Neurobiology of Aging 123 (2023) 111–128

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Study of Alzheimer's disease- and frontotemporal dementia-associated genes in the Cretan Aging Cohort

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ARTICLE INFO

Article history:
Received 26 January 2022
Revised 3 July 2022
Accepted 4 July 2022
Available online 11 July 2022

Keywords:
Genetics
Alzheimer's disease
Frontotemporal dementia
TARDBP
Glutamate dehydrogenase

ABSTRACT

Using exome sequencing, we analyzed 196 participants of the Cretan Aging Cohort (CAC; 95 with Alzheimer's disease [AD], 20 with mild cognitive impairment [MCI], and 81 cognitively normal controls). The *APOE* ε4 allele was more common in AD patients (23.2%) than in controls (7.4%; $p < 0.01$) and the *PSEN2* p.Arg29His and p.Cys391Arg variants were found in 3 AD and 1 MCI patient, respectively. Also, we found the frontotemporal dementia (FTD)-associated *TARDBP* gene p.Ile383Val variant in 2 elderly patients diagnosed with AD and in 2 patients, non CAC members, with the amyotrophic lateral sclerosis/FTD phenotype. Furthermore, the p.Ser498Ala variant in the positively selected *GLUD2* gene was less frequent in AD patients (2.11%) than in controls (16%; $p < 0.01$), suggesting a possible protective effect. While the same trend was found in another local replication cohort (n = 406) and in section of the ADNI cohort (n = 808), this finding did not reach statistical significance and therefore it should be considered preliminary. Our results attest to the value of genetic testing to study aged adults with AD phenotype.

1. Introduction

In addition to age, a major risk factor for Alzheimer's disease (AD; the commonest form of dementia in the elderly) is positive family history for dementia (Lautenschlager et al., 1996). This genetic predisposition is most pronounced for the rare, young-onset, familial form of AD, where causative variants in 3 genes (*PSEN1, PSEN2* and *APP)* have been reported (Bird, 2005; Loy, 2014; Nussbaum and Ellis, 2003). On the other hand, for the frequent sporadic, late-onset, form of AD, intensive research toward the identification of risk factors has brought to light the ε4 allele of the *APOE* gene, a genotype that significantly increases the risk for the disease and reduces the age of disease onset

Abbreviations: AD, Alzheimer's disease; hGDH1, human glutamate dehydrogenase 1; hGDH2, human glutamate dehydrogenase 2; NGS, Next Generation Sequencing; WES, Whole Exome Sequencing; WGS, Whole Genome Sequencing; FTD, Frontotemporal Dementia; CAC, Cretan Aging Cohort; MCI, Mild Cognitive Impairment; MMSE, Mini Mental Status Examination; EDTA, Ethylenediaminetetraacetic Acid; VaD, Vascular Dementia; LBD, Lewy Body Dementia.

Part of the data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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https://doi.org/10.1016/j.neurobiolaging.2022.07.002

(Corder et al., 1993; Liu et al., 2013). Furthermore, numerous variants in many different genes have been reported to be associated with AD (such as *TREM2, ADAM10, CR1, CLU, EPHA1, PICALM, UNC5C, SORL1, PLD3, etc.*), conferring though lower risk compared to the risk attributed to the *APOE* ε4 genotype (Baker et al., 2019; Bird, 2005; Cruchaga et al., 2014; Del-Aguila et al., 2015; Jansen et al., 2019; Kunkle et al., 2019; Lacour et al., 2017; Lambert et al., 2013; Ridge et al., 2016; Van Cauwenberghe et al., 2016). In addition, genes implicated in glutamate metabolism, including the *GLUD1* and *GLUD2* genes (encoding for human glutamate dehydrogenase 1 and 2; hGDH1 and hGDH2, respectively), appear to play a major role in neurodegenerative processes (Bao et al., 2009; Lawingco et al., 2020; Plaitakis et al., 2010). The isoenzymes hGDH1 and hGDH2 are involved in brain glutamate metabolism and glutamatergic signaling, an area of increasing interest for the pathophysiology of AD (Ghosh et al., 2020; Sanabria-Castro et al., 2017). These isoenzymes have been a long-time focus of our and other research groups working on the pathophysiology of neurodegeneration (Bao et al., 2009; Burbaeva et al., 2005; Dimovasili et al., 2021; Kim and Baik, 2019; Mathioudakis et al., 2019; Plaitakis et al., 2010; Plaitakis and Zaganas, 2001; Zaganas et al., 2009; Zaganas et al., 2014).

Despite intense efforts to decipher the genetic mechanisms related to AD, including well-conducted GWAS studies that explain a sizeable proportion of the disease risk (Kunkle et al., 2019; Lawingco et al., 2020; Shen and Jia, 2016), research so far seems to have only scratched the surface of such complex and multifactorial processes. However, new hope was kindled by the development of Next Generation Sequencing (NGS) technologies employed in Whole Exome Sequencing (WES), and Whole Genome Sequencing (WGS) (Foo et al., 2012; Goodwin et al., 2016; Kumar et al., 2013). Using an NGS approach several rare variants of interest for AD have surfaced, such as rare variants in the *TREM2* gene (Bellenguez et al., 2017; Cukier et al., 2017; Del-Aguila et al., 2015; Ming et al., 2021; Sims et al., 2017). These studies have enabled better understanding of the AD-associated pathophysiological processes involving the TREM2 protein, which acts as a receptor and enhances the uptake of lipoprotein (e.g., LDL, HDL) and apolipoprotein (e.g., APOA1/2, APOE 2/3/4, CLU) particles in microglia (Ulland and Colonna, 2018; Ulrich et al., 2017).

Hampering these genetic studies is the less-than-optimal accuracy of the clinical criteria for the diagnosis of AD and the overlapping phenotypes with other diseases, such as frontotemporal dementia (FTD) (Arvanitakis et al., 2019). As a matter of fact, the sensitivity and specificity of clinical diagnosis of AD can be as low as 70% and 40%, respectively (Beach et al., 2012). Thus, it is not uncommon to revise the antemortem diagnosis of AD to a different dementia disorder after performing autopsy (Grandal Leiros et al., 2018; Mok et al., 2004). To overcome this clinical uncertainty, imaging and biological markers are increasingly used in the differential diagnosis of dementia (Bourbouli et al., 2017; Niemantsverdriet et al., 2018; Paraskevas et al., 2017; Vemuri et al., 2011). Among these biological markers, genetic testing is offering a promising approach for accurate diagnosis, and especially for differentiating AD from FTD (Blauwendraat et al., 2018; Cruchaga et al., 2012a; Goldman and Van Deerlin, 2018; Lautenschlager et al., 1996; Loy et al., 2014; Perrone et al., 2018).

The most common genetic change causing FTD is the *C9orf72* hexanucleotide repeat expansion. This expansion is also the most common genetic cause of Amyotrophic Lateral Sclerosis (ALS), which forms part of the same pathophysiological spectrum with FTD (Blauwendraat et al., 2018; Hinz and Geschwind, 2017). Other frequent genetic causes of FTD are pathogenic variants in the progranulin (*GRN*), the Microtubule Associated Protein Tau (*MAPT*) and the Transactive Response DNA Binding Protein (*TARDBP*) genes (Ahmed et al., 2007; Baker et al., 2006; Borroni et al., 2009; Cruts et al., 2006; Hutton et al., 1998; Kabashi et al., 2008; Kwiatkowski et al., 2009; Mackenzie et al., 2006; Neumann et al., 2006; Synofzik et al., 2012; Vance et al., 2009). Interestingly, rare patients diagnosed with FTD have been found to harbor pathogenic variants in the *PSEN1* and *PSEN2* genes that, as described above, are a cause of AD (Blauwendraat et al., 2018; Lohmann et al., 2012; Mendez and McMurtray, 2006). Inversely, even though variants in *MAPT, GRN* and *C9orf72* are typically related with FTD phenotypes, recent studies have demonstrated that these genetic alterations are also associated with other forms of dementia (Guven et al., 2016; Jin et al., 2012; Pastor et al., 2016).

In the present report, based on a multidisciplinary study (Thalis-Multidisciplinary Network for the Study of Alzheimer's Disease; Thalis-MNSAD), we aimed to investigate the genetic factors that contribute to cognitive impairment in the Cretan Aging Cohort (CAC) (Zaganas et al., 2019), a culturally homogeneous population of well-studied older adults residing in the prefecture of Heraklion, Crete, Greece. WES data were obtained from a representative subgroup of AD and Mild Cognitive Impairment (MCI) patients, as well as cognitively intact controls, who had been thoroughly characterized by neuropsychiatric evaluations and assessment of numerous clinical, epidemiological and biological factors. Here we report the results of an initial genetic characterization of the CAC in respect to *APOE* ε4 genotype and variants in the *PSEN1, PSEN2, APP, GLUD1, GLUD2* and 16 FTD-associated genes.

2. Methods

2.1. Participants

The participants in the initial genetic study were selected from the CAC, a sample of 3140 community-dwelling adults, aged 60–100 years, who were recruited from a set of Primary Health Care (PHC) facilities in the district of Heraklion, Crete, Greece (Zaganas et al., 2019). To create this cohort, all individuals over 60 years of age visiting the PHC centers, for any reason, were asked by the collaborating PHC physicians to participate in this study and to provide informed consent. Consenting individuals were invited to a structured interview based on a detailed questionnaire that included the Mini Mental Status Examination (MMSE) and questions on demographics (i.e., age, gender, marital status, education, place of residence), current physical and mental health problems and medication use. Based on the MMSE score, a universal cutoff of 23/24 points was used for referral of patients for further evaluation (Fig. 1a).

In the second phase of the study, those participants showing potential cognitive impairment as defined by a MMSE score of <24 ($n = 636$) were referred for a thorough neuropsychiatric and neuropsychological assessment to establish a final diagnosis and 344 of them accepted. Among those with MMSE ≥ 24, a subgroup of 181 participants (matched for place of residence with the MMSE <24 group) were also invited for further evaluation in the second phase of the study and 161 accepted (Fig. 1a). This second phase of the study also employed detailed questionnaires in the context of a semistructured interview to assess the medical and other determinants of health status in detail. Neuropsychological assessment was performed by trained neuropsychologists, using a battery of validated tests that evaluated among others, memory, visuoconstructive ability, speech, visuomotor processing, attention, executive functions, depressive symptomatology and anxiety, quality of life, daily functional capacity, and behavioral disturbances. Finally, blood was drawn and used for DNA extraction, as described below,

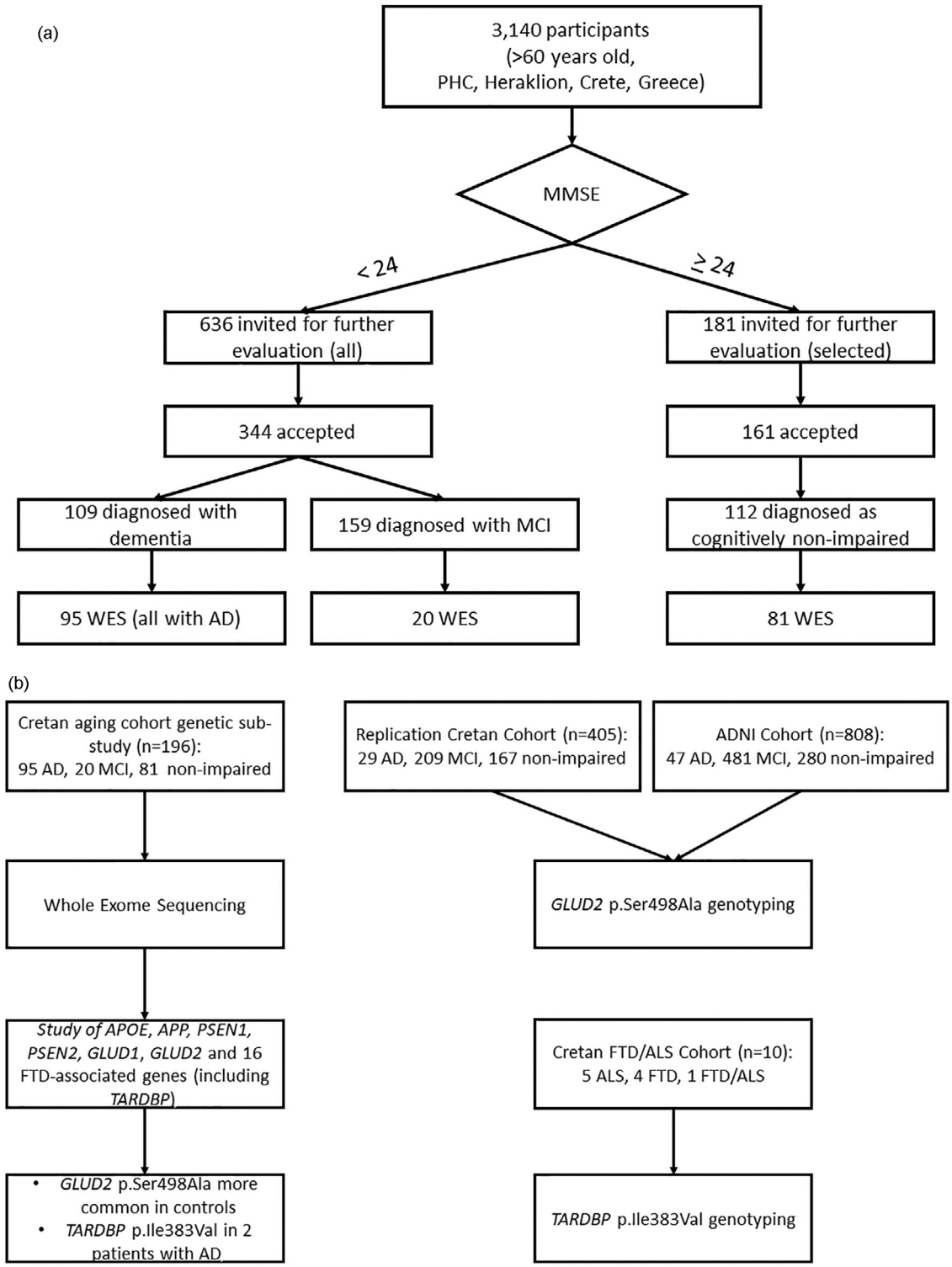

Fig. 1. (a) Flow diagram of the present study concerning the Cretan Aging Cohort Genetic substudy. (b) Flow diagram of the analyses performed in the present study. Following identification of the p.Ser498Ala *GLUD2* variant as being more common in controls, we have genotyped this variant independently in 2 additional cohorts (a local replication cohort and a subcohort of the ADNI database). Similarly, after the identification of the *TARDBP* p.Ile383Val variant in 2 patients with AD, we searched for the same variant in a small Cretan FTD/ALS cohort. Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; MCI, mild cognitive impairment; WES, whole exome sequencing.

Table 1
Comparison of dementia, MCI, and control groups genotyped in our study

	Cretan Aging Cohort (n = 196)			Local replication cohort: SKEPSI + other CAC (n = 405)		
	AD (n = 95)	MCI (n = 20)	Controls (n = 81)	AD (n = 29)	MCI (n = 209)	Controls (n = 167)
Age (mean ± SD), years	80.7 ± 5.2***	75.4 ± 4.7	72.9 ± 6.9	74.9 ± 7.9***	74.3 ± 8.0***	66.7 ± 7.4
Sex (% females)	69.5**	65.0	51.9	48.3**	61.1*	73.8
Formal education (mean ± SD, years)	4.1 ± 3.0***	5.2 ± 3.1	6.1 ± 2.6	7.2 ± 4.3***	6.0 ± 4.3*	9.6 ± 5.0
Family history of dementia in 1st degree relative (n, %)	41 (43.2%)*	9 (45.0%)	21 (25.9%)	NA	NA	NA
MMSE (mean ± SD)	17.5 ± 5.7***	23.4 ± 3.2***	28.4 ± 1.2	22.8 ± 4.9***	24.1 ± 3.5***	26.8 ± 3.3
Age at disease onset (mean ± SD), years	76.9 ± 6.8	NA	NA	72.5 ± 6.8	NA	NA
APOE ε4: n (%)	22 (23.2)**	5 (25.0)	6 (7.4)	NA	NA	NA
Municipality						
Heraklion (City of Heraklion, Kato Asites)	44	7	35	25	145	151
Hersonissos (Episkopi, Malia)	6	2	6	0	10	2
Minoa Pediados (Garipa, Kasteli, Thrapsano)	17	5	10	2	22	2
Archanes-Asterousia (Houdetsi, Peza, Pirgos)	22	5	15	2	26	8
Viannos (Ebaros, Pefkos)	3	1	5	0	0	0
Gortina (Agia Varvara)	3	0	10	0	6	4

The demographic and clinical characteristics and the *APOE ε4* status are presented here separately for the initial Cretan Aging Cohort (CAC) and the local replication cohort that included 174 additional CAC participants and 231 participants from the "SKEPSI" cohort.
Key: NA, not available.
*$p < 0.05$ compared to the control group.
**$p < 0.01$ compared to the control group.
***$p < 0.001$ compared to the control group.

and measurement of plasma and serum biomarkers, such as IL-6 and TNFα (Basta et al., 2020).

All information obtained through history, physical and mental status examination, neuropsychological examination, questionnaires, as well as all other additional data (imaging studies, laboratory results) available, was reviewed by a certified neurologist (I.Z.) and a neuropsychologist (P.S.) and consensus diagnoses were reached using published criteria and taking into account the reports from the clinicians who had examined the patients, as well as the neuropsychological reports. For the diagnosis of dementia and MCI, the DSM-IV criteria (American Psychiatric Association, 1994) and the IWG (Winblad et al., 2004) criteria were used, respectively. Probable Alzheimer' disease (AD), vascular dementia (VaD), Lewy body dementia (LBD), behavioral variant frontotemporal dementia (bvFTD), and other types of frontotemporal dementia were diagnosed according to the published criteria by NINCDS-ADRDA (McKhann et al., 1984), NINDS-AIREN (Román et al., 1993), DLB Consortium (McKeith et al., 2005), International Consortium on bvFTD (Rascovsky et al., 2011), and Neary et al. (1998).

2.2. Family history information

As part of the assessment of the 505 participants in the second phase of the CAC study, a detailed family history for dementia and other neuropsychiatric diseases was obtained both through the semistructured questionnaire described above and also in the context of a special second interview of the patient and/or caregivers. The family history included the names, ages and, if deceased, age and cause of death of up to 3rd degree relatives. The presence and age at onset of neuropsychiatric diseases (including dementia) was also recorded. Based on this information, detailed family trees were constructed using the HaploPainter 1.043 software (Thiele and Nürnberg, 2005).

2.3. Blood collection and DNA extraction

Whole peripheral blood from consenting participants was collected in Ethylenediaminetetraacetic Acid (EDTA) vacutainer tubes which were rushed on ice to the laboratory and stored at -20°C until DNA extraction. In total, blood was collected from 380 individuals (109 participants with dementia, 159 with MCI and 112 cognitively nonimpaired). Genomic DNA was extracted from 400μL of whole peripheral blood by processing with the QIAamp DNA Blood Mini kit, Qiagen (CA, USA). DNA concentration and purity were assessed spectrophotometrically at 260/280 nm. Each DNA sample was coded through unique identifiers, to ensure the anonymity of the participants and traceability of the sample and was stored at -20°C for future analyses.

