig. 3A and B for regional association plots at the RAB38 gene showing many nonrisk variants within the gene's transcription site.

Progressive non-fluent aphasia

The joint-cohort (discovery and replication) analysis revealed association for ARHGAP35 (P = 2.95 □ 10□7) and SERPINA1 (P = 3.02 □ 10□7) with PNFA (Table 1 and Supplementary Table 2). The regional plots for ARHGAP35 and SERPINA1 (Fig. 2A and B, respectively) show a robust LD block only for ARHGAP35 for which all variants show association P-values50.05 with PNFA (also refer to Supplementary Table 2A). In SERPINA1 many LD independent variants with PNFA association P-values50.05 can be observed.

Semantic dementia

No gene exceeded the gene-wide significance threshold 7.39 □ 10□7, possibly because of the smaller sample size for this subtype, thus reduced power. The top gene identified in the combined analysis was WDR66 (P = 9.50 □ 10□6, Table 1).

Frontotemporal dementia-motor neuron disease

No gene reached gene-wide significant association in the FTD-MND subtype. However, the top genes for FTDMND were C9orf72 and IFNK with gene-based association P-value in joint-cohort analysis 1.23 □ 10□6 and 1.77 □ 10□6, respectively. Neither gene showed associations with any other subtypes of FTD (Table 1).

Frontotemporal dementia meta-analysis

The meta-analysis across all subtypes (bvFTD, semantic dementia, PNFA and FTD-MND) identified association of TOMM40 and APOE. It is worth noting that the bvFTD samples make nearly two-thirds of the total sample; hence, P-values for association with bvFTD dominated the metaanalysis of FTD subtypes.

Risk of APOE alleles on frontotemporal dementia subtypes

Based on the gene-based association results with TOMM40 and APOE we extended our analysis to the epsilon alleles and genotypes. We compared each FTD case cohort (discovery, replication and combined) against a total of 9390 ancestry-matched controls using Fisher's exact test. For replication cohorts, we used rs769449 as a proxy for rs429358. The distribution of epsilon alleles and genotypes in our cohort is given in Supplementary Tables 3 and 4, respectively. We established the significance threshold for allele associations as 4.17 □ 10□3 (0.05/12) correcting for three epsilon alleles and four FTD subtypes. We identified that the "2 allele significantly reduces the risk of bvFTD [odds ratio (OR) = 0.772, P = 3.88 □ 10□4] and semantic dementia (OR = 0.651, P = 3.64 □ 10□3). We observed marginal association (P50.05) of "2 allele with PNFA (OR = 0.706, P = 0.019) and moderate with FTD-MND (OR = 0.571, P = 6.01 □ 10□3). The "4 allele significantly increased risk of bvFTD (OR = 1.278, P = 8.14 □ 10□6) and semantic dementia (OR = 1.438, P = 2.93 □ 10□4). The association for the disease increasing effect of "4 allele was marginal (P50.05) for PNFA (OR = 1.298, P = 0.011), and the result was inconclusive for FTDMND (OR = 1.188, P = 0.202) possibly due to underpowered sample size.

We also quantified the risk of homozygous "4/"4 genotype on FTD subtypes. We used 1.25 □ 10□2 as a significance threshold for association testing of four subtypes with homozygous "4/"4 genotype. The

homozygous "4/"4 genotype showed significant association with increased risk for bvFTD (OR = 1.627, P = 0.012), PNFA (OR = 2.367, P = 8.52 □ 10□3) and semantic dementia (OR = 2.333, P = 9.08 □ 10□3) with notable P- and OR-values for PNFA and semantic dementia compared to the effect size of a single copy of "4 allele for respective FTD subtypes. We did not perform association between homozygous "2/"2 genotypes with FTD subtypes due to its low frequency in our cohort.

Functional characterization of associated genes

We extracted the gene expression profiles of APOE, TOMM40, ARHGAP35 and SERPINA1 across different human brain tissues from the GTeX database (Mele et al., 2015) (see Supplementary Fig. 4A–D for respective genes). The APOE, TOMM40 and ARHGAP35 genes are strongly expressed in different brain tissues. Notably the anterior cingulate cortex (Brodmann area 24) and the frontal cortex (Brodmann area 9) are the top tissues for ARHGAP35 gene expression. The anterior cingulate cortex is one of the early affected regions in FTD patients (Seeley et al., 2006, 2008); this area is reported to be involved in language control and resolving non-verbal conflict (Abutalebi et al., 2012). The SERPINA1 gene did not show strong expression in the brain tissues.