2.4. Whole exome sequencing for members of the CAC

Of the 380 individuals with blood samples available, 201 were selected for WES analyses in this study. These 201 samples were all used for the Principal Component Analysis (PCA;see below), but 5 of these were excluded from other studies due to a diagnosis of non-AD dementia (1 FTD, 1 LBD, 3 VaD). Among those 196 well-characterized individuals that were studied further, 95 were patients diagnosed as probable AD (Fig. 1). In addition, we included 81 individuals who were classified as cognitively intact controls and 20 individuals diagnosed with MCI (Fig. 1b). The geographic origin (place of residence) within Heraklion, Crete prefecture and the demographic and clinical characteristics of the genotyped participants are shown in Table 1.

WES was performed at Minotech Genomics Facility, Institute of Molecular Biology and Biotechnology (IMBB-FORTH, Crete). The Ion Torrent PROTON (Ion PI chip v3) platform was employed for exon capture, following library preparation and template sequencing using Ion Ampliseq Exome kit (MA, USA) and Ion PI Hi-Q OT2 200 kit (MA, USA), respectively. For all the sequenced libraries, the mean

number of Q20 bases was 6.81Gbp ranging between 2.93 and 12.89 Gbp, the mean length of a sequence was 181.7 bp, with the shortest being 146 bp and the longest 195 bp. Bioinformatics processing of retrieved data, including mapping to human reference genome 19 (hg19), variant calling and quality control analyses was performed using the Ion Torrent Suite (MA, USA) software with the implementation of algorithms in the form of plugins, specifically designed for Ion technology.

Variant annotation was performed using the Ion Reporter v5.0 (MA, USA) and Ingenuity Variant Analysis (Qiagen, CA, USA) tools after application of specific filters. For our analyses, we selected 4 genes associated with AD (*APOE, APP, PSEN1, PSEN2),* 2 genes associated with glutamate metabolism, which has been shown to contribute to the AD pathogenesis (*GLUD1, GLUD2)* and 16 FTD-associated genes (*MAPT, GRN, TARDBP, VCP, FUS, CHCHD10, CHMP2B, SQSTM1, TBK1, CTSF, UBQLN1, HNRNPA1, HNRNPA2B1, UBQLN1, UBQLN2, OPTN)* (Bourbouli et al., 2021; Wagner et al., 2021; Xiao et al., 2021) (Fig. 1b). All variants of the 22 genes selected for this analysis were also manually analyzed taking into account data from online databases (Exome Aggregation Consortium, gnomAD, ClinVar, Ensembl/GRCh37.p13 and OMIM databases) and published literature. Moreover, possibly pathogenic changes were further prioritized using 2 *in silico* prediction algorithms, Sorting Intolerant from Tolerant (SIFT) (https://sift.bii.a-star.edu.sg/) and Polymorphism Phenotyping (PolyPhen-2) (http://genetics.bwh.harvard.edu/pph2/). In addition, the Combined Annotation-Dependent Depletion (CADD) score (Rentzsch et al., 2019) for each variant, as provided by the Ingenuity Variant Analysis software, was taken into consideration. CADD is a widely used tool to measure the deleteriousness of genetic variants (single nucleotide variants and short insertion and deletions). For the *APP, PSEN1, PSEN2, APOE, GLUD1* and *GLUD2* genes, the cut-off CADD score was set at 10, with the exception of the p.Ser498Ala *GLUD2* variant. Finally, for the 16 FTD associated genes, the variants reported here are considered as Disease-causing Mutations (DM) by Human Gene Mutation Database (HMGD), while at the same time having a CADD score >15.

2.5. APP, PSEN1, PSEN2, APOE, GLUD1, *and* GLUD2 *gene variant verification*

All single nucleotide variants reported here for the *APOE, APP, PSEN1, PSEN2, GLUD1,* and *GLUD2* genes were verified by Sanger sequencing and/or restriction fragment length polymorphism (RFLP) analysis to exclude false positive results (primers and conditions for genotyping available on request). Specifically, *APOE* genotyping was validated for all subjects by PCR/RFLP using the HhaI restriction enzyme, as previously described (Kim et al., 2010). In short, an *APOE* region spanning the rs429358 and rs7412 SNPs, which are needed for the characterization of *APOE* alleles as $\varepsilon 2/\varepsilon 3/\varepsilon 4$, was amplified by PCR using specific primers and the resulting products were digested by HhaI. DNA fragments were visualized by 13% polyacrylamide gel electrophoresis and 3X Gel Red staining (Gel RED Nucleic Acid, Biotium, CA, USA). *GLUD2* p.Ser498Ala variant genotyping was performed by PCR amplification of the adjacent *GLUD2* region and digestion of the products with AciI. Fragments were visualized by 1% agarose gel electrophoresis.

2.6. *Extension of the p.Ser498Ala* GLUD2 *variant genotyping*

Analyses involving the p.Ser498Ala *GLUD2* variant were performed, in addition to the initial 196 individuals, on an additional sample of 405 persons (Fig. 1b, Table 1) recruited from the same region of Crete. This additional sample included: (1) 174 individuals of the CAC for whom WES data were not available (4 with AD, 139 with MCI and 31 cognitively nonimpaired), and (2) 231 participants of a second local cohort that has been established through the "SKEPSI" research program (Karademas et al., 2019). The latter cohort also included residents of the prefecture of Heraklion, Crete, who either responded to advertisements in local media inviting persons aged 50 years or older to be tested for "memory and other cognitive difficulties they may be experiencing" or were referred for neuropsychological testing by local physicians. Participants in this cohort were characterized and diagnosis (AD in 25, MCI in 70 and normal cognition in 136) was reached in a manner essentially identical to that described above for the CAC.

The additional 231 de-identified aliquoted DNA samples from the "SKEPSI" cohort were sent to Professor Constantinos Deltas and Dr. Konstantinos Voskarides at the Molecular Medicine Research Centre of the University of Cyprus, Nicosia, Cyprus who provided expertise and facilities of their Biobank (University of Cyprus Biobank, Nicosia, Cyprus). From there, samples were sent to LGC Genomics (UK) for genotyping of Single Nucleotide Polymorphisms by proprietary KASP assays. KASP genotyping is based on competitive allele-specific Polymerase Chain Reaction (PCR), while bi-allelic discrimination is achieved by attaching a fluorescent-dyed tail sequence to the allele-specific forward markers––one labeled with FAM dye and the other with HEX dye. As the markers amplify, they interact with an equivalent universal FRET (fluorescent resonant energy transfer) cassette, which begins to emit fluorescence because of the interaction. Genotypes are automatically called by Kraken software based on the fluorescent signal, and manually confirmed by a lab technician.

As supplementary analyses, we used the data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. (Fig. 1b). For the present study, we included only ADNI individuals for which the p.498 residue (c.1492 nucleotide) of *GLUD2* was known by genotyping (n = 808), to establish the presence or absence of the p.Ser498Ala (c.1492T>G) *GLUD2* variant. Of these 808 participants, 47 have been diagnosed as AD, 481 as MCI and 280 as cognitively normal controls.

2.7. *Genotyping of Cretan patients with ALS, FTD, and FTD/ALS for the* TARDBP *p.Ile383Val variant*

To search for the *TARDBP* p.Ile383Val pathogenic variant in Cretan patients with the ALS, FTD or FTD/ALS phenotype we analyzed (Fig. 1b) WES data from **10** patients (median age 61,5 years, range 47-79 years; 4 females, 6 males; 5 ALS, 4 FTD, 1 FTD/ALS) available through an ongoing diagnostic/research program at the Neurology/Neurogenetics Laboratory at the Medical School, University of Crete (Bourbouli et al., 2021; Michaelidou et al., 2020; Zaganas et al., 2020; Zaganas et al., 2021). Informed consent was obtained from the patients or their legal representatives, according to a study protocol that has also been approved by the Institutional Review Board of the University Hospital of Heraklion, Crete, Greece. As part of our standard diagnostic work-up, all 10 patients with the ALS, FTD and FTD/ALS phenotype included in our study underwent imaging at a 1.5 Tesla MRI scanner and scans were evaluated by an experienced radiologist and normalized against controls of similar age. The purpose of obtaining brain MRIs in these 10 patients was to exclude other conditions that can masquerade as ALS or FTD and to ensure that brain imaging findings (e.g., frontal or temporal atrophy) were compatible with the clinical diagnoses. After testing for *C9orf72* hexanucleotide repeat expansion to exclude ALS/FTD caused by this type of variant, WES was performed by sequencing of 2 × 100 bp DNA fragments and aiming at coverage of at least 50x. Exon-enriched DNA libraries were prepared with the Agilent V5 Sure-Select Target Enrichment System and sequenced on an Illumina HiSeq 2500 (at Otogenetics Corporation,

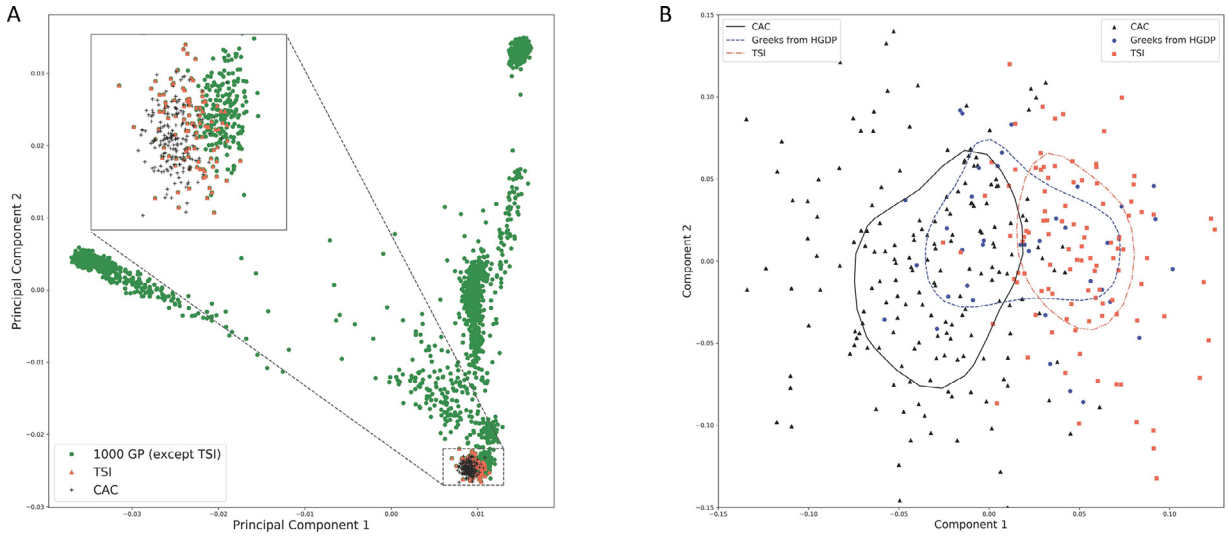

Fig. 2. (A) Population clustering. Principal component analysis was used to map the Cretan Aging Cohort (CAC) relative to the complete panel of 26 populations from the 1000 Genomes Project. Individuals from the CAC and Italians from Tuscany, Italy (TSI) are depicted with different shapes (compared to the rest of the world) based on the high genetic similarity between the 2 geographically adjacent populations. The embedded figure on the top left zooms on the part of the PCA that contains the CAC and TSI populations. Despite the high genetic affinity between these populations, CAC members are slightly centered toward the lower-left side of the plot. (B) Regional genetic variation of the CAC. Contour plot of the geographic differentiation of individuals from CAC after projecting them on 2 top principal components relatively to Greeks from Human Genome Diversity Project (HGDP) and Tuscany from the 1000 Genomes Project. Samples are marked based on the region of inhabitance as indicated. In total we inferred 3 Gaussian Kernel Density Estimations (KDEs), one for each population. The KDEs are normalized from 0 to 1 and the contour lines are on the level of 0.5. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Norcross, GA, USA) or HiSeq4000 (at Macrogen, Seoul, Korea) platform. Finally, WES data analysis was performed at the Neurology Laboratory, University of Crete using the Ingenuity software (Qiagen, USA). In this analysis, we specifically searched for the *TARDBP* p.Ile383Val variant in the WES data of these patients. This variant's presence was also confirmed by PCR amplification and Sanger sequencing of exon 6 of the *TARDBP* gene.

2.8. Principal component analysis

PCA was performed on the sequenced dataset to determine whether genetic outliers existed and to investigate possible population stratification (Fig. 2). The analyses were performed using PLINK v.1.9 by combining sequenced data from the CAC with individuals from the complete population panel of the 1000 Genomes Project (phase3, release 20150502). Following data merging, we took the intersection of variants and performed LD pruning in PLINK (with options —indep 50 5 2) to obtain a thinned set of data containing only independent variants (n = 25,439).

PCA was also used (Fig. 2) to project the 201 individuals from the CAC with available WES data on the first 2 principal components relatively to 38 Greeks from the CEPH/Human Genome Diversity Panel (Lazaridis et al., 2014) and 107 Italians from the 1000 Genomes project (1000 Genomes Project, phase3, release 20150502). The HGDP dataset, obtained from http://hagsc.org/hgdp/files.html, does not include any samples from Crete. Following data merging, we took the intersection of variants and performed LD pruning in PLINK v1.9 (with options –indep 50 5 2) to obtain an independent subset of variants. We then applied PCA on this independent set. The directions of geographic differentiation were shown in a contour plot. For each population we applied a Gaussian Kernel Density Estimation (KDE) using the top 2 principal components using the Scott's rule of thumb (Scott, 2015) for bandwidth estimation. All 3 kernel estimates were subsequently normalized from 0 to 1 and a contour line at the level of 0.5 was added on the plots.

2.9. Statistical analysis

Statistical analysis of *APOE* allelic distribution and *GLUD2* p.Ser498Ala variant among cases with AD dementia, MCI and controls, was performed using the χ^2 and Fisher's exact tests, and evaluated at $p = 0.05$. Group differences in age and education were assessed using independent samples *t*-tests.

3. Results

Overall, our results showed that, in the CAC, the *GLUD2* p.Ser498Ala variant was more common in patients with AD compared to controls, even though this finding did not reach statistical significance in 2 other replication cohorts, and thus should be considered preliminary. Also, again in the CAC, we found the FTD-associated *TARDBP* p.Ile383Val pathogenic variant in 2 patients, 82- and 80-year-old, respectively, initially diagnosed with AD. The same variant was found in 2 other Cretans, nonmembers of the CAC, with the ALS and the ALS/FTD phenotype. These results are detailed in the following section.

3.1. Family history

Among the 196 persons from the CAC (95 with AD dementia, 20 with MCI and 81 cognitively normal controls) with available WES data, 71 had family history of dementia with at least one first degree relative affected (Table 1). Specifically, 41 (43.2%) and 9 (45.0%) of the AD and MCI patients, respectively, had at least one first degree relative affected with dementia. Both patient groups had higher frequency of positive family history for dementia in a first degree relative compared to cognitively normal controls (21/81, 25.9%; $p = 0.017$ for the comparison with the AD group).

3.2. APP, PSEN1, *and* PSEN2 *variants*

Next, within our sample, we sought to identify genetic variants that had already been characterized as either pathogenic variants or variants of unknown significance (VUS) in the 3 known familial AD causative genes (*APP, PSEN1* and *PSEN2*, see methods).

Regarding the *APP* gene, 3 variants of potential interest were detected. Specifically, the p.Val375Ile, p.Gln686Glu and p.Asn195Asp variants were found in a patient affected with AD, a patient affected with MCI and a cognitive normal control, respectively (Table 2). In the *PSEN1* gene, the p.Glu318Gly variant was present in 2 AD patients and in 2 controls (Table 2). Concerning the *PSEN2* gene, a very rare in public databases variant (p.Arg29His) was present in 3 individuals with AD, while it was absent from normal controls (Table 2). In contrast, the *PSEN2* p.Arg62His variant was present in one patient with AD, one patient with MCI and 3 control individuals. Finally, the p.Cys391Arg variant of *PSEN2* was detected in a single patient with MCI (Table 2).

3.3. APOE ε *alleles and variant*

Given the importance of *APOE* alleles for AD risk, we investigated the *APOE* $\varepsilon2/\varepsilon3/\varepsilon4$ allelic distribution among individuals with dementia and controls in our sample, using the WES data and verifying results with RFLP analyses. Results showed that the *APOE* $\varepsilon4$ allele was present in heterozygous state in 33 out of the 196 samples of our cohort. Of these, 22 belonged to the AD group (23.2 %), 5 to the MCI group (25.0%) and 6 to the control group (7.4%). No homozygous $\varepsilon4$ carriers were detected. As expected, by comparing AD and control groups, the *APOE* $\varepsilon4$ allele was significantly more frequent in the former group ($p < 0.01$; Table 1). Screening the *APOE* gene for other variants of interest, in addition to the ε alleles, we detected the p.Gly145Asp variant in one individual with AD (Table 2).

3.4. *FTD-associated gene variants in the CAC*

Analyzing the CAC WES data for potentially causative variants (described as DM in HGMD and at the same time having a CADD score>15) in 16 FTD-associated genes, we identified the **p.Ile383Val** (c.1147A>G; rs367543041) *TARDBP* gene variant in 2 patients, an 80-year-old woman and an 82-year-old man, both initially diagnosed as suffering from AD (Table 2).

The 80-year-old woman presented with progressively deteriorating short-term memory problems and difficulty in performing everyday activities of at least one-year duration. Her family history was characterized by dementia in her deceased mother with onset at 90 years of age, and depression and dementia in her deceased brother with onset at the age of 70 years. On examination, she had difficulty in completing several of the neuropsychological tests, mainly due to forgetting the orders given and difficulty in concentration. On several occasions, her answers were enriched by description of remote events. She scored 17 of 30 in the MMSE test, having difficulties in recall, calculations, and temporal orientation. The rest of the neurological examination was unremarkable, and a clinical diagnosis of probable AD was reached.

The second patient was an 82-year-old male who had presented memory problems for at least 5 years and severe functional impairment in the last 2 years. More recently, the patient had shown depressive symptoms and occasional visual hallucinations. His past medical history was notable for arterial hypertension and diabetes mellitus and his medications included donepezil and citalopram. Reportedly, 3 of his 10 siblings had symptoms of dementia before dying, and another one was suffering from dementia, but was living abroad and thus was inaccessible to testing. His 78-year-old

Table 2
Rare coding variants in *APP, PSEN1, PSEN2, GLUD1, GLUD2* and *TARDBP* genes and distribution in AD, MCI, and control groups in the Cretan Aging Cohort (n = 196).