We used the HaploReg (version 4.1) software (Ward and Kellis, 2012) to investigate functionally annotated variants linked with variants used in deriving gene-based P-values of TOMM40 (those in negligible LD r250.2 with epsilon variants), ARHGAP35, and SERPINA1, respectively. We found that all SNPs used in deriving gene-based P-values of TOMM40, ARHGAP35 and SERPINA1 are in strong LD (r240.8, in 1000 Genomes phase 1 European panel) with at least one variant residing in the regulatory regions such as chromatin marks or DNase hypersensitive sites, suggesting a possible regulatory role (see Supplementary Tables 5A–C for HaploReg results for variants in TOMM40, ARHGAP35 and SERPINA1, respectively). Overall we identified 21, 56 and 93 regulatory variants in LD with SNPs driving gene-based P-values of TOMM40, ARHGAP35 and SERPINA1 genes, respectively. We further ranked these regulatory variants based on their functional relevance using the RegulomeDB (version 1.1) software (Boyle et al., 2012) (see Supplementary Tables 6A–C for detailed RegulomeDB results of these variants mapped to TOMM40, ARHGAP35 and SERPINA1 genes, respectively).

Discussion

Here we report novel genetic insight into FTD and its clinical subtypes using a joint-SNP gene-based approach. We identified association of the TOMM40 and APOE genes with bvFTD, and the ARHGAP35 and SERPINA1 genes with PNFA.

Our study suggested TOMM40 as the top gene in bvFTD. The TOMM40 gene encodes a channel forming subunit of the translocase of the mitochondrial outer membrane (TOM complex), which facilitates translocation of unfolded proteins from the cytosol into the mitochondrial intermembrane space for use in oxidative phosphorylation (Mager et al., 2011). Recently, Bannwarth et al. (2014) reported mitochondrial origin in pathogenesis of FTDALS diseases through association of variants in CHCHD10. There is growing evidence suggesting a role of mitochondria in neurodegenerative disorders, also including Parkinson's disease (Parker et al., 1989; Schapira et al., 1990), Huntington's disease (Moran et al., 2012) and Alzheimer's disease (Petrozzi et al., 2007; Hroudova et al., 2014). Our conditional analysis suggests the TOMM40 association with bvFTD being independent from the epsilon alleles; however, interdependence with the epsilon alleles cannot be fully excluded at this stage. Future, more sophisticated, sequencing studies might further confirm the independence we highlight here.

The association of the APOE gene with bvFTD was primarily driven by SNPs rs7412 and rs429358 (or variants in strong LD such as rs769449) suggesting that, if on one hand the TOMM40 association is independent from the epsilon alleles, on the other the APOE association (which is, however, lower comparatively to that of TOMM40) is dependent on the epsilon alleles lending support for the inference to be made that two different haplotypes at this locus might confer risk differently. The SNPs rs7412 and rs429358 determine the APOE epsilon alleles "2, "3 and "4. We quantified the risk of epsilon alleles across clinical subtypes of FTD diagnosed using the Neary's criteria against neurologically normal controls, and saw that the "2 and "4 alleles showed protective and increased disease risk effects, respectively, for FTD subtypes (strong associations for bvFTD and semantic dementia, and marginal associations for PNFA and FTD-MND). Interestingly, individuals carrying homozygous copies of the "4 allele revealed higher risk for PNFA and semantic dementia (OR42.3) suggesting dose-dependent effect for each copy of a gene. The pattern of association of epsilon alleles with FTD subtypes might reflect the potential overlap between

patients diagnosed with clinical FTD and Alzheimer's disease (van der Zee et al., 2008; Bang et al., 2015) or a genuine association with FTD and its subtypes given the increasing number of studies arguing in favour of the latter hypothesis (Engelborghs et al., 2006; Agosta et al., 2009; Seripa et al., 2011; Rubino et al., 2013; Ferrari et al.,2015).