Gene (transcript)	Chromosomal location	SNP nomenclature (rs)	c.DNA	Protein effect	Distribution in CAC groups			CADD score	Predicted consequence	Population frequency(%, gnomAD)
					AD, n = 95(age at onset, y)	MCI, n = 20	Controls, n = 81			
APP (NM_000484.4)	chr21: 27,423,395	NA	c.583A>G	p.Asn195Asp	0	0	1	13.8	Missense	0.000
	chr21: 27,354,758	141331202	c.1123G>A	p.Val375Ile	1 (87)	0	0	26.6	Missense	0.002
PSEN1 (NM_000021.4)	chr21: 27,269,893	1389784830	c.2056C>G	p.Gln686Glu	0	1	0	20.5	Missense	0.000
	chr14: 73,673,178	rs17125721	c.953A>G	p.Glu318Gly	2 (80, 85)	0	2	22.3	Missense	1.490
PSEN2 (NM_000447.3)	chr1: 227,069,694	NA	c.86G>A	p.Arg29His	3 (76, 78, 104)	0	0	21.6	Missense	<0.001
	chr1: 227,071,449	58973334	c.185G>A	p.Arg62His	1 (74)	1	3	13.0	Missense	0.920
	chr1: 227,081,806	NA	c.1171T>C	p.Cys391Arg	0	1	0	28.6	Missense	0.000
APOE (NM_000041.4)	chr19: 45,411,987	267606664	c.434G>A	p.Gly145Asp	1 (84)	0	0	24.3	Missense	0.020
GLUD1 (*NM_005271.5*)	Chr10: 88,820,709	922599385	c.1022A>G	p.Asp341Gly	0	0	1	25.4	Missense	0.000
GLUD2 (*NM_012084.4*)	ChrX: 120181641	191769566	c.103G>A	p.Gly35Arg	13	6	7	10.1	Missense	9.940
	ChrX: 120182779	62623672	c.1241A>G	p.Asp414Gly	1	0	0	22.7	Missense	0.220
TARDBP (NM_007375.4)	ChrX: 120183030	9697983	c.1492T>G	p.Ser498Ala	2	3	13*	<10.0	Missense	2.760
	Chr1: 11,082,613	80356740	c.1147A>G	p.Ile383Val	2 (77, 79)	0	0	17.2	Missense	0.002
	Chr1: 11,082,266	80356718	c.800A>G	p.Asn267Ser	0	0	1	15.7	Missense	0.008

Key: MCI, mild cognitive impairment; NA, not available.
*$p = 0.002$ when compared to the AD group and $p = 0.01$ when compared to the total group of cognitively impaired (AD and MCI combined; n = 115).

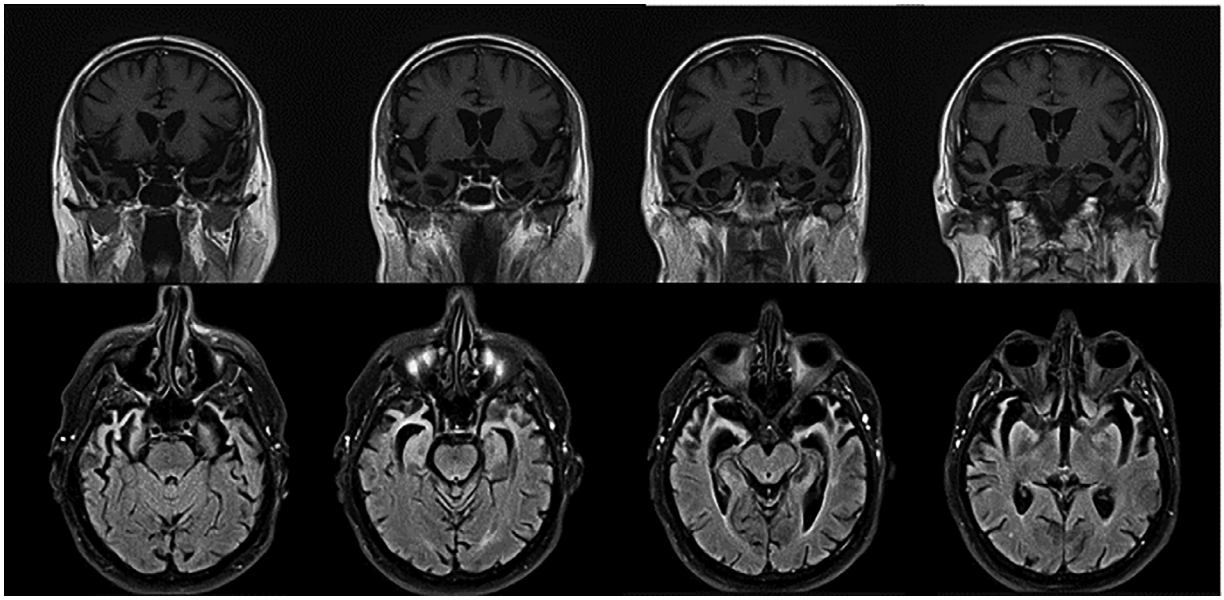

Fig. 3. Brain MRI imaging of a Cretan patient (nonmember of the CAC) displaying the FTD/ALS phenotype and harboring the p.Ile383Val *TARDBP* pathogenic variant. Shown here are coronal T1 and horizontal FLAIR sections, where atrophy of the anterior temporal and the frontal lobes are evident.

sister was reported as having memory problems, with formal testing revealing that the most appropriate diagnosis for her would be MCI. On examination, the patient had severe cognitive dysfunction, including severe aphasia that hindered his ability to communicate (MMSE 2/30). Again, based on the history and clinical features, a clinical diagnosis of probable AD was made.

Interestingly, besides p.Ile383Val, a second *TARDBP* variant (c.800A>G, p.Asn267Ser rs80356718), classified as likely pathogenic, was detected in a cognitive normal 73-year old individual from our CAC. Beyond *TARDBP*, in the other 15 FTD-associated genes included in our analysis, no other causative variant was identified based on the prespecified criteria (see Methods).

3.5. *The p.Ile383Val* TARDBP *variant in 2 patients with ALS, FTD or FTD/ALS from Crete (nonmembers of the CAC)*

Through a parallel diagnostic/research program in the Neurogenetics Laboratory, Medical School, University of Crete, we detected by WES the p.Ile383Val *TARDBP* pathogenic variant in 2 additional Cretan patients, nonmembers of the CAC, presenting with an FTD/ALS and ALS phenotype, respectively. Specifically, the first patient, a 60-year-old man, had presented initially marked behavioral changes and language deficits, and later weakness in the left upper extremity, all gradually deteriorating (Bourbouli et al., 2021). Two years later, progressive weakness developed in the right upper extremity and the bulbar musculature, and a gastrostomy and a tracheostomy had to be placed. Notably, the patient had no family history of dementia or motor neuron disease. On examination, the patient showed severe aphasia and behavioral derangement. He had severe tetraparesis, widespread fasciculations and atrophies in all 4 extremities. Tendon reflexes were elicited in the upper extremities but abolished in the lower extremities. MRI imaging showed marked atrophy of the anterior poles of the temporal lobes bilaterally (Fig. 3). Based on the history, neurological and neuropsychological examination, neurophysiological data and imaging findings, the diagnosis of FTD/ALS overlap syndrome was reached. The second patient, a 64-year-old woman, had presented, 5 years before genetic diagnosis, weakness of the upper extremities that later progressed to the lower extremities and the bulbar muscles, leading to weight loss, and necessitating a gastrostomy placement. The history, the electrophysiological findings and the clinical picture were compatible with ALS. The patient's sister, not available for testing, has also been reportedly diagnosed with ALS.

3.6. GLUD1 *and* GLUD2 *gene variants*

Analysis of the neurodegeneration-associated *GLUD1* and *GLUD2* genes revealed that the *GLUD2* p.Ser498Ala (c.1492T>G) variant was more frequent in cognitively nonimpaired than in cognitively impaired individuals in our cohort (Table 3). Specifically, it was present in 2 (2.11%) of the 95 patients with AD, 3 (15.0%) of the 20 patients with MCI and 13 (16.05%) of the 81 cognitively normal individuals ($\boldsymbol{p = 0.002}$ for the comparison of patients with AD to cognitively nonimpaired controls). This difference remained significant after grouping together patients with AD and patients with MCI (p.Ser498Ala *GLUD2* variant present in 5/115 [4.35%] vs. 13/81 [16.05%] of controls; $p = 0.011$; Table 3).

When considering X-chromosomes, the *GLUD2* p.Ser498Ala variant was present in 2 of 161 (1.24%) X-chromosomes of patients with AD compared to 13 of 123 (10.56%) X-chromosomes of cognitively nonimpaired controls ($p = 0.001$; Table 3). Again, this difference remained significant after lumping together persons diagnosed with AD or MCI (p.Ser498Ala *GLUD2* variant present in 5/194 [2.58%] of X-chromosomes as compared to 13/123 [10.56%] of control X-chromosomes; $p = 0.006$).

In light of these results, we then expanded the *GLUD2* p.Ser498Ala genotype analysis to the second cohort of well-characterized persons residing in the prefecture of Heraklion, Crete ($n = 405$), comprising 174 additional individuals of the CAC and 231 aged adults from the "SKEPSI" program, characterized in a manner similar to the CAC (Karademas et al., 2019). In this second cohort, there was also a tendency for control individuals to have a higher frequency of the p.Ser498Ala *GLUD2* variant (14/168, 8.33%) compared to cognitively impaired individuals (affected with AD or MCI; 12/237, 5.06%), even though this did not reach statistical significance (Table 3). A similar nonsignificant trend of lower percentage of the p.Ser498Ala *GLUD2* variant in X-chromosomes of patients with dementia or MCI (14/378 [3.70%]) as compared to controls was found (14/292 [4.79%]).

Table 3
Frequency of the *GLUD2* p.Ser498Ala variant in (1) the WES-genotyped initial Cretan Aging Cohort (n = 196), (2) the second local (replication) cohort (n = 405) that includes 174 additional Cretan Aging Cohort participants and 231 participants from the "SKEPSI" cohort, and (3) the ADNI subcohort (individuals with the *GLUD2* residue 498 genotype available)

Cohort		AD		MCI		AD + MCI		Controls	
		Individuals	X-Chromosomes	Individuals	X-Chromosomes	Individuals	X-Chromosomes	Individuals	X-Chromosomes
1) Initial CAC (n = 196)	Males	0/29	0/29	2/7	2/7	2/36	2/36	5/39	5/39
	Females	2/66*	2/132*	1/13	1/26	3/79*	3/158*	8/42	8/84
	Total	2/95** (2.11%)	2/161*** (1.24%)	3/20 (15.00%)	3/33 (9.09%)	5/115* (4.35%)	5/194** (2.58%)	13/81 (16.05%)	13/123 (10.56%)
2) Replication cohort: remaining CAC + SKEPSI (n = 405)	Males	0/15	0/15	2/81	2/81	2/96	2/96	2/44	2/44
	Females	2/14	3/28	8/127	9/254	10/141	12/282	12/124	12/248
	Total	2/29 (6.90%)	3/43 (7.00%)	10/208 (4.80%)	11/335 (3.28%)	12/237 (5.06%)	14/378 (3.70%)	14/168 (8.33%)	14/292 (4.79%)
3) ADNI cohort (n = 808)	Males	1/29	1/29	7/281	7/281	8/310	8/310	2/136	2/136
	Females	3/18	3/36	5/201	6/402	8/219	9/438	7/144	8/288
	Total	4/47 (8.51%)	4/65 (6.15%)	12/481 (2.49%)	13/683 (1.90%)	16/528 (3.03%)	17/748 (2.27%)	9/280 (3.21%)	10/424 (2.35%)

*$p < 0.05$ compared to the control group.
**$p < 0.01$ compared to the control group.
***$P < 0.001$ compared to the control group.
Key: AD, Alzheimer's disease; CAC, Cretan Aging Cohort; MCI, mild cognitive impairment.

It should be noted that the p.Ser498Ala *GLUD2* genotype in the combined sample of 601 Cretan individuals, including the initial cohort of 196 individuals and the replication cohort of 405 individuals, was in Hardy-Weinberg equilibrium (data not shown).

As an additional analysis, we used the data from the ADNI cohort. As in the previous 2 Cretan cohorts, analysis of individuals genotyped for the p.498 residue (c.1492 nucleotide) of *GLUD2* (n = 808) showed that the p.Ser498Ala (c.1492T>G) *GLUD2* variant was slightly more frequent in controls (9/280; 3.21%) compared to MCI and AD patients combined (16/528; 3.03%), even though this difference did not reach statistical significance (Table 3). A similar, nonsignificant trend was observed for X-chromosomes, as this variant was found in 17 of 748 (2.27%) X-chromosomes of cognitively impaired individuals vs. 10 of 424 (2.35%) X-chromosomes of controls (Table 3).

Further analysis of the *GLUD1* and *GLUD2* genes revealed a rare in public databases, not previously studied *GLUD2* gene variant (p.Asp414Gly) in a patient with AD and one novel missense variant of *GLUD1* (p.Asp341Gly) in one control individual (Table 2). Also, the p.Gly35Arg *GLUD2* variant was found in 13 AD patients, 6 MCI patients and 7 controls (Table 2).

3.7. Principal component analysis

Population stratification can be an issue in the analysis of population-based genetic data (Tian et al., 2008). We therefore used PCA to characterize the WES-genotyped 201 individuals from the CAC (196 included in the studies described above plus 5 additional individuals) in the context of broader global diversity using the complete panel of 26 populations from the 1000 Genomes Project (phase3, release 20150502). As expected, individuals from the CAC formed a well-defined cluster (Fig. 2) proximal to the population from Tuscany, Italy (TSI).

For both PCA analyses, the initial CAC data set comprised 201 individuals and 339,005 nonduplicate variants. For the PCA we applied standard QC procedures, excluding duplicated and related samples identified by calculating the pairwise identity by descent for each sample using PLINK v1.9. Specifically, from each pair with a pi-hat > 0.1 the sample with the lower sequencing quality was excluded. In addition, variants were excluded based on MAF<5% and Hardy–Weinberg equilibrium exact $p < 0.0001$, resulting in 66,295 and 62,481 variants, respectively. Following LD pruning the resulting data set comprised of 179 unrelated individuals and 25,439 variants, of which 24,608 overlapped between the CAC and the populations from HGDP and 1000 Genomes Project, while the remaining 831 nonoverlapping variants were unique to our cohort (Fig. 2A).

Moreover, a contour plot was used to delineate whether the genetic makeup of the CAC differed from other Greek or geographically adjacent populations (Fig. 2B). For this reason, Italians from Tuscany were used based on the evidence of their high genetic similarity with Greeks (Elhaik et al., 2014). We observed a distinctive pattern of individuals from our cohort clustering on one side of the general Greek population, whereas Italians from Tuscany occupy the opposite side.

4. Discussion

4.1. Main findings

In the present study, which provides an initial genetic characterization by WES of 196 individuals from the CAC (Zaganas et al., 2019), we identified several rare variants of potential significance in the *APP, PSEN1, PSEN2*, and *GLUD2* genes. Importantly, we found

the *GLUD2* p.Ser498Ala variant to be more common in cognitively nonimpaired individuals than in cognitively impaired patients (affected with AD or MCI). This increased frequency of the p.Ser498Ala *GLUD2* variant in controls was also found in an additional local cohort (n = 405; also originating from the prefecture of Heraklion, Crete) and a subcohort of the ADNI patient group (n = 808), even though in both latter cohorts this difference did not reach statistical significance. Thus, this finding should be considered as preliminary and could have emerged due to the homogeneity of the Cretan population and its separation from other populations, as shown by our PCA analyses. Finally, we identified in the CAC 2 aged patients initially diagnosed with AD that carried the p.Ile383Val *TARDBP* variant. This variant has been repeatedly shown to cause FTD and/or ALS, in reports from studies in the Greek and other populations. We have identified the same variant in 2 additional Cretan patients (nonmembers of the CAC), presenting with FTD/ALS and ALS phenotypes, respectively. The variants described here have not been associated with diseases other than MCI, AD and ALS/FTD, with the exception of the p.Ser498Ala *GLUD2* gene variant being associated with the age at onset of Parkinson's disease (see in the following section).

4.2. Possible disease-causing variants in APP, PSEN1, and PSEN2 genes

To characterize our sample, we chose first to identify putatively disease-causing variants in known AD-associated genes. Regarding the 3 established early-onset familial AD causative genes (*APP, PSEN1,* and *PSEN2)* we sought to identify pathogenic variants within our sample. Even though the age range of our cohort exceeds that of the typical early-onset familial AD, the presence of pathogenic variants in AD-causative genes is not unexpected in late-onset AD (Cruchaga et al., 2012a; Fernández et al., 2017). Specifically, while rare variants in the *APP, PSEN1,* and *PSEN2* genes typically cause early-onset AD, variants in these genes (especially in *PSEN2*) can also cause or predispose to late-onset AD (Cruchaga et al., 2012a; Sherrington et al., 1996).

Regarding the *APP* gene (OMIM 104760), more than 30 familial AD-causing variants have been described so far (Chávez-Gutiérrez and Szaruga, 2020; D'Argenio and Sarnataro, 2020), in addition to a rare protective variant (p.Ala673Thr) observed in Iceland (Jonsson et al., 2012). Most of these pathogenic variants cluster in the portion of the protein that undergoes processing during amyloidogenesis. In our CAC samples, the previously noncharacterized, with low gnomAD frequency, p.Val375Ile, p.Gln686Glu and p.Asn195Asp *APP* variants were detected in a patient affected with AD, a patient affected with MCI and a cognitive normal control, respectively (Table 2). According to *in silico* predictions (CADD score), both p.Val375Ile and p.Gln686Glu are classified as possibly damaging for the protein product (Table 2). In addition, p.Gln686Glu is flanked by disease-causing *APP* variants (Chávez-Gutiérrez and Szaruga, 2020), resides at the site of cleavage by α-secretase (Maruyama et al., 1991; Nadezhdin et al., 2011; Nussbaum and Ellis, 2003) and is therefore expected to affect amyloidogenic processing of APP. Thus, given that the p.Val375Ile and p.Gln686Glu variants cannot be clearly categorized as pathogenic by their presence in one individual with MCI and one with AD, respectively, their characteristics suggest that they are worth of further study. In contrast, p.Asn195Asp, found in one control subject, is predicted by its low CADD score to be a benign polymorphism (Table 2).

PSEN1 (OMIM 104311) pathogenic variants are the most common cause of early-onset autosomal dominant AD, with more than 220 variants in numerous families described thus far (D'Argenio and Sarnataro, 2020), showing complete penetrance and early disease onset (25–65 years of age) (Van Cauwenberghe et al., 2016). In the CAC, only the *PSEN1* p.Glu318Gly variant was present in 2 AD patients and in 2 controls (Table 2). In some populations, the possibility was raised that the *PSEN1* p.Glu318Gly variant was a risk factor associated with familial AD (Albani et al., 2007; Benitez et al., 2013; Helisalmi et al., 2000; Taddei et al., 2002); however, these findings were not verified in other populations (Dermaut et al., 1999; Hippen et al., 2016; Jin et al., 2012; Mattila et al., 1998; Zekanowski et al., 2004). The p.Glu318Gly variant, located on exon 9 of *PSEN1*, is not evolutionary conserved and is predicted to be benign for the protein's function, according to Polyphen2. These features, in addition to its presence in 2 cognitively normal controls in our sample, argue against its pathogenicity, despite its rather high CADD score (22.3).

In contrast to *PSEN1* pathogenic variants, the 19 *PSEN2* (OMIM 600759) AD-causing variants described thus far show incomplete penetrance and are associated with a significantly older disease onset (D'Argenio and Sarnataro, 2020; Van Cauwenberghe et al., 2016). Among the 3 autosomal dominant AD causative genes, *PSEN2* showed the largest number of missense variants in our sample, with these variants spanning the whole length of the gene and, some of them, being detected in several individuals. Specifically, a previously reported (Guerreiro et al., 2010), very rare in public databases, variant of *PSEN2*, p.Arg29His, was present in 3 individuals with AD, while it was absent from controls (Table 2). The p.Arg29His variant has a high CADD score (21.6), indicating a probable damaging protein effect that is also supported by the evolutionary conserved position of the variant. However, several studies classify it as nonpathogenic (Cacace et al., 2016; Cai et al., 2015).

PSEN2 p.Arg62His (Cruts et al., 1998; Sassi et al., 2014; Sleegers et al., 2004) was present in one patient with AD and in one with MCI in the CAC, whereas 3 controls were also carriers (Table 2). Residue 62 of presenilin 2 is not conserved among different species and another variant in human *PSEN2* that occurs at the same position (p.Arg62Cys) has been reported as benign (Sassi et al., 2014; Sleegers et al., 2004). The p.Arg62His *PSEN2* variant is possibly a benign variant as it does not appear to lead to a functional effect on the protein product (Walker et al., 2005), is common in public databases (0.92% in gnomAD), and has a low CADD score (Table 2). However, there is possibility that it could be a disease modifier by decreasing AD disease onset (Cruchaga et al., 2012b).

At last, a unique variant of *PSEN2* (p.Cys391Arg), which has not been previously reported in the literature and is not listed in public variant databases, was detected in a 74-year-old patient with MCI (Table 2). Polyphen2 prediction places it at a very high risk of being damaging and it has a high CADD score (28.6) and a nearby *PSEN2* variant (p.Val393Met) is AD causative (Lindquist et al., 2008). The presence of *PSEN2* (p.Cys391Arg) in an MCI patient in the CAC does not necessarily preclude probable pathogenicity, given that this individual could develop dementia in the future.

As an additional step toward validating our cohort for known genetic risk factors for AD, the frequency of the *APOE* (OMIM 107741) ε4 allele (which approximately triples the risk for AD) was assessed. In accordance with previous studies (Bettens et al., 2013; Corder et al., 1993; Saunders et al., 1993), we found the *APOE* ε4 allele to be more frequent in AD (n = 22/95, 23.2%) and MCI (5/20, 25%) patients than in cognitively intact controls (6/81, 7.4%). This distribution (Table 1) supports the validity of the genetic makeup of the CAC, since it replicates the results of similar studies in other populations (Bertram et al., 2007).

In addition to ε4 genotyping, we screened the *APOE* gene for missense variants, detecting the p.Gly145Asp alteration in one individual with AD. *APOE* p.Gly145Asp has been previously reported (Iron et al., 1995) as cosegregating with p.Arg176Cys (Weisgraber allele). In contrast, in the case we report here, the p.Gly145Asp

carrier's ε genotype was $\varepsilon 3/\varepsilon 3$. Of note, Polyphen2 algorithm indicates that this is a probably damaging variant and it has a high CADD score (24.3).

4.3. GLUD1 *and* GLUD2 *genes*

Next, we turned our attention to the *GLUD1* (OMIM 138130) and *GLUD2* (OMIIM 300144) genes that are among the candidate genes implicated in AD pathophysiology (Mathioudakis et al., 2019). Variants in these 2 genes have been previously described in neurological conditions. Specifically, epilepsy occurs in the context of the hyperinsulinism/hypermammonemia syndrome associated with activating *GLUD1* mutations (Raizen et al., 2005; Stanley et al., 1998). Also, in Parkinson's disease (PD), the p.Ser498Ala *GLUD2* variant is associated with earlier disease onset in hemizygous males (Plaitakis et al., 2010). More importantly, selective overexpression of *GLUD1* in mice brains resulted in upregulation of glutamate release and consequently, excitotoxicity (Bao et al., 2009). These mice were exhibiting a phenotype compatible with progressive neurodegeneration, and more specifically age-dependent degenerative changes in the CA1 region of the hippocampus (Bao et al., 2009). Very recently 2 variants in genes involved in glutamate signaling (*DLG2, MINK1*) have emerged as risk modifying in late-onset AD (Lawingco et al., 2020), highlighting the importance of glutamatergic pathways in AD pathogenesis.

In the *GLUD1* gene, only one variant (p.Asp341Gly) was present in a single cognitively intact participant. This variant, even though novel, is predicted to confer a benign alteration to the protein, according to algorithmic predictions (Table 2). Also present in our cohort was a rare, not previously studied, variant of *GLUD2* (p.Asp414Gly) which was uniquely present in one patient affected with AD, but it is also probably a benign polymorphism, according to Polyphen2 predictions. A previously described variant in the leader peptide of *GLUD2* (p.Gly35Arg) was as common in AD patients as in controls (Table 3). This variant has been found in the past not to affect the frequency or the age at onset of PD (Plaitakis et al., 2010) and the targeting efficiency of the mitochondrial peptide of hGDH2 (Kalef-Ezra et al., 2016).

To our surprise, the *GLUD2* - p.Ser498Ala variant (denoted p.Ser445Ala in previous studies), which has been previously described as an accelerating factor for PD-associated neurodegeneration in male hemizygotes (Plaitakis et al., 2010), was more frequent in cognitively normal individuals in our cohort compared to patients with dementia (Table 3). As shown in the recently solved crystal structure of hGDH2 (Dimovasili et al., 2021), this variant is located on the small descending α-helix of the antenna of the enzyme that undergoes major changes during the catalytic cycle (Fig. 4). Functional characterization of this variant showed that it results in gain of function, as it displays a basal activity higher than that of the wild-type hGDH2 (Plaitakis et al., 2010). The effect on PD onset was seen only in males and not in females; this could relate to the presence of an additional wild-type allele in females (Plaitakis et al., 2010). Also, recently, it was shown that expression of this p.Ser498Ala *GLUD2* variant in a Parkinson's disease mouse model exacerbates movement disorders, increases loss of nigral dopaminergic neurons and decreases expression of glutamate transporters (Zhang et al., 2020).

The X-linked intronless *GLUD2* gene has emerged in the common ancestor of human and great apes less than 23 million years ago, through retroposition of the autosomal intron-containing *GLUD1* gene (Burki and Kaessmann, 2004). The newly formed *GLUD2* gene has acquired, through random mutations and natural selection, adaptive changes that permitted its functional diversification from the parental *GLUD1* gene and its persistence through evolution due to the acquisition of an evolutionary advantage. It is thought that the newly acquired properties of *GLUD2* (GTP resistance, low basal activity that is amenable to ADP activation) permitted its function in the nervous tissue, especially during intense glutamatergic transmission (Zaganas et al., 2014). The hGDH2 isoenzyme, encoded by the *GLUD2* gene, is predominantly expressed in brain, testis and kidney (Shashidharan et al., 1994; Zaganas et al., 2012). There it is present in mitochondria and is strongly affecting the energetic status of the cell by being allosterically regulated by various compounds, such as ADP and L-leucine, that constitute key metabolic intermediates (Zaganas et al., 2009). Also, there is evidence that steroid hormones could affect hGDH2 function by inhibiting it more potently than hGDH1 (Borompokas et al., 2010).

We can only speculate about the mechanism through which the hGDH2-Ala498 variant could protect from AD. It is tempting to hypothesize that the increased activity of the Ala498-hGDH2 protein degrades excess glutamate and delays the onset of neurodegeneration in brain areas such as the hippocampus. Compatible with this view is the fact that glutamate neurotoxicity is thought to contribute in AD pathogenesis and that memantine, which is used as a treatment agent for AD, acts by negating the detrimental effect of glutamate over-excitation (Lewerenz and Maher, 2015; Zádori et al., 2014).

Is this compatible with the detrimental effect of the same *GLUD2* p.Ser498Ala variant observed in PD (Plaitakis et al., 2010)? One can think that this could be attributed to the existence of different glutamate pools in human brain, which are differentially affected by the p.Ser498Ala *GLUD2* change. Also, differential localization of the hGDH2 enzyme in different brain structures, such as the medial temporal lobes and the hippocampi, involved primarily in AD pathogenesis, compared to the striatum and substantia nigra, mainly affected during PD onset, could account for the opposite effects of this *GLUD2* variant in these 2 disorders.

4.4. TARDBP *variants in the Cretan population*

Another important finding in our study was the identification in the CAC of 2 aged patients initially diagnosed with AD that carried the p.Ile383Val *TARDBP* variant. We have identified the same variant in 2 additional Cretan patients, one previously reported with FTD/ALS (Bourbouli et al., 2021)) and one with ALS. The *TARDBP* gene (OMIM 605078) encodes for TDP-43, a 43kD protein that is increasingly recognized as a main mediator in neurodegenerative processes (Palomo et al., 2019). Pathogenic variants in the *TARDBP* gene are a cause of familial and sporadic ALS and, less frequently, of FTD (Caroppo et al., 2016; Corcia et al., 2012; Zou et al., 2017). The p.Ile383Val pathogenic variant in exon 6 of *TARDBP* affects a highly conserved amino acid residue in the glycine-rich C-terminal part of TDP-43, known to be involved in protein-protein interactions (Ayala et al., 2008). Specifically, this region, which encompasses ~60% of the TDP-43 protein and more than 70% of the entire mRNA transcript, is necessary for the splicing inhibitory activity of TDP-43 for certain RNA transcripts and influences the solubility and cellular localization of TDP-43 (Ayala et al., 2008). This variant has been repeatedly shown to cause FTD, ALS and FTD/ALS, in reports from studies in the Greek (Charoniti et al., 2021; Ramos et al., 2019) and other populations (Cheng et al., 2016; Floris et al., 2015; Gelpi et al., 2014; Mol et al., 2021; Özoğuz et al., 2015; Ramos et al., 2020; Rutherford et al., 2008; Ticozzi et al., 2011). Our data are a call for a systematic study of this variant's geographic distribution and significance, as it could be associated with multifaceted phenotypic expression, including that of typical AD.

Regarding the p.Asn267Ser *TARDBP* variant that was detected in a cognitive healthy individual from our cohort, it has already been

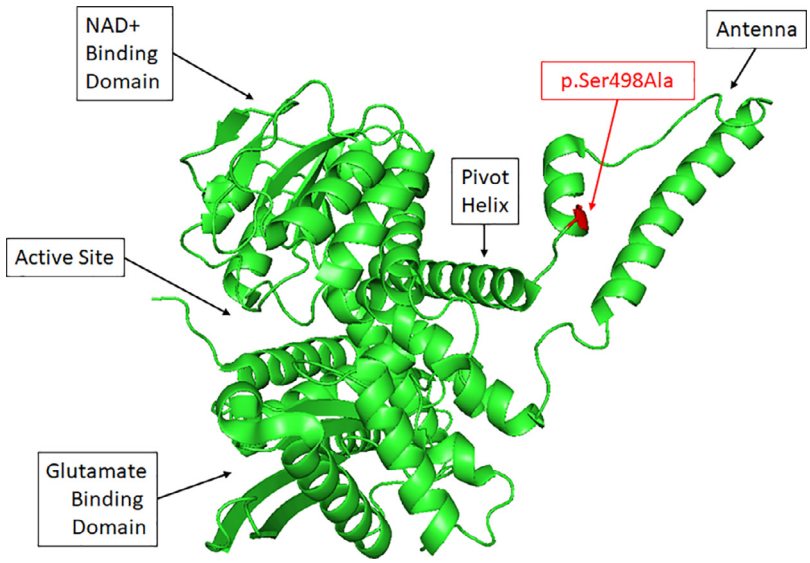

Fig. 4. Location of the Ser498 residue (in red) on the recently solved hGDH2 structure (Dimovasili et al., 2021). Shown is a cartoon representation of the hGDH2 structure (apo-form; PDB code: 6G2U). For simplicity, only one of the 6 subunits that compose the hGDH2 hexamer is shown (in green). The main functional parts of the subunit (NAD+ binding domain, glutamate binding domain, pivot helix and antenna) are also shown. This diagram was produced using the PyMOL Molecular Graphics System, Schrodinger, LLC. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

described in the literature as a causative variant in ALS and FTD patients (Borroni et al., 2009; Corrado et al., 2009; Filippelli et al., 2017; Floris et al., 2015; Narain et al., 2018). Moreover, the same variant has been detected in patients with corticobasal syndrome (Huey et al., 2012), PD (Gagliardi et al., 2018; Rayaprolu et al., 2013), and sporadic AD (Fernández et al., 2017). *In silico* analyses suggest that the substitution of Asn to Ser, creates a new phosphorylation site, potentially leading to reduced levels of TDP-43 (Borroni et al., 2009). Obviously, the phenotypic heterogeneity associated with this variant in conjunction with the variability in neurodegenerative disease onset and progression, suggest that the healthy individual from our cohort harboring the p.Asn267Ser variant could develop a disease phenotype later in his life.

4.5. Advantages and limitations

Even though WES is increasingly used for studying complex phenotypes, in most studies its efficiency is hampered by the heterogeneous genetic background of the participants involved, the diverging phenotypes for each disease and the differential effect of cultural and environmental factors on each individual (Lubke and McArtor, 2014). Indeed, one of the harder problems to overcome with genetic analyses on large, yet heterogeneous, populations, is collecting a group of patients with a clearly defined phenotype. More importantly, most populations consist of several ethnic groups who have only recently admixed, complicating case/control comparisons, since it is possible for 2 different groups to have variable SNP frequencies and disease prevalence. In contrast, the CAC described here constitutes a relatively genetically and culturally homogeneous population of well characterized individuals that enables the study of the effects of genetic variants largely uninfluenced by confounding factors. The genetic homogeneity of our sample was supported by performing PCA analysis, which showed a rather uniform clustering of the make-up of our cohort compared to other populations, including non-Cretan Greeks (Fig. 2).

One important limitation of our study is the small number of participants involved, both in the initial study of the CAC and in the 2 replication cohorts. Specifically, WES data from 196 participants of the CAC were included in our initial study. The genotyping analyses for the p.Ser498Ala *GLUD2* variant were further extended to 411 additional individuals from Crete and 808 individuals from the ADNI cohort, but the low number of AD patients in both these cohorts presented an additional limiting factor. In part, failure to reach significance in these p.Ser498Ala *GLUD2* variant genotypic analyses can be attributed to marginally sufficient statistical power: in order to ensure 90% power at $\alpha = 0.05$ (one-tailed) given the ratio of group sizes in the combined supplementary Cretan sample and the observed proportions of positive samples in the initial CAC sample, a minimum total sample size of n = 380 cases was required. However, at the smaller effect size observed in the combined Cretan sample, a much larger total sample is required to reach significance (n = 1720). In addition, post-hoc power calculations indicated that whereas power was sufficient to detect a significant difference in the observed proportions between the AD and cognitively nonimpaired control groups in the CAC (90.4%, at $p < 0.05$ two-tailed), it was insufficient in the case of the additional Cretan cohort and the subsection of the ADNI cohort. As supported by these post-hoc power analyses for the p.Ser498Ala *GLUD2* gene variant in the CAC, we believe that the genetic homogeneity of our population and the detailed phenotypic characterization of the participants could have allowed us to overcome this sample size limitation. In addition, in accordance with previous studies, our data show that the *APOE* $\varepsilon 4$ allele was 3 times more common in our AD patients than in controls. These results validate the use of the CAC sample in search of AD-related genetic defects. Finally, our results with the p.Ile383Val *TARDBP* variant are not affected by sample size, since this variant has repeatedly been described as pathogenic, even though not for AD patients, as in our study.

5. Conclusions

In the present study, we studied 196 participants of the CAC (95 AD, 20 MCI, 81 nonimpaired controls) using WES and then proceeded by genotyping to further investigate our initial findings in additional replication cohorts, both from Crete and the ADNI. Through these studies, we identified several variants of potential clinical significance in the *APP, PSEN1* and *PSEN2* genes. In the CAC,

the *GLUD2* p.Ser498Ala variant was more common in noncognitively impaired subjects (controls) than in AD patients, suggesting a possible protective effect. However, this finding did not reach statistical significance in another local replication cohort and in section of the ADNI cohort and therefore it should be considered preliminary. Finally, the AD phenotype was observed in 2 patients carrying the p.Ile383Val *TARDBP* variant, a variant repeatedly associated in the literature with FTD and/or ALS. The same *TARDBP* variant (p.Ile383Val) was found in 2 other Cretan patients, nonmembers of the CAC, suffering from ALS and FTD/ALS, respectively. These results attest to the value of genetic biomarkers in the characterization and study of aged adults with AD phenotype and expand the phenotypic spectrum of *TARDBP* variants to include AD-like presentation.

Disclosure statement

1. All authors declare that they have nothing to disclose.
2. This work has been supported mainly by a grant from the European Union (European Social Fund – ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program: THALES entitled "UOC-Multidisciplinary network for the study of Alzheimer's Disease" (Grant Code: MIS 377299). Part of the study was supported by the grant "Older adulthood: Development of Cognitive Assessment and Quality of Life and Efficacy of Intervention Programs (SKEPSI)," funded by the European Union Regional Development Funds and National funding. Data collection and sharing for part of this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.
3. All authors verify that the data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.
4. We state that all procedures that took place during the completion of this study, comply with the ethical standards for human subjects.

CRediT authorship contribution statement

Lambros Mathioudakis: Investigation, Writing – original draft, Writing – review & editing. **Christina Dimovasili:** Investigation, Writing – original draft, Writing – review & editing. **Mara Bourbouli:** Investigation, Writing – review & editing. **Helen Latsoudis:** Investigation, Writing – review & editing. **Evgenia Kokosali:** Investigation. **Garyfallia Gouna:** Investigation. **Emmanouella Vogiatzi:** Investigation. **Maria Basta:** Investigation. **Stefania Kapetanaki:** Investigation. **Simeon Panagiotakis:** Investigation. **Alexandros Kanterakis:** Investigation, Formal analysis, Visualization. **Dimitrios Boumpas:** Investigation. **Christos Lionis:** Investigation. **Andreas Plaitakis:** Conceptualization, Formal analysis, Writing – review & editing. **Panagiotis Simos:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – review & editing. **Alexandros Vgontzas:** Conceptualization, Supervision, Funding acquisition. **Dimitrios Kafetzopoulos:** Methodology, Resources, Investigation. **Ioannis Zaganas:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Acknowledgements

The excellent assistance of Cynthia Manassaki in coordinating the overall project is cordially acknowledged. Also, this work would not be possible without the help from the nurses (Aikaterini Albantaki, Georgia Fragkiadaki, Marina Lironi, Maria Maniou, Sofia Marinaki, Maria Titaki), physicians (George Duijker, Irini Kalogridaki, Eleni Klouva, Eva Ladoukaki, Kornilia Makri, Polivios Papadokostakis, Emmanouil Papamastorakis, Rodanthi Pateli, Dimitroula Prokopiadou, Emmanouil Symvoulakis, Ioanna Stefanaki, Nikolaos Tsakountakis, Ioanna Tsiligianni, Aggeliki Vasilaki, Theodoros Vasilopoulos, Nikolaos Fountoulakis, Irini Koutentaki), neuropsychologist (Sofia Tziraki) and medical students (Christina Belogianni, Ioanna Kardari, Vassiliki Kounali, Annieza Selmanai) involved in patient recruitment and data collection. Some of the data for this study were collected in collaboration with Professor Fofi Constantinidou, Center for Applied Neuroscience, University of Cyprus, Nicosia, Cyprus. We thank Professor Constantinos Deltas and Dr. Konstantinos Voskarides at the Molecular Medicine Research Center of the University of Cyprus for providing expertise and facilities of their Biobank for implementing part of this project (University of Cyprus Biobank, Nicosia, Cyprus).