In the CNS, APOE is synthesized in response to neuronal injury or stress to initiate the neuronal repair mechanisms. The "4 carriers are hypothesized to have reduced neuronal repair capacity compared to the other alleles (Rubino et al., 2013). The protein products of APOE were also reported to modulate neuroinflammation (Tai et al., 2015). The hypothesis of enhanced inflammatory response in FTD patients is supported by both neuroimaging and genetic studies (Cagnin et al., 2004; Rainero et al., 2009). Tau pathology is found in up to □50% of FTLD cases (Halliday et al., 2012); interestingly the knock-in study in mice showed association between epsilon alleles and the concentration of hyper-phosphorylated tau in neurons: "4 knock in mice showed higher concentration of hyper-phosphorylated tau than "3 knock in mice (Inbar et al., 2010).

It is worth noting that in this scenario the APOE locus and the epsilon allelic variability might impact processes such as modulation of neuronal repair mechanisms, neuroinflammation, broad lipid metabolism, synaptic plasticity, neuronal toxicity and tau phosphorylation (Verghese et al., 2011). It is likely that variability in the genes or isoforms turnover or larger haplotype blocks at this locus, coupled with ageing, might influence negative outcomes in brain and thus support our findings from a biological and functional perspective. More work should be directed towards testing these possibilities in the future.

Our study is the first to report association of the ARHGAP35 and SERPINA1 genes with PNFA. The ARHGAP35 gene encodes the glucocorticoid receptor DNA-binding factor 1, which is a repressor of glucocorticoid receptor (hGR) transcription. At the cellular level, the glucocorticoid receptor mediates the maintenance of basal and stress-related homeostasis. The second gene we found associated with PNFA was SERPINA1, which was previously reported to be associated with cortisol level (Bolton et al., 2014) (top variants: rs11621961, rs12589136, rs2749527) and serum lipid profile (Inouye et al., 2012) (top variant: rs1303). The non-synonymous variant rs1303 (Glu400Asp) in SERPINA1, which is also in moderate LD with morning plasma cortisol level associated variant rs12589136 (Bolton et al., 2014), showed PNFA association P-values50.05 in both discovery and replication cohorts (Supplementary Table 2B). The top

SERPINA1 variant in the PNFA discovery cohort rs11628917 (this variant in moderate LD with rs1303) is an established blood eQTL (Westra et al., 2013), with the C allele increasing SERPINA1 expression in blood (Inouye et al., 2012; Westra et al., 2013). We observed that the C allele at rs11628917 increased the risk of PNFA in both discovery (OR = 2.893, P = 2.58 □ 10□6) and replication (OR = 1.385, P = 0.077) cohorts. The SERPINA1 gene encodes protease inhibitor □1-antitrypsin enzyme, which inhibits cleavage of the reactive centre loop of the corticosteroid binding globulin (CBG) by ceasing neutrophil elastase activity (Lewis and Elder, 2014). The reactive centre loop cleavage by neutrophil elastase reduces the CBG binding affinity to cortisol. During stress CBG activity is positively correlated with the glucocorticoid access to the brain (Moisan et al., 2014). Increased glucocorticoid level in brain can activate glucocorticoid signalling through binding to the low affinity glucocorticoid receptors and result in reduced neurogenesis and impaired neuroplasticity (Anacker et al., 2011). This hypothesis suggesting the role of enhanced glucocorticoid signalling leading to neurodegeneration in PNFA patients is based on our current preliminary report on association of ARHGAP35 and SERPINA1 with PNFA; this finding will need to be further explored and replicated in an independent cohort.

In conclusion, we report genetic associations for FTD and its subtypes—notably of the TOMM40 and APOE genes with bvFTD and the ARHGAP35 and SERPINA1 genes with PNFA—using the joint-SNP gene-based approach.

This approach improves power of the association test by combining signals across variants in a functional unit such as a gene. Replication and functional characterization of these findings will further establish their role in pathology of FTD and help towards a better management of the disease.

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Supplementary material

Supplementary material is available at Brain online.

Appendix 1

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. Herna´ ndez; 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. Clarimo´ n; A. Lleo´ ; R. Blesa; M. Landqvist Waldo¨ ; 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.

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