References

Ahmed, Z., Mackenzie, I.R.A., Hutton, M.L., Dickson, D.W., 2007. Progranulin in frontotemporal lobar degeneration and neuroinflammation. J. Neuroinflamm. 4 (1), 7.

Albani, D., Roiter, I., Artuso, V., Batelli, S., Prato, F., Pesaresi, M., Galimberti, D., Scarpini, E., Bruni, A., Franceschi, M., Piras, M.R., Confaloni, A., Forloni, G., 2007. Presenilin-1 mutation E318G and familial Alzheimer's disease in the Italian population. Neurobiol. Aging 28 (11), 1682–1688.

American Psychiatric Association, 1994. DSM-IV Criteria. American Psychiatric Press, Washington, D.C..

Arvanitakis, Z., Shah, R.C., Bennett, D.A., 2019. Diagnosis and management of dementia: review. JAMA 322 (16), 1589–1599.

Ayala, Y.M., Zago, P., D'Ambrogio, A., Xu, Y.-F., Petrucelli, L., Buratti, E., Baralle, F.E., 2008. Structural determinants of the cellular localization and shuttling of TDP-43. J. Cell Sci. 121 (22), 3778–3785.

Baker, E., Sims, R., Leonenko, G., Frizzati, A., Harwood, J.C., Grozeva, D., Gerad/Perades, Charge, Adgc, Eadi, consortia, I., Morgan, K., Passmore, P., Holmes, C., Powell, J., Brayne, C., Gill, M., Mead, S., Bossù, P., Spalletta, G., Goate, A.M., Cruchaga, C., Maier, W., Heun, R., Jessen, F., Peters, O., Dichgans, M., FröLich, L., Ramirez, A., Jones, L., Hardy, J., Ivanov, D., Hill, M., Holmans, P., Allen, N.D., Morgan, B.P., Seshadri, S., Schellenberg, G.D., Amouyel, P., Williams, J., Escott-Price, V., 2019. Gene-based analysis in HRC imputed genome wide association data identifies three novel genes for Alzheimer's disease. PLoS One 14 (7), e0218111.

Baker, M., Mackenzie, I.R., Pickering-Brown, S.M., Gass, J., Rademakers, R., Lindholm, C., Snowden, J., Adamson, J., Sadovnick, A.D., Rollinson, S., Cannon, A., Dwosh, E., Neary, D., Melquist, S., Richardson, A., Dickson, D., Berger, Z., Eriksen, J., Robinson, T., Zehr, C., Dickey, C.A., Crook, R., McGowan, E., Mann, D., Boeve, B., Feldman, H., Hutton, M., 2006. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 442 (7105), 916–919.

Bao, X., Pal, R., Hascup, K.N., Wang, Y., Wang, W.T., Xu, W., Hui, D., Agbas, A., Wang, X., Michaelis, M.L., Choi, I.Y., Belousov, A.B., Gerhardt, G.A., Michaelis, E.K., 2009. Transgenic expression of Glud1 (glutamate dehydrogenase 1) in neurons: in vivo model of enhanced glutamate release, altered synaptic plasticity, and selective neuronal vulnerability. J. Neurosci. 29 (44), 13929–13944.

Basta, M., Koutentaki, E., Vgontzas, A., Zaganas, I., Vogiatzi, E., Gouna, G., Bourbouli, M., Panagiotakis, S., Kapetanaki, S., Fernandez-Mendoza, J., Simos, P., 2020. Objective daytime napping is associated with disease severity and inflammation in patients with mild to moderate dementia1. J. Alzheimers Dis. 74 (3), 803–815.

Beach, T.G., Monsell, S.E., Phillips, L.E., Kukull, W., 2012. Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. J. Neuropathol. Exp. Neurol. 71 (4), 266–273.

Bellenguez, C., Charbonnier, C., Grenier-Boley, B., Quenez, O., Le Guennec, K., Nicolas, G., Chauhan, G., Wallon, D., Rousseau, S., Richard, A.C., Boland, A., Bourque, G., Munter, H.M., Olaso, R., Meyer, V., Rollin-Sillaire, A., Pasquier, F., Letenneur, L., Redon, R., Dartigues, J.F., Tzourio, C., Frebourg, T., Lathrop, M., Deleuze, J.F., Hannequin, D., Genin, E., Amouyel, P., Debette, S., Lambert, J.C., Campion, D., 2017. Contribution to Alzheimer's disease risk of rare variants in TREM2, SORL1, and ABCA7 in 1779 cases and 1273 controls. Neurobiol. Aging 59, 220.e221–220.e229.

Benitez, B.A., Karch, C.M., Cai, Y., Jin, S.C., Cooper, B., Carrell, D., Bertelsen, S., Chibnik, L., Schneider, J.A., Bennett, D.A., Fagan, A.M., Holtzman, D., Morris, J.C., Goate, A.M., Cruchaga, C., 2013. The PSEN1, p.E318G variant increases the risk of Alzheimer's disease in APOE-ε4 carriers. PLos Genet. 9 (8), e1003685.

Bertram, L., McQueen, M.B., Mullin, K., Blacker, D., Tanzi, R.E., 2007. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nat. Genet. 39 (1), 17–23.

Bettens, K., Sleegers, K., Van Broeckhoven, C., 2013. Genetic insights in Alzheimer's disease. Lancet Neurol. 12 (1), 92–104.

Bird, T.D., 2005. Genetic factors in Alzheimer's disease. N. Engl. J. Med. 352 (9), 862–864.

Blauwendraat, C., Wilke, C., Simón-Sánchez, J., Jansen, I.E., Reifschneider, A., Capell, A., Haass, C., Castillo-Lizardo, M., Biskup, S., Maetzler, W., Rizzu, P., Heutink, P., Synofzik, M., 2018. The wide genetic landscape of clinical frontotemporal dementia: systematic combined sequencing of 121 consecutive subjects. Genet. Med. 20 (2), 240–249.

Borompokas, N., Papachatzaki, M.M., Kanavouras, K., Mastorodemos, V., Zaganas, I., Spanaki, C., Plaitakis, A., 2010. Estrogen modification of human glutamate dehydrogenases is linked to enzyme activation state. J. Biol. Chem. 285 (41), 31380–31387.

Borroni, B., Bonvicini, C., Alberici, A., Buratti, E., Agosti, C., Archetti, S., Papetti, A., Stuani, C., Di Luca, M., Gennarelli, M., Padovani, A., 2009. Mutation within TARDBP leads to frontotemporal dementia without motor neuron disease. Hum. Mutat. 30 (11), E974–E983.

Bourbouli, M., Paraskevas, G.P., Rentzos, M., Mathioudakis, L., Zouvelou, V., Bougea, A., Tychalas, A., Kimiskidis, V.K., Constantinides, V., Zafeiris, S., Tzagournissakis, M., Papadimas, G., Karadima, G., Koutsis, G., Kroupis, C., Kartanou, C., Kapaki, E., Zaganas, I., 2021. Genotyping and plasma/cerebrospinal fluid profiling of a cohort of frontotemporal dementia-amyotrophic lateral sclerosis patients. Brain Sci 11 (9), 1239.

Bourbouli, M., Rentzos, M., Bougea, A., Zouvelou, V., Constantinides, V.C., Zaganas, I., Evdokimidis, I., Kapaki, E., Paraskevas, G.P., 2017. Cerebrospinal fluid TAR DNA-binding protein 43 combined with tau proteins as a candidate biomarker for amyotrophic lateral sclerosis and frontotemporal dementia spectrum disorders. Dement. Geriatr. Cogn. Disord. 44 (3-4), 144–152.

Burbaeva, G., Boksha, I.S., Tereshkina, E.B., Savushkina, O.K., Starodubtseva, L.I., Turishcheva, M.S., 2005. Glutamate metabolizing enzymes in prefrontal cortex of Alzheimer's disease patients. Neurochem. Res. 30 (11), 1443–1451.

Burki, F., Kaessmann, H., 2004. Birth and adaptive evolution of a hominoid gene that supports high neurotransmitter flux. Nat. Genet. 36 (10), 1061–1063.

Cacace, R., Sleegers, K., Van Broeckhoven, C., 2016. Molecular genetics of early-onset Alzheimer's disease revisited. Alzheimers Dement 12 (6), 733–748.

Cai, Y., An, S.S.A., Kim, S., 2015. Mutations in presenilin 2 and its implications in Alzheimer's disease and other dementia-associated disorders. Clin. Interv. Aging 10, 1163–1172.

Caroppo, P., Camuzat, A., Guillot-Noel, L., Thomas-Antérion, C., Couratier, P., Wong, T.H., Teichmann, M., Golfier, V., Auriacombe, S., Belliard, S., Laurent, B., Lattante, S., Millecamps, S., Clot, F., Dubois, B., van Swieten, J.C., Brice, A., Le Ber, I., 2016. Defining the spectrum of frontotemporal dementias associated with TARDBP mutations. Neurol. Genet. 2 (3), e80.

Charoniti, E., Papastefanopoulou, V., Florou-Hatziyiannidou, C., Koros, C., Stanitsa, E., Papatriantafyllou, J.D., Papageorgiou, S.G., Kroupis, C., 2021. TARDBP p.I383V, a recurrent alteration in Greek FTD patients. J. Neurol. Sci. 428, 117566.

Chávez-Gutiérrez, L., Szaruga, M., 2020. Mechanisms of neurodegeneration - insights from familial Alzheimer's disease. Semin. Cell Dev. Biol. 105, 75–85.

Cheng, Y.W., Lee, M.J., Chen, T.F., Cheng, T.W., Lai, Y.M., Hua, M.S., Chiu, M.J., 2016. A single nucleotide TDP-43 mutation within a Taiwanese family: A multifaceted demon. Amyotroph Lateral Scler Frontotemporal Degener. 17 (3-4), 292–294.

Corcia, P., Valdmanis, P., Millecamps, S., Lionnet, C., Blasco, H., Mouzat, K., Daoud, H., Belzil, V., Morales, R., Pageot, N., Danel-Brunaud, V., Vandenberghe, N., Pradat, P.F., Couratier, P., Salachas, F., Lumbroso, S., Rouleau, G.A., Meininger, V., Camu, W., 2012. Phenotype and genotype analysis in amyotrophic lateral sclerosis with TARDBP gene mutations. Neurology 78 (19), 1519–1526.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261 (5123), 921–923.

Corrado, L., Ratti, A., Gellera, C., Buratti, E., Castellotti, B., Carlomagno, Y., Ticozzi, N., Mazzini, L., Testa, L., Taroni, F., Baralle, F.E., Silani, V., D'Alfonso, S., 2009. High frequency of TARDBP gene mutations in Italian patients with amyotrophic lateral sclerosis. Hum. Mutat. 30 (4), 688–694.

Cruchaga, C., Chakraverty, S., Mayo, K., Vallania, F.L.M., Mitra, R.D., Faber, K., Williamson, J., Bird, T., Diaz-Arrastia, R., Foroud, T.M., Boeve, B.F., Graff-Radford, N.R., Jean St., P., Lawson, M., Ehm, M.G., Mayeux, R., Goate, A.M.for the, N.I.A.L.N.F.S.C., 2012a. Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer's disease families. PLoS One 7 (2), e31039.

Cruchaga, C., Haller, G., Chakraverty, S., Mayo, K., Vallania, F.L., Mitra, R.D., Faber, K., Williamson, J., Bird, T., Diaz-Arrastia, R., Foroud, T.M., Boeve, B.F., Graff-Radford, N.R., St Jean, P., Lawson, M., Ehm, M.G., Mayeux, R., Goate, A.M., 2012b. Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer's disease families. PLoS One 7 (2), e31039.

Cruchaga, C., Karch, C.M., Jin, S.C., Benitez, B.A., Cai, Y., Guerreiro, R., Harari, O., Norton, J., Budde, J., Bertelsen, S., Jeng, A.T., Cooper, B., Skorupa, T., Carrell, D., Levitch, D., Hsu, S., Choi, J., Ryten, M., Sassi, C., Bras, J., Gibbs, R.J., Hernandez, D.G., Lupton, M.K., Powell, J., Forabosco, P., Ridge, P.G., Corcoran, C.D., Tschanz, J.T., Norton, M.C., Munger, R.G., Schmutz, C., Leary, M., Demirci, F.Y., Bamne, M.N., Wang, X., Lopez, O.L., Ganguli, M., Medway, C., Turton, J., Lord, J., Braae, A., Barber, I., Brown, K., Pastor, P., Lorenzo-Betancor, O., Brkanac, Z., Scott, E., Topol, E., Morgan, K., Rogaeva, E., Singleton, A., Hardy, J., Kamboh, M.I., George-Hyslop, P.S., Cairns, N., Morris, J.C., Kauwe, J.S.K., Goate, A.M., 2014. Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease. Nature 505 (7484), 550–554.

Cruts, M., Gijselinck, I., van der Zee, J., Engelborghs, S., Wils, H., Pirici, D., Rademakers, R., Vandenberghe, R., Dermaut, B., Martin, J.-J., van Duijn, C., Peeters, K., Sciot, R., Santens, P., De Pooter, T., Mattheijssens, M., Van den Broeck, M., Cuijt, I., Vennekens, K.l., De Deyn, P.P., Kumar-Singh, S., Van Broeckhoven, C., 2006. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 442 (7105), 920–924.

Cruts, M., van Duijn, C.M., Backhovens, H., Van den Broeck, M., Wehnert, A., Serneels, S., Sherrington, R., Hutton, M., Hardy, J., St George-Hyslop, P.H., Hofman, A., Van Broeckhoven, C., 1998. Estimation of the genetic contribution of presenilin-1 and -2 mutations in a population-based study of presenile Alzheimer disease. Hum. Mol. Genet. 7 (1), 43–51.

Cukier, H.N., Kunkle, B.K., Hamilton, K.L., Rolati, S., Kohli, M.A., Whitehead, P.L., Jaworski, J., Vance, J.M., Cuccaro, M.L., Carney, R.M., Gilbert, J.R., Farrer, L.A., Martin, E.R., Beecham, G.W., Haines, J.L., Pericak-Vance, M.A., 2017. Exome Sequencing of Extended Families with Alzheimer's Disease Identifies Novel Genes Implicated in Cell Immunity and Neuronal Function. J Alzheimers Dis Parkinsonism 7 (4).

D'Argenio, V., Sarnataro, D., 2020. New insights into the molecular bases of familial Alzheimer's disease. J. Pers. Med. 10 (2), 26.

Del-Aguila, J.L., Koboldt, D.C., Black, K., Chasse, R., Norton, J., Wilson, R.K., Cruchaga, C., 2015. Alzheimer's disease: rare variants with large effect sizes. Curr. Opin. Genet. Dev. 33, 49–55.

Dermaut, B., Cruts, M., Slooter, A.J., Van Gestel, S., De Jonghe, C., Vanderstichele, H., Vanmechelen, E., Breteler, M.M., Hofman, A., van Duijn, C.M., Van Broeckhoven, C., 1999. The Glu318Gly substitution in presenilin 1 is not causally related to Alzheimer disease. Am. J. Hum. Genet. 64 (1), 290–292.

Dimovasili, C., Fadouloglou, V.E., Kefala, A., Providaki, M., Kotsifaki, D., Kanavouras, K., Sarrou, I., Plaitakis, A., Zaganas, I., Kokkinidis, M., 2021. Crystal structure of glutamate dehydrogenase 2, a positively selected novel human enzyme involved in brain biology and cancer pathophysiology. J. Neurochem. 157 (3), 802–815.

Elhaik, E., Tatarinova, T., Chebotarev, D., Piras, I.S., Maria Calò, C., De Montis, A., Atzori, M., Marini, M., Tofanelli, S., Francalacci, P., Pagani, L., Tyler-Smith, C., Xue, Y., Cucca, F., Schurr, T.G., Gaieski, J.B., Melendez, C., Vilar, M.G., Owings, A.C., Gómez, R., Fujita, R., Santos, F.R., Comas, D., Balanovsky, O., Balanovska, E., Zalloua, P., Soodyall, H., Pitchappan, R., Ganeshprasad, A., Hammer, M., Matisoo–Smith, L., Wells, R.S., 2014. Geographic population structure analysis of worldwide human populations infers their biogeographical origins. Nat. Commun. 5, 3513.

Fernández, M.V., Kim, J.H., Budde, J.P., Black, K., Medvedeva, A., Saef, B., Deming, Y., Del-Aguila, J., Ibañez, L., Dube, U., Harari, O., Norton, J., Chasse, R., Morris, J.C., Goate, A., group, N.-L.f.s., Ncrad, Cruchaga, C., 2017. Analysis of neurodegenerative Mendelian genes in clinically diagnosed Alzheimer Disease. PLos Genet. 13 (11), e1007045.

Filippelli, E., Valentino, P., Annesi, G., Nisticò, R., Quattrone, A., 2017. Camptocormia as presenting in lower motor neuron disease with TARDBP mutation: case report. Neurolog. Sci. 38 (10), 1885–1887.

Floris, G., Borghero, G., Cannas, A., Di Stefano, F., Murru, M.R., Corongiu, D., Cuccu, S., Tranquilli, S., Cherchi, M.V., Serra, A., Loi, G., Marrosu, M.G., Chiò, A., Marrosu, F., 2015. Clinical phenotypes and radiological findings in frontotemporal dementia related to TARDBP mutations. J. Neurol. 262 (2), 375–384.

Foo, J.N., Liu, J.J., Tan, E.K., 2012. Whole-genome and whole-exome sequencing in neurological diseases. Nat. Rev. Neurol. 8 (9), 508–517.
Gagliardi, M., Arabia, G., Nisticò, R., Iannello, G., Procopio, R., Manfredini, L., Annesi, G., Quattrone, A., 2018. Mutational analysis of TARDBP gene in patients affected by Parkinson's disease from Calabria. J. Neurol. Sci. 390, 209–211.
Gelpi, E., van der Zee, J., Turon Estrada, A., Van Broeckhoven, C., Sanchez-Valle, R., 2014. TARDBP mutation p.Ile383Val associated with semantic dementia and complex proteinopathy. Neuropathol. Appl. Neurobiol. 40 (2), 225–230.
Ghosh, S., Durgvanshi, S., Agarwal, S., Raghunath, M., Sinha, J.K., 2020. Current Status of Drug Targets and Emerging Therapeutic Strategies in the Management of Alzheimer's Disease. Curr Neuropharmacol 18 (9), 883–903.
Goldman, J.S., Van Deerlin, V.M., 2018. Alzheimer's disease and frontotemporal dementia: the current state of genetics and genetic testing since the advent of next-generation sequencing. Mol. Diagn. Ther. 22 (5), 505–513.
Goodwin, S., McPherson, J.D., McCombie, W.R., 2016. Coming of age: ten years of next-generation sequencing technologies. Nat. Rev. Genet. 17 (6), 333–351.
Grandal Leiros, B., Pérez Méndez, L.I., Zelaya Huerta, M.V., Moreno Eguinoa, L., García-Bragado, F., Tuñón Álvarez, T., Roldán Larreta, J.J., 2018. Prevalencia y concordancia entre diagnóstico clínico y anatomopatológico de demencia en una clínica psicogeriátrica. Neurología 33 (1), 13–17.
Guerreiro, R.J., Baquero, M., Blesa, R., Boada, M., Brás, J.M., Bullido, M.J., Calado, A., Crook, R., Ferreira, C., Frank, A., Gómez-Isla, T., Hernández, I., Lleó, A., Machado, A., Martínez-Lage, P., Masdeu, J., Molina-Porcel, L., Molinuevo, J.L., Pastor, P., Pérez-Tur, J., Relvas, R., Oliveira, C.R., Ribeiro, M.H., Rogaeva, E., Sa, A., Samaranch, L., Sánchez-Valle, R., Santana, I., Tàrraga, L., Valdivieso, F., Singleton, A., Hardy, J., Clarimón, J., 2010. Genetic screening of Alzheimer's disease genes in Iberian and African samples yields novel mutations in presenilins and APP. Neurobiol. Aging 31 (5), 725–731.
Guven, G., Lohmann, E., Bras, J., Gibbs, J.R., Gurvit, H., Bilgic, B., Hanagasi, H., Rizzu, P., Heutink, P., Emre, M., Erginel-Unaltuna, N., Just, W., Hardy, J., Singleton, A., Guerreiro, R., 2016. Mutation frequency of the major frontotemporal dementia genes, MAPT, GRN and C9ORF72 in a Turkish cohort of dementia patients. PLoS One 11 (9), e0162592.
Helisalmi, S., Hiltunen, M., Mannermaa, A., Koivisto, A.M., Lehtovirta, M., Alafuzoff, I., Ryynänen, M., Soininen, H., 2000. Is the presenilin-1 E318G missense mutation a risk factor for Alzheimer's disease? Neurosci. Lett. 278 (1-2), 65–68.
Hinz, F.I., Geschwind, D.H., 2017. Molecular genetics of neurodegenerative dementias. Cold Spring Harb. Perspect. Biol. 9 (4).
Hippen, A.A., Ebbert, M.T., Norton, M.C., Tschanz, J.T., Munger, R.G., Corcoran, C.D., Kauwe, J.S., 2016. Presenilin E318G variant and Alzheimer's disease risk: the Cache County study. BMC Genomics 17 Suppl 3 (Suppl 3), 438.
Huey, E.D., Ferrari, R., Moreno, J.H., Jensen, C., Morris, C.M., Potocnik, F., Kalaria, R.N., Tierney, M., Wassermann, E.M., Hardy, J., Grafman, J., Momeni, P., 2012. FUS and TDP43 genetic variability in FTD and CBS. Neurobiol. Aging 33 (5) 1016.e1019-1016.e1017.
Hutton, M., Lendon, C.L., Rizzu, P., Baker, M., Froelich, S., Houlden, H., Pickering-Brown, S., Chakraverty, S., Isaacs, A., Grover, A., Hackett, J., Adamson, J., Lincoln, S., Dickson, D., Davies, P., Petersen, R.C., Stevens, M., de Graaff, E., Wauters, E., van Baren, J., Hillebrand, M., Joosse, M., Kwon, J.M., Nowotny, P., Che, L.K., Norton, J., Morris, J.C., Reed, L.A., Trojanowski, J., Basun, H., Lannfelt, L., Neystat, M., Fahn, S., Dark, F., Tannenberg, T., Dodd, P.R., Hayward, N., Kwok, J.B.J., Schofield, P.R., Andreadis, A., Snowden, J., Craufurd, D., Neary, D., Owen, F., Oostra, B.A., Hardy, J., Goate, A., van Swieten, J., Mann, D., Lynch, T., Heutink, P., 1998. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 393 (6686), 702–705.
Iron, A., Richard, P., de Zulueta, M.P., Thomas, G., Thomas, M., 1995. Genotyping of a patient homozygous for a rare apolipoprotein E1 [Gly127–>Asp; Arg158–>Cys] (Weisgraber allele). J. Inherit. Metab. Dis. 18 (6), 723–726.
Jansen, I.E., Savage, J.E., Watanabe, K., Bryois, J., Williams, D.M., Steinberg, S., Sealock, J., Karlsson, I.K., Hägg, S., Athanasiu, L., Voyle, N., Proitsi, P., Witoelar, A., Stringer, S., Aarsland, D., Almdahl, I.S., Andersen, F., Bergh, S., Bettella, F., Bjornsson, S., Brækhus, A., Bråthen, G., de Leeuw, C., Desikan, R.S., Djurovic, S., Dumitrescu, L., Fladby, T., Hohman, T.J., Jonsson, P.V., Kiddle, S.J., Rongve, A., Saltvedt, I., Sando, S.B., Selbæk, G., Shoai, M., Skene, N.G., Snaedal, J., Stordal, E., Ulstein, I.D., Wang, Y., White, L.R., Hardy, J., Hjerling-Leffler, J., Sullivan, P.F., van der Flier, W.M., Dobson, R., Davis, L.K., Stefansson, H., Stefansson, K., Pedersen, N.L., Ripke, S., Andreassen, O.A., Posthuma, D., 2019. Genome-wide meta–analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat. Genet. 51 (3), 404–413.
Jin, S.C., Pastor, P., Cooper, B., Cervantes, S., Benitez, B.A., Razquin, C., Goate, A., Cruchaga, C., 2012. Pooled-DNA sequencing identifies novel causative variants in PSEN1, GRN and MAPT in a clinical early-onset and familial Alzheimer's disease Ibero-American cohort. Alzheimers Res. Ther. 4 (4), 34.
Jonsson, T., Atwal, J.K., Steinberg, S., Snaedal, J., Jonsson, P.V., Bjornsson, S., Stefansson, H., Sulem, P., Gudbjartsson, D., Maloney, J., Hoyte, K., Gustafson, A., Liu, Y., Lu, Y., Bhangale, T., Graham, R.R., Huttenlocher, J., Bjornsdottir, G., Andreassen, O.A., Jönsson, E.G., Palotie, A., Behrens, T.W., Magnusson, O.T., Kong, A., Thorsteinsdottir, U., Watts, R.J., Stefansson, K., 2012. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 488 (7409), 96–99.
Kabashi, E., Valdmanis, P.N., Dion, P., Spiegelman, D., McConkey, B.J., Velde, C.V., Bouchard, J.-P., Lacomblez, L., Pochigaeva, K., Salachas, F., Pradat, P.-F., Camu, W., Meininger, V., Dupre, N., Rouleau, G.A., 2008. TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis. Nat. Genet. 40 (5), 572–574.
Kalef-Ezra, E., Kotzamani, D., Zaganas, I., Katrakili, N., Plaitakis, A., Tokatlidis, K., 2016. Import of a major mitochondrial enzyme depends on synergy between two distinct helices of its presequence. Biochem. J. 473 (18), 2813–2829.
Karademas, E.C., Simos, P., Zaganas, I., Tziraki, S., Panagiotakis, S., Basta, M., Vgontzas, A.N., 2019. The impact of mild cognitive impairment on the self-regulation process: A comparison study of persons with mild cognitive impairment and cognitively healthy older adults. J. Health Psychol. 24 (3), 351–361.
Kim, A.Y., Baik, E.J., 2019. Glutamate Dehydrogenase as a Neuroprotective Target Against Neurodegeneration. Neurochem. Res. 44 (1), 147–153.
Kim, S.W., Heo, J.H., Kim, C.H., Yoo, D.C., Won, D.H., Lee, S.G., Cho, K.J., Song, J.H., Park, S.J., Yang, Y.G., Choi, D.W., 2010. Rapid and direct detection of apolipoprotein E genotypes using whole blood from humans. J. Toxicol. Environ. Health A 73 (21-22), 1502–1510.
Kumar, V., Westra, H.J., Karjalainen, J., Zhernakova, D.V., Esko, T., Hrdlickova, B., Almeida, R., Zhernakova, A., Reinmaa, E., Võsa, U., Hofker, M.H., Fehrmann, R.S., Fu, J., Withoff, S., Metspalu, A., Franke, L., Wijmenga, C., 2013. Human disease-associated genetic variation impacts large intergenic non-coding RNA expression. PLoS Genet. 9 (1), e1003201.
Kunkle, B.W., Grenier-Boley, B., Sims, R., Bis, J.C., Damotte, V., Naj, A.C., Boland, A., Vronskaya, M., van der Lee, S.J., Amlie-Wolf, A., Bellenguez, C., Frizatti, A., Chouraki, V., Martin, E.R., Sleegers, K., Badarinarayan, N., Jakobsdottir, J., Hamilton-Nelson, K.L., Moreno-Grau, S., Olaso, R., Raybould, R., Chen, Y., Kuzma, A.B., Hiltunen, M., Morgan, T., Ahmad, S., Vardarajan, B.N., Epelbaum, J., Hoffmann, P., Boada, M., Beecham, G.W., Garnier, J.-G., Harold, D., Fitzpatrick, A.L., Valladares, O., Moutet, M.-L., Gerrish, A., Smith, A.V., Qu, L., Bacq, D., Denning, N., Jian, X., Zhao, Y., Del Zompo, M., Fox, N.C., Choi, S.-H., Mateo, I., Hughes, J.T., Adams, H.H., Malamon, J., Sanchez-Garcia, F., Patel, Y., Brody, J.A., Dombroski, B.A., Naranjo, M.C.D., Daniilidou, M., Eiriksdottir, G., Mukherjee, S., Wallon, D., Uphill, J., Aspelund, T., Cantwell, L.B., Garzia, F., Galimberti, D., Hofer, E., Butkiewicz, M., Fin, B., Scarpini, E., Sarnowski, C., Bush, W.S., Meslage, S., Kornhuber, J., White, C.C., Song, Y., Barber, R.C., Engelborghs, S., Sordon, S., Voijnovic, D., Adams, P.M., Vandenberghe, R., Mayhaus, M., Cupples, L.A., Albert, M.S., De Deyn, P.P., Gu, W., Himali, J.J., Beekly, D., Squassina, A., Hartmann, A.M., Orellana, A., Blacker, D., Rodriguez-Rodriguez, E., Lovestone, S., Garcia, M.E., Doody, R.S., Munoz-Fernadez, C., Sussams, R., Lin, H., Fairchild, T.J., Benito, Y.A., Holmes, C., Karamujić-Čomić, H., Frosch, M.P., Thonberg, H., Maier, W., Roshchupkin, G., Ghetti, B., Giedraitis, V., Kawalia, A., Li, S., Huebinger, R.M., Kilander, L., Moebus, S., Hernández, I., Kamboh, M.I., Brundin, R., Turton, J., Yang, Q., Katz, M.J., Concari, L., Lord, J., Beiser, A.S., Keene, C.D., Helisalmi, S., Kloszewska, I., Kukull, W.A., Koivisto, A.M., Lynch, A., Tarraga, L., Larson, E.B., Haapasalo, A., Lawlor, B., Mosley, T.H., Lipton, R.B., Solfrizzi, V., Gill, M., Longstreth, W.T., Montine, T.J., Frisardi, V., Diez-Fairen, M., Rivadeneira, F., Petersen, R.C., Deramecourt, V., Alvarez, I., Salani, F., Ciaramella, A., Boerwinkle, E., Reiman, E.M., Fievet, N., Rotter, J.I., Reisch, J.S., Hanon, O., Cupidi, C., Andre Uitterlinden, A.G., Royall, D.R., Dufouil, C., Maletta, R.G., de Rojas, I., Sano, M., Brice, A., Cecchetti, R., George-Hyslop, P.S., Ritchie, K., Tsolaki, M., Tsuang, D.W., Dubois, B., Craig, D., Wu, C.-K., Soininen, H., Avramidou, D., Albin, R.L., Fratiglioni, L., Germanou, A., Apostolova, L.G., Keller, L., Koutroumani, M., Arnold, S.E., Panza, F., Gkatzima, O., Asthana, S., Hannequin, D., Whitehead, P., Atwood, C.S., Caffarra, P., Hampel, H., Quintela, I., Carracedo, Á., Lannfelt, L., Rubinsztein, D.C., Barnes, L.L., Pasquier, F., Frölich, L., Barral, S., McGuinness, B., Beach, T.G., Johnston, J.A., Becker, J.T., Passmore, P., Bigio, E.H., Schott, J.M., Bird, T.D., Warren, J.D., Boeve, B.F., Lupton, M.K., Bowen, J.D., Proitsi, P., Boxer, A., Powell, J.F., Burke, J.R., Kauwe, J.S.K., Burns, J.M., Mancuso, M., Buxbaum, J.D., Bonuccelli, U., Cairns, N.J., McQuillin, A., Cao, C., Livingston, G., Carlson, C.S., Bass, N.J., Carlsson, C.M., Hardy, J., Carney, R.M., Bras, J., Carrasquillo, M.M., Guerreiro, R., Allen, M., Chui, H.C., Fisher, E., Masullo, C., Crocco, E.A., DeCarli, C., Bisceglio, G., Dick, M., Ma, L., Duara, R., Graff-Radford, N.R., Evans, D.A., Hodges, A., Faber, K.M., Scherer, M., Fallon, K.B., Riemenschneider, M., Fardo, D.W., Heun, R., Farlow, M.R., Kölsch, H., Ferris, S., Leber, M., Foroud, T.M., Heuser, I., Galasko, D.R., Giegling, I., Gearing, M., Hüll, M., Geschwind, D.H., Gilbert, J.R., Morris, J., Green, R.C., Mayo, K., Growdon, J.H., Feulner, T., Hamilton, R.L., Harrell, L.E., Drichel, D., Honig, L.S., Cushion, T.D., Huentelman, M.J., Hollingworth, P., Hulette, C.M., Hyman, B.T., Marshall, R., Jarvik, G.P., Meggy, A., Abner, E., Menzies, G.E., Jin, L.-W., Leonenko, G., Real, L.M., Jun, G.R., Baldwin, C.T., Grozeva, D., Karydas, A., Russo, G., Kaye, J.A., Kim, R., Jessen, F., Kowall, N.W., Vellas, B., Kramer, J.H., Vardy, E., LaFerla, F.M., Jöckel, K.-H., Lah, J.J., Dichgans, M., Leverenz, J.B., Mann, D., Levey, A.I., Pickering-Brown, S., Lieberman, A.P., 2019. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat. Genet. 51 (3), 414–430.
Kwiatkowski, T.J., Bosco, D.A., Leclerc, A.L., Tamrazian, E., Vanderburg, C.R., Russ, C., Davis, A., Gilchrist, J., Kasarskis, E.J., Munsat, T., Valdmanis, P., Rouleau, G.A., Hosler, B.A., Cortelli, P., de Jong, P.J., Yoshinaga, Y., Haines, J.L., Pericak–Vance, M.A., Yan, J., Ticozzi, N., Siddique, T., McKenna-Yasek, D., Sapp, P.C., Horvitz, H.R., Landers, J.E., Brown, R.H., 2009. Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. Science (New York, N.Y.) 323 (5918), 1205–1208.
Lacour, A., Espinosa, A., Louwersheimer, E., Heilmann, S., Hernández, I., Wolfsgruber, S., Fernández, V., Wagner, H., Rosende-Roca, M., Mauleón, A., Moreno–Grau, S., Vargas, L., Pijnenburg, Y.A., Koene, T., Rodríguez-Gómez, O., Ortega, G., Ruiz, S., Holstege, H., Sotolongo-Grau, O., Kornhuber, J., Peters, O., Frölich, L., Hüll, M., Rüther, E., Wiltfang, J., Scherer, M., Riedel-Heller, S.,

Alegret, M., Nöthen, M.M., Scheltens, P., Wagner, M., Tárraga, L., Jessen, F., Boada, M., Maier, W., van der Flier, W.M., Becker, T., Ramirez, A., Ruiz, A., 2017. Genome-wide significant risk factors for Alzheimer's disease: role in progression to dementia due to Alzheimer's disease among subjects with mild cognitive impairment. Mol. Psychiatry 22 (1), 153–160.

Lambert, J.C., Ibrahim-Verbaas, C.A., Harold, D., Naj, A.C., Sims, R., Bellenguez, C., DeStafano, A.L., Bis, J.C., Beecham, G.W., Grenier-Boley, B., Russo, G., Thorton-Wells, T.A., Jones, N., Smith, A.V., Chouraki, V., Thomas, C., Ikram, M.A., Zelenika, D., Vardarajan, B.N., Kamatani, Y., Lin, C.F., Gerrish, A., Schmidt, H., Kunkle, B., Dunstan, M.L., Ruiz, A., Bihoreau, M.T., Choi, S.H., Reitz, C., Pasquier, F., Cruchaga, C., Craig, D., Amin, N., Berr, C., Lopez, O.L., De Jager, P.L., Deramecourt, V., Johnston, J.A., Evans, D., Lovestone, S., Letenneur, L., Morón, F.J., Rubinsztein, D.C., Eiriksdottir, G., Sleegers, K., Goate, A.M., Fiévet, N., Huentelman, M.W., Gill, M., Brown, K., Kamboh, M.I., Keller, L., Barberger-Gateau, P., McGuiness, B., Larson, E.B., Green, R., Myers, A.J., Dufouil, C., Todd, S., Wallon, D., Love, S., Rogaeva, E., Gallacher, J., St George-Hyslop, P., Clarimon, J., Lleo, A., Bayer, A., Tsuang, Yu, D.W., Tsolaki, L., Bossù, M., Spalletta, P., Proitsi, G., Collinge, P., Sorbi, J., Sanchez-Garcia, S., Fox, F., Hardy, N.C., Deniz Naranjo, J., Bosco, M.C., Clarke, P., Brayne, R., Galimberti, C., Mancuso, D., Matthews, M., Moebus, F., Mecocci, S., Del Zompo, P., Maier, M., Hampel, W., Pilotto, H., Bullido, A., Panza, M., Caffarra, F., Nacmias, P., Gilbert, B., Mayhaus, J.R., Lannefelt, M., Hakonarson, L., Pichler, H., Carrasquillo, S., Ingelsson, M.M., Beekly, M., Alvarez, D., Zou, V., Valladares, F., Younkin, O., Coto, S.G., Hamilton-Nelson, E., Gu, K.L., Razquin, W., Pastor, C., Mateo, P., Owen, I., Faber, M.J., Jonsson, K.M., Combarros, P.V., O'Donovan, O., Cantwell, M.C., Soininen, L.B., Blacker, H., Mead, D., Mosley, S., Jr, T.H., Bennett, D.A., Harris, T.B., Fratiglioni, L., Holmes, C., de Bruijn, R.F., Passmore, P., Montine, T.J., Bettens, K., Rotter, J.I., Brice, A., Morgan, K., Foroud, T.M., Kukull, W.A., Hannequin, D., Powell, J.F., Nalls, M.A., Ritchie, K., Lunetta, K.L., Kauwe, J.S., Boerwinkle, E., Riemenschneider, M., Boada, M., Hiltuenen, M., Martin, E.R., Schmidt, R., Rujescu, D., Wang, L.S., Dartigues, J.F., Mayeux, R., Tzourio, C., Hofman, A., Nöthen, M.M., Graff, C., Psaty, B.M., Jones, L., Haines, J.L., Holmans, P.A., Lathrop, M., Pericak-Vance, M.A., Launer, L.J., Farrer, L.A., van Duijn, C.M., Van Broeckhoven, C., Moskvina, V., Seshadri, S., Williams, J., Schellenberg, G.D., Amouyel, P., 2013. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat. Genet. 45 (12), 1452–1458.

Lautenschlager, N.T., Cupples, L.A., Rao, V.S., Auerbach, S.A., Becker, R., Burke, J., Chui, H., Duara, R., Foley, E.J., Glatt, S.L., Green, R.C., Jones, R., Karlinsky, H., Kukull, W.A., Kurz, A., Larson, E.B., Martelli, K., Sadovnick, A.D., Volicer, L., Waring, S.C., Growdon, J.H., Farrer, L.A., 1996. Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old? Neurology 46 (3), 641–650.

Lawingco, T., Chaudhury, S., Brookes, K.J., Guetta-Baranes, T., Guerreiro, R., Bras, J., Hardy, J., Francis, P., Thomas, A., Belbin, O., Morgan, K., 2020. Genetic variants in glutamate-, Aβ−, and tau-related pathways determine polygenic risk for Alzheimer's disease. Neurobiol. Aging.

Lazaridis, I., Patterson, N., Mittnik, A., Renaud, G., Mallick, S., Kirsanow, K., Sudmant, P.H., Schraiber, J.G., Castellano, S., Lipson, M., Berger, B., Economou, C., Bollongino, R., Fu, Q., Bos, K.I., Nordenfelt, S., Li, H., de Filippo, C., Prüfer, K., Sawyer, S., Posth, C., Haak, W., Hallgren, F., Fornander, E., Rohland, N., Delsate, D., Francken, M., Guinet, J.M., Wahl, J., Ayodo, G., Babiker, H.A., Bailliet, G., Balanovska, E., Balanovsky, O., Barrantes, R., Bedoya, G., Ben-Ami, H., Bene, J., Berrada, F., Bravi, C.M., Brisighelli, F., Busby, G.B., Cali, F., Churnosov, M., Cole, D.E., Corach, D., Damba, L., van Driem, G., Dryomov, S., Dugoujon, J.M., Fedorova, S.A., Gallego Romero, I., Gubina, M., Hammer, M., Henn, B.M., Hervig, T., Hodoglugil, U., Jha, A.R., Karachanak-Yankova, S., Khusainova, R., Khusnutdinova, E., Kittles, R., Kivisild, T., Klitz, W., Kučinskas, V., Kushniarevich, A., Laredj, L., Litvinov, S., Loukidis, T., Mahley, R.W., Melegh, B., Metspalu, E., Molina, J., Mountain, J., Näkkäläjärvi, K., Nesheva, D., Nyambo, T., Osipova, L., Parik, J., Platonov, F., Posukh, O., Romano, V., Rothhammer, F., Rudan, I., Ruizbakiev, R., Sahakyan, H., Sajantila, A., Salas, A., Starikovskaya, E.B., Tarekegn, A., Toncheva, D., Turdikulova, S., Uktveryte, I., Utevska, O., Vasquez, R., Villena, M., Voevoda, M., Winkler, C.A., Yepiskoposyan, L., Zalloua, P., Zemunik, T., Cooper, A., Capelli, C., Thomas, M.G., Ruiz-Linares, A., Tishkoff, S.A., Singh, L., Thangaraj, K., Villems, R., Comas, D., Sukernik, R., Metspalu, M., Meyer, M., Eichler, E.E., Burger, J., Slatkin, M., Pääbo, S., Kelso, J., Reich, D., Krause, J., 2014. Ancient human genomes suggest three ancestral populations for present-day Europeans. Nature 513 (7518), 409–413.

Lewerenz, J., Maher, P., 2015. Chronic glutamate toxicity in neurodegenerative diseases-what is the evidence? Front. Neurosci. 9, 469.

Lindquist, S.G., Hasholt, L., Bahl, J.M., Heegaard, N.H., Andersen, B.B., Nørremølle, A., Stokholm, J., Schwartz, M., Batbayli, M., Laursen, H., Pardossi-Piquard, R., Chen, F., St George-Hyslop, P., Waldemar, G., Nielsen, J.E., 2008. A novel presenilin 2 mutation (V393M) in early-onset dementia with profound language impairment. Eur. J. Neurol. 15 (10), 1135–1139.

Liu, C.C., Liu, C.C., Kanekiyo, T., Xu, H., Bu, G., 2013. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat. Rev. Neurol. 9 (2), 106–118.

Lohmann, E., Guerreiro, R.J., Erginel-Unaltuna, N., Gurunlian, N., Bilgic, B., Gurvit, H., Hanagasi, H.A., Luu, N., Emre, M., Singleton, A., 2012. Identification of PSEN1 and PSEN2 gene mutations and variants in Turkish dementia patients. Neurobiol. Aging 33 (8), 1850 e1817-1827.

Loy, C.T., Schofield, P.R., Turner, A.M., Kwok, J.B., 2014. Genetics of dementia. Lancet 383 (9919), 828–840.

Lubke, G., McArtor, D., 2014. Multivariate genetic analyses in heterogeneous populations. Behav. Genet. 44 (3), 232–239.

Mackenzie, I.R.A., Baker, M., Pickering-Brown, S., Hsiung, G.-Y.R., Lindholm, C., Dwosh, E., Gass, J., Cannon, A., Rademakers, R., Hutton, M., Feldman, H.H., 2006. The neuropathology of frontotemporal lobar degeneration caused by mutations in the progranulin gene. Brain 129 (11), 3081–3090.

Maruyama, K., Kametani, F., Usami, M., Yamao-Harigaya, W., Tanaka, K., 1991. Secretase," Alzheimer amyloid protein precursor secreting enzyme is not sequence-specific. Biochem. Biophys. Res. Commun. 179 (3), 1670–1676.

Mathioudakis, L., Bourbouli, M., Daklada, E., Kargatzi, S., Michaelidou, K., Zaganas, I., 2019. Localization of human glutamate dehydrogenases provides insights into their metabolic role and their involvement in disease processes. Neurochem. Res. 44 (1), 170–187.

Mattila, K.M., Forsell, C., Pirttilä, T., Rinne, J.O., Lehtimäki, T., Röyttä, M., Lilius, L., Eerola, A., St George-Hyslop, P.H., Frey, H., Lannfelt, L., 1998. The Glu318Gly mutation of the presenilin-1 gene does not necessarily cause Alzheimer's disease. Ann. Neurol. 44 (6), 965–967.

McKeith, I.G., Dickson, D.W., Lowe, J., Emre, M., O'Brien, J.T., Feldman, H., Cummings, J., Duda, J.E., Lippa, C., Perry, E.K., Aarsland, D., Arai, H., Ballard, C.G., Boeve, B., Burn, D.J., Costa, D., Del Ser, T., Dubois, B., Galasko, D., Gauthier, S., Goetz, C.G., Gomez-Tortosa, E., Halliday, G., Hansen, L.A., Hardy, J., Iwatsubo, T., Kalaria, R.N., Kaufer, D., Kenny, R.A., Korczyn, A., Kosaka, K., Lee, V.M., Lees, A., Litvan, I., Londos, E., Lopez, O.L., Minoshima, S., Mizuno, Y., Molina, J.A., Mukaetova-Ladinska, E.B., Pasquier, F., Perry, R.H., Schulz, J.B., Trojanowski, J.Q., Yamada, M., 2005. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 65 (12), 1863–1872.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34 (7), 939–944.

Mendez, M.F., McMurtray, A., 2006. Frontotemporal dementia-like phenotypes associated with presenilin-1 mutations. Am. J. Alzheimer's Dis. Other Dement. 21 (4), 281–286.

Michaelidou, K., Tsiverdis, I., Erimaki, S., Papadimitriou, D., Amoiridis, G., Papadimitriou, A., Mitsias, P., Zaganas, I., 2020. Whole exome sequencing establishes diagnosis of Charcot-Marie-Tooth 4J, 1C, and X1 subtypes. Mol Genet Genomic Med 8 (4), e1141.

Ming, C., Wang, M., Wang, Q., Neff, R., Wang, E., Shen, Q., Reddy, J.S., Wang, X., Allen, M., Ertekin-Taner, N., De Jager, P.L., Bennett, D.A., Haroutunian, V., Schadt, E., Zhang, B., 2021. Whole genome sequencing–based copy number variations reveal novel pathways and targets in Alzheimer's disease. Alzheimer's Dement. In press.

Mok, W., Chow, T.W., Zheng, L., Mack, W.J., Miller, C., 2004. Clinicopathological concordance of dementia diagnoses by community versus tertiary care clinicians. Am. J. Alzheimer's Dis. Other Dement. 19 (3), 161–165.

Mol, M.O., van Rooij, J.G.J., Wong, T.H., Melhem, S., Verkerk, A., Kievit, A.J.A., van Minkelen, R., Rademakers, R., Pottier, C., Kaat, L.D., Seelaar, H., van Swieten, J.C., Dopper, E.G.P., 2021. Underlying genetic variation in familial frontotemporal dementia: sequencing of 198 patients. Neurobiol. Aging 97 148.e149-148.e116.

Nadezhdin, K.D., Bocharova, O.V., Bocharov, E.V., Arseniev, A.S., 2011. Structural and dynamic study of the transmembrane domain of the amyloid precursor protein. Acta Naturae 3 (1), 69–76.

Narain, P., Pandey, A., Gupta, S., Gomes, J., Bhatia, R., Vivekanandan, P., 2018. Targeted next-generation sequencing reveals novel and rare variants in Indian patients with amyotrophic lateral sclerosis. Neurobiol. Aging 71 265.e269-265.e214.

Neary, D., Snowden, J.S., Gustafson, L., Passant, U., Stuss, D., Black, S., Freedman, M., Kertesz, A., Robert, P.H., Albert, M., Boone, K., Miller, B.L., Cummings, J., Benson, D.F., 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51 (6), 1546–1554.

Neumann, M., Sampathu, D.M., Kwong, L.K., Truax, A.C., Micsenyi, M.C., Chou, T.T., Bruce, J., Schuck, T., Grossman, M., Clark, C.M., McCluskey, L.F., Miller, B.L., Masliah, E., Mackenzie, I.R., Feldman, H., Feiden, W., Kretzschmar, H.A., Trojanowski, J.Q., Lee, V.M.-Y., 2006. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 314 (5796), 130–133.

Niemantsverdriet, E., Feyen, B.F.E., Le Bastard, N., Martin, J.-J., Goeman, J., De Deyn, P.P., Bjerke, M., Engelborghs, S., 2018. Added diagnostic value of cerebrospinal fluid biomarkers for differential dementia diagnosis in an autopsy–confirmed cohort. J. Alzheimers Dis. 63, 373–381.

Nussbaum, R.L., Ellis, C.E., 2003. Alzheimer's disease and Parkinson's disease. N. Engl. J. Med. 348 (14), 1356–1364.

Özoğuz, A., Uyan, Ö., Birdal, G., Iskender, C., Kartal, E., Lahut, S., Ömür, Ö., Agim, Z.S., Eken, A.G., Sen, N.E., Kavak, P., Saygı, C., Sapp, P.C., Keagle, P., Parman, Y., Tan, E., Koç, F., Deymeer, F., Oflazer, P., Hanağası, H., Gürvit, H., Bilgiç, B., Durmuş, H., Ertaş, M., Kotan, D., Akalın, M.A., Güllüoğlu, H., Zarifoğlu, M., Aysal, F., Döşoğlu, N., Bilguvar, K., Günel, M., Keskin, Ö., Akgün, T., Özçelik, H., Landers, J.E., Brown, R.H., Başak, A.N., 2015. The distinct genetic pattern of ALS in Turkey and novel mutations. Neurobiol. Aging 36 (4), 1764 e1769-1764.e1718.

Palomo, V., Tosat-Bitrian, C., Nozal, V., Nagaraj, S., Martin-Requero, A., Martinez, A., 2019. TDP-43: a key therapeutic target beyond amyotrophic lateral sclerosis. ACS Chem. Neurosci. 10 (3), 1183–1196.

Paraskevas, G.P., Kasselimis, D., Kourtidou, E., Constantinides, V., Bougea, A., Potagas, C., Evdokimidis, I., Kapaki, E., 2017. Cerebrospinal fluid biomarkers as a

diagnostic tool of the underlying pathology of primary progressive aphasia. J. Alzheimers Dis. 55, 1453–1461.
Pastor, P., Moreno, F., Clarimón, J., Ruiz, A., Combarros, O., Calero, M., de Munain, A.L., Bullido, M.J., de Pancorbo, M.M., Carro, E., Antonell, A., Coto, E., Ortega-Cubero, S., Hernandez, I., Tárraga, L., Boada, M., Lleó, A., Dols-Icardo, O., Kulisevsky, J., Vázquez-Higuera, J.L., Infante, J., Rábano, A., Fernández-Blázquez, M.Á., Valentí, M., Indakoetxea, B., Barandiarán, M., Gorostidi, A., Frank-García, A., Sastre, I., Lorenzo, E., Pastor, M.A., Elcoroaristizabal, X., Lennarz, M., Maier, W., Rámirez, A., Serrano-Ríos, M., Lee, S.E., Sánchez-Juan, P., 2016. MAPT H1 haplotype is associated with late-onset Alzheimer's disease risk in APOE ε4 non-carriers: results from the Dementia Genetics Spanish Consortium. J. Alzheimers Dis. 49, 343–352.
Perrone, F., Cacace, R., Van Mossevelde, S., Van den Bossche, T., De Deyn, P.P., Cras, P., Engelborghs, S., van der Zee, J., Van Broeckhoven, C., 2018. Genetic screening in early-onset dementia patients with unclear phenotype: relevance for clinical diagnosis. Neurobiol. Aging 69 292.e297-292.e214.
Plaitakis, A., Latsoudis, H., Kanavouras, K., Ritz, B., Bronstein, J.M., Skoula, I., Mastorodemos, V., Papapetropoulos, S., Borompokas, N., Zaganas, I., Xiromerisiou, G., Hadjigeorgiou, G.M., Spanaki, C., 2010. Gain-of-function variant in GLUD2 glutamate dehydrogenase modifies Parkinson's disease onset. Eur. J. Hum. Genet. 18 (3), 336–341.
Plaitakis, A., Zaganas, I., 2001. Regulation of human glutamate dehydrogenases: implications for glutamate, ammonia and energy metabolism in brain. J. Neurosci. Res. 66 (5), 899–908.
Raizen, D.M., Brooks-Kayal, A., Steinkrauss, L., Tennekoon, G.I., Stanley, C.A., Kelly, A., 2005. Central nervous system hyperexcitability associated with glutamate dehydrogenase gain of function mutations. J. Pediatr. 146 (3), 388–394.
Ramos, E.M., Dokuru, D.R., Van Berlo, V., Wojta, K., Wang, Q., Huang, A.Y., Deverasetty, S., Qin, Y., van Blitterswijk, M., Jackson, J., Appleby, B., Bordelon, Y., Brannelly, P., Brushaber, D.E., Dickerson, B., Dickinson, S., Domoto-Reilly, K., Faber, K., Fields, J., Fong, J., Foroud, T., Forsberg, L.K., Gavrilova, R., Ghoshal, N., Goldman, J., Graff-Radford, J., Graff-Radford, N., Grant, I., Grossman, M., Heuer, H.W., Hsiung, G.R., Huey, E., Irwin, D., Kantarci, K., Karydas, A., Kaufer, D., Kerwin, D., Knopman, D., Kornak, J., Kramer, J.H., Kremers, W., Kukull, W., Litvan, I., Ljubenkov, P., Lungu, C., Mackenzie, I., Mendez, M.F., Miller, B.L., Onyike, C., Pantelyat, A., Pearlman, R., Petrucelli, L., Potter, M., Rankin, K.P., Rascovsky, K., Roberson, E.D., Rogalski, E., Shaw, L., Syrjanen, J., Tartaglia, M.C., Tatton, N., Taylor, J., Toga, A., Trojanowski, J.Q., Weintraub, S., Wong, B., Wszolek, Z., Rademakers, R., Boeve, B.F., Rosen, H.J., Boxer, A.L., Coppola, G., 2020. Genetic screening of a large series of North American sporadic and familial frontotemporal dementia cases. Alzheimers Dement 16 (1), 118–130.
Ramos, E.M., Koros, C., Dokuru, D.R., Van Berlo, V., Kroupis, C., Wojta, K., Wang, Q., Andronas, N., Matsi, S., Beratis, I.N., Huang, A.Y., Lee, S.E., Bonakis, A., Florou-Hatziyiannidou, C., Fragkiadaki, S., Kontaxopoulou, D., Agiomyrgiannakis, D., Kamtsadeli, V., Tsinia, N., Papastefanopoulou, V., Stamelou, M., Miller, B.L., Stefanis, L., Papatriantafyllou, J.D., Papageorgiou, S.G., Coppola, G., 2019. Frontotemporal dementia spectrum: first genetic screen in a Greek cohort. Neurobiol. Aging 75, 224.e221–224.e228.
Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., van Swieten, J.C., Seelaar, H., Dopper, E.G., Onyike, C.U., Hillis, A.E., Josephs, K.A., Boeve, B.F., Kertesz, A., Seeley, W.W., Rankin, K.P., Johnson, J.K., Gorno-Tempini, M.L., Rosen, H., Prioleau-Latham, C.E., Lee, A., Kipps, C.M., Lillo, P., Piguet, O., Rohrer, J.D., Rossor, M.N., Warren, J.D., Fox, N.C., Galasko, D., Salmon, D.P., Black, S.E., Mesulam, M., Weintraub, S., Dickerson, B.C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T.W., Manes, F., Grafman, J., Cappa, S.F., Freedman, M., Grossman, M., Miller, B.L., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134 (Pt 9), 2456–2477.
Rayaprolu, S., Fujioka, S., Traynor, S., Soto-Ortolaza, A.I., Petrucelli, L., Dickson, D.W., Rademakers, R., Boylan, K.B., Graff-Radford, N.R., Uitti, R.J., Wszolek, Z.K., Ross, O.A., 2013. TARDBP mutations in Parkinson's disease. Parkinsonism Relat. Disord. 19 (3), 312–315.
Rentzsch, P., Witten, D., Cooper, G.M., Shendure, J., Kircher, M., 2019. CADD: predicting the deleteriousness of variants throughout the human genome. Nucleic. Acids. Res. 47 (D1), D886–d894.
Ridge, P.G., Hoyt, K.B., Boehme, K., Mukherjee, S., Crane, P.K., Haines, J.L., Mayeux, R., Farrer, L.A., Pericak-Vance, M.A., Schellenberg, G.D., Kauwe, J.S.K., 2016. Assessment of the genetic variance of late-onset Alzheimer's disease. Neurobiol. Aging 41, 200.e213–200.e220.
Román, G.C., Tatemichi, T.K., Erkinjuntti, T., Cummings, J.L., Masdeu, J.C., Garcia, J.H., Amaducci, L., Orgogozo, J.M., Brun, A., Hofman, A., et al., 1993. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 43 (2), 250–260.
Rutherford, N.J., Zhang, Y.J., Baker, M., Gass, J.M., Finch, N.A., Xu, Y.F., Stewart, H., Kelley, B.J., Kuntz, K., Crook, R.J., Sreedharan, J., Vance, C., Sorenson, E., Lippa, C., Bigio, E.H., Geschwind, D.H., Knopman, D.S., Mitsumoto, H., Petersen, R.C., Cashman, N.R., Hutton, M., Shaw, C.E., Boylan, K.B., Boeve, B., Graff-Radford, N.R., Wszolek, Z.K., Caselli, R.J., Dickson, D.W., Mackenzie, I.R., Petrucelli, L., Rademakers, R., 2008. Novel mutations in TARDBP (TDP-43) in patients with familial amyotrophic lateral sclerosis. PLoS Genet. 4 (9), e1000193.
Sanabria-Castro, A., Alvarado-Echeverría, I., Monge-Bonilla, C., 2017. Molecular Pathogenesis of Alzheimer's Disease: An Update. Ann Neurosci 24 (1), 46–54.
Sassi, C., Guerreiro, R., Gibbs, R., Ding, J., Lupton, M.K., Troakes, C., Al-Sarraj, S., Niblock, M., Gallo, J.M., Adnan, J., Killick, R., Brown, K.S., Medway, C., Lord, J., Turton, J., Bras, J., Morgan, K., Powell, J.F., Singleton, A., Hardy, J., 2014. Investigating the role of rare coding variability in Mendelian dementia genes (APP, PSEN1, PSEN2, GRN, MAPT, and PRNP) in late-onset Alzheimer's disease. Neurobiol. Aging 35 (12), 2881 e2881-2881.e2886.
Saunders, A.M., Strittmatter, W.J., Schmechel, D., George-Hyslop, P.H., Pericak–Vance, M.A., Joo, S.H., Rosi, B.L., Gusella, J.F., Crapper-MacLachlan, D.R., Alberts, M.J., et al., 1993. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 43 (8), 1467–1472.
Scott, D., 2015. Multivariate Density Estimation: Theory, Practice, and Visualization, Second Edition John Wiley & Sons, Inc, Hoboken, New Jersey, USA.
Shashidharan, P., Michaelidis, T.M., Robakis, N.K., Kresovali, A., Papamatheakis, J., Plaitakis, A., 1994. Novel human glutamate dehydrogenase expressed in neural and testicular tissues and encoded by an X-linked intronless gene. J. Biol. Chem. 269 (24), 16971–16976.
Shen, L., Jia, J., 2016. An overview of genome-wide association studies in Alzheimer's disease. Neurosci Bull 32 (2), 183–190.
Sherrington, R., Froelich, S., Sorbi, S., Campion, D., Chi, H., Rogaeva, E.A., Levesque, G., Rogaev, E.I., Lin, C., Liang, Y., Ikeda, M., Mar, L., Brice, A., Agid, Y., Percy, M.E., Clerget-Darpoux, F., Piacentini, S., Marcon, G., Nacmias, B., Amaducci, L., Frebourg, T., Lannfelt, L., Rommens, J.M., St George-Hyslop, P.H., 1996. Alzheimer's disease associated with mutations in presenilin 2 is rare and variably penetrant. Hum. Mol. Genet. 5 (7), 985–988.
Sims, R., van der Lee, S.J., Naj, A.C., Bellenguez, C., Badarinarayan, N., Jakobsdottir, J., Kunkle, B.W., Boland, A., Raybould, R., Bis, J.C., Martin, E.R., Grenier-Boley, B., Heilmann-Heimbach, S., Chouraki, V., Kuzma, A.B., Sleegers, K., Vronskaya, M., Ruiz, A., Graham, R.R., Olaso, R., Hoffmann, P., Grove, M.L., Vardarajan, B.N., Hiltunen, M., Nöthen, M.M., White, C.C., Hamilton-Nelson, K.L., Epelbaum, J., Maier, W., Choi, S.H., Beecham, G.W., Dulary, C., Herms, S., Smith, A.V., Funk, C.C., Derbois, C., Forstner, A.J., Ahmad, S., Li, H., Bacq, D., Harold, D., Satizabal, C.L., Valladares, O., Squassina, A., Thomas, R., Brody, J.A., Qu, L., Sánchez-Juan, P., Morgan, T., Wolters, F.J., Zhao, Y., Garcia, F.S., Denning, N., Fornage, M., Malamon, J., Naranjo, M.C.D., Majounie, E., Mosley, T.H., Dombroski, B., Wallon, D., Lupton, M.K., Dupuis, J., Whitehead, P., Fratiglioni, L., Medway, C., Jian, X., Mukherjee, S., Keller, L., Brown, K., Lin, H., Cantwell, L.B., Panza, F., McGuinness, B., Moreno-Grau, S., Burgess, J.D., Solfrizzi, V., Proitsi, P., Adams, H.H., Allen, M., Seripa, D., Pastor, P., Cupples, L.A., Price, N.D., Hannequin, D., Frank-García, A., Levy, D., Chakrabarty, P., Caffarra, P., Giegling, I., Beiser, A.S., Giedraitis, V., Hampel, H., Garcia, M.E., Wang, X., Lannfelt, L., Mecocci, P., Eiriksdottir, G., Crane, P.K., Pasquier, F., Boccardi, V., Henández, I., Barber, R.C., Scherer, M., Tarraga, L., Adams, P.M., Leber, M., Chen, Y., Albert, M.S., Riedel-Heller, S., Emilsson, V., Beekly, D., Braae, A., Schmidt, R., Blacker, D., Masullo, C., Schmidt, H., Doody, R.S., Spalletta, G., Longstreth Jr., W.T., Fairchild, T.J., Bossù, P., Lopez, O.L., Frosch, M.P., Sacchinelli, E., Ghetti, B., Yang, Q., Huebinger, R.M., Jessen, F., Li, S., Kamboh, M.I., Morris, J., Sotolongo-Grau, O., Katz, M.J., Corcoran, C., Dunstan, M., Braddel, A., Thomas, C., Meggy, A., Marshall, R., Gerrish, A., Chapman, J., Aguilar, M., Taylor, S., Hill, M., Fairén, M.D., Hodges, A., Vellas, B., Soininen, H., Kloszewska, I., Daniilidou, M., Uphill, J., Patel, Y., Hughes, J.T., Lord, J., Turton, J., Hartmann, A.M., Cecchetti, R., Fenoglio, C., Serpente, M., Arcaro, M., Caltagirone, C., Orfei, M.D., Ciaramella, A., Pichler, S., Mayhaus, M., Gu, W., Lleó, A., Fortea, J., Blesa, R., Barber, I.S., Brookes, K., Cupidi, C., Maletta, R.G., Carrell, D., Sorbi, S., Moebus, S., Urbano, M., Pilotto, A., Kornhuber, J., Bosco, P., Todd, S., Craig, D., Johnston, J., Gill, M., Lawlor, B., Lynch, A., Fox, N.C., Hardy, J., Albin, R.L., Apostolova, L.G., Arnold, S.E., Asthana, S., Atwood, C.S., Baldwin, C.T., Barnes, L.L., Barral, S., Beach, T.G., Becker, J.T., Bigio, E.H., Bird, T.D., Boeve, B.F., Bowen, J.D., Boxer, A., Burke, J.R., Burns, J.M., Buxbaum, J.D., Cairns, N.J., Cao, C., Carlson, C.S., Carlsson, C.M., Carney, R.M., Carrasquillo, M.M., Carroll, S.L., Diaz, C.C., Chui, H.C., Clark, D.G., Cribbs, D.H., Crocco, E.A., DeCarli, C., Dick, M., Duara, R., Evans, D.A., Faber, K.M., Fallon, K.B., Fardo, D.W., Farlow, M.R., Ferris, S., Foroud, T.M., Galasko, D.R., Gearing, M., Geschwind, D.H., Gilbert, J.R., Graff-Radford, N.R., Green, R.C., Growdon, J.H., Hamilton, R.L., Harrell, L.E., Honig, L.S., Huentelman, M.J., Hulette, C.M., Hyman, B.T., Jarvik, G.P., Abner, E., Jin, L.W., Jun, G., Karydas, A., Kaye, J.A., Kim, R., Kowall, N.W., Kramer, J.H., LaFerla, F.M., Lah, J.J., Leverenz, J.B., Levey, A.I., Li, G., Lieberman, A.P., Lunetta, K.L., Lyketsos, C.G., Marson, D.C., Martiniuk, F., Mash, D.C., Masliah, E., McCormick, W.C., McCurry, S.M., McDavid, A.N., McKee, A.C., Mesulam, M., Miller, B.L., Miller, C.A., Miller, J.W., Morris, J.C., Murrell, J.R., Myers, A.J., O'Bryant, S., Olichney, J.M., Pankratz, V.S., Parisi, J.E., Paulson, H.L., Perry, W., Peskind, E., Pierce, A., Poon, W.W., Potter, H., Quinn, J.F., Raj, A., Raskind, M., Reisberg, B., Reitz, C., Ringman, J.M., Roberson, E.D., Rogaeva, E., Rosen, H.J., Rosenberg, R.N., Sager, M.A., Saykin, A.J., Schneider, J.A., Schneider, L.S., Seeley, W.W., Smith, A.G., Sonnen, J.A., Spina, S., Stern, R.A., Swerdlow, R.H., Tanzi, R.E., Thornton-Wells, T.A., Trojanowski, J.Q., Troncoso, J.C., Van Deerlin, V.M., Van Eldik, L.J., Vinters, H.V., Vonsattel, J.P., Weintraub, S., Welsh-Bohmer, K.A., Wilhelmsen, K.C., Williamson, J., Wingo, T.S., Woltjer, R.L., Wright, C.B., Yu, C.E., Yu, L., Garzia, F., Golamaully, F., Septier, G., Engelborghs, S., Vandenberghe, R., De Deyn, P.P., Fernadez, C.M., Benito, Y.A., Thonberg, H., Forsell, C., Lilius, L., Kinhult-Stählbom, A., Kilander, L., Brundin, R., Concari, L., Helisalmi, S., Koivisto, A.M., Haapasalo, A., Dermecourt, V., Fievet, N., Hanon, O., Dufouil, C., Brice, A., Ritchie, K., Dubois, B., Himali, J.J., Keene, C.D., Tschanz, J., Fitzpatrick, A.L., Kukull, W.A., Norton, M., Aspelund, T., Larson, E.B., Munger, R., Rotter, J.I., Lipton, R.B., Bullido, M.J., Hofman, A., Montine, T.J., Coto, E., Boerwinkle, E., Petersen, R.C., Alvarez, V., Rivadeneira, F., Reiman, E.M., Gallo, M., O'Donnell, C.J., Reisch, J.S., Bruni, A.C., Royall, D.R., Dichgans, M., Sano, M., Galimberti, D., St George-Hyslop, P., Scarpini, E., Tsuang, D.W., Mancuso, M., Bonuc-

celli, U., Winslow, A.R., Daniele, A., Wu, C.K., Peters, O., Nacmias, B., Riemenschneider, M., Heun, R., Brayne, C., Rubinsztein, D.C., Bras, J., Guerreiro, R., Al-Chalabi, A., Shaw, C.E., Collinge, J., Mann, D., Tsolaki, M., Clarimón, J., Sussams, R., Lovestone, S., O'Donovan, M.C., Owen, M.J., Behrens, T.W., Mead, S., Goate, A.M., Uitterlinden, A.G., Holmes, C., Cruchaga, C., Ingelsson, M., Bennett, D.A., Powell, J., Golde, T.E., Graff, C., De Jager, P.L., Morgan, K., Ertekin-Taner, N., Combarros, O., Psaty, B.M., Passmore, P., Younkin, S.G., Berr, C., Gudnason, V., Rujescu, D., Dickson, D.W., Dartigues, J.F., DeStefano, A.L., Ortega-Cubero, S., Hakonarson, H., Campion, D., Boada, M., Kauwe, J.K., Farrer, L.A., Van Broeckhoven, C., Ikram, M.A., Jones, L., Haines, J.L., Tzourio, C., Launer, L.J., Escott-Price, V., Mayeux, R., Deleuze, J.F., Amin, N., Holmans, P.A., Pericak–Vance, M.A., Amouyel, P., van Duijn, C.M., Ramirez, A., Wang, L.S., Lambert, J.C., Seshadri, S., Williams, J., Schellenberg, G.D, 2017. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. Nat. Genet. 49 (9), 1373–1384.

Sleegers, K., Roks, G., Theuns, J., Aulchenko, Y.S., Rademakers, R., Cruts, M., van Gool, W.A., Van Broeckhoven, C., Heutink, P., Oostra, B.A., van Swieten, J.C., van Duijn, C.M., 2004. Familial clustering and genetic risk for dementia in a genetically isolated Dutch population. Brain 127 (Pt 7), 1641–1649.

Stanley, C.A., Lieu, Y.K., Hsu, B.Y., Burlina, A.B., Greenberg, C.R., Hopwood, N.J., Perlman, K., Rich, B.H., Zammarchi, E., Poncz, M., 1998. Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. N. Engl. J. Med. 338 (19), 1352–1357.

Synofzik, M., Maetzler, W., Grehl, T., Prudlo, J., vom Hagen, J.M., Haack, T., Rebassoo, P., Munz, M., Schöls, L., Biskup, S., 2012. Screening in ALS and FTD patients reveals 3 novel UBQLN2 mutations outside the PXX domain and a pure FTD phenotype. Neurobiol. Aging 33 (12), 2949 e2913-2949.e2917..

Taddei, K., Fisher, C., Laws, S.M., Martins, G., Paton, A., Clarnette, R.M., Chung, C., Brooks, W.S., Hallmayer, J., Miklossy, J., Relkin, N., St George-Hyslop, P.H., Gandy, S.E., Martins, R.N., 2002. Association between presenilin-1 Glu318Gly mutation and familial Alzheimer's disease in the Australian population. Mol. Psychiatry 7 (7), 776–781.

Thiele, H., Nürnberg, P., 2005. HaploPainter: a tool for drawing pedigrees with complex haplotypes. Bioinformatics 21 (8), 1730–1732.

Tian, C., Gregersen, P.K., Seldin, M.F., 2008. Accounting for ancestry: population substructure and genome-wide association studies. Hum. Mol. Genet. 17 (R2), R143–R150.

Ticozzi, N., LeClerc, A.L., van Blitterswijk, M., Keagle, P., McKenna-Yasek, D.M., Sapp, P.C., Silani, V., Wills, A.M., Brown Jr., R.H., Landers, J.E., 2011. Mutational analysis of TARDBP in neurodegenerative diseases. Neurobiol. Aging 32 (11), 2096–2099.

Ulland, T.K., Colonna, M., 2018. TREM2 — a key player in microglial biology and Alzheimer disease. Nat. Rev. Neurol. 14 (11), 667–675.

Ulrich, J.D., Ulland, T.K., Colonna, M., Holtzman, D.M., 2017. Elucidating the role of TREM2 in Alzheimer's disease. Neuron 94 (2), 237–248.

Van Cauwenberghe, C., Van Broeckhoven, C., Sleegers, K., 2016. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genet. Med. 18 (5), 421–430.

Vance, C., Rogelj, B., Hortobágyi, T., De Vos, K.J., Nishimura, A.L., Sreedharan, J., Hu, X., Smith, B., Ruddy, D., Wright, P., Ganesalingam, J., Williams, K.L., Tripathi, V., Al-Saraj, S., Al-Chalabi, A., Leigh, P.N., Blair, I.P., Nicholson, G., de Belleroche, J., Gallo, J.-M., Miller, C.C., Shaw, C.E., 2009. Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. Science 323 (5918), 1208–1211.

Vemuri, P., Simon, G., Kantarci, K., Whitwell, J.L., Senjem, M.L., Przybelski, S.A., Gunter, J.L., Josephs, K.A., Knopman, D.S., Boeve, B.F., Ferman, T.J., Dickson, D.W., Parisi, J.E., Petersen, R.C., Jack, C.R., 2011. Antemortem differential diagnosis of dementia pathology using structural MRI: differential-STAND. Neuroimage 55 (2), 522–531.

Wagner, M., Lorenz, G., Volk, A.E., Brunet, T., Edbauer, D., Berutti, R., Zhao, C., Anderl-Straub, S., Bertram, L., Danek, A., Deschauer, M., Dill, V., Fassbender, K., Fliessbach, K., Götze, K.S., Jahn, H., Kornhuber, J., Landwehrmeyer, B., Lauer, M., Obrig, H., Prudlo, J., Schneider, A., Schroeter, M.L., Uttner, I., Vukovich, R., Wiltfang, J., Winkler, A.S., Zhou, Q., Ludolph, A.C., Oexle, K., Otto, M., Diehl-Schmid, J., Winkelmann, J.The German FTLD Consortium, 2021. Clinico-genetic findings in 509 frontotemporal dementia patients. Mol. Psychiatry 26 (10), 5824–5832.

Walker, E.S., Martinez, M., Brunkan, A.L., Goate, A., 2005. Presenilin 2 familial Alzheimer's disease mutations result in partial loss of function and dramatic changes in Abeta 42/40 ratios. J. Neurochem. 92 (2), 294–301.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.O., Nordberg, A., Bäckman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., van Duijn, C., Visser, P., Petersen, R.C., 2004. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J. Intern. Med. 256 (3), 240–246.

Xiao, X., Yuan, Z., Guo, L., Liao, X., Zhou, Y., Zhang, W., Zhou, L., Wang, X., Liu, X., Liu, H., Wang, J., Li, J., Shen, L., Jiao, B., 2021. The role of frontotemporal dementia associated genes in patients with Alzheimer's disease. Neurobiol. Aging 107, 153–158.

Zádori, D., Veres, G., Szalárdy, L., Klivényi, P., Toldi, J., Vécsei, L., 2014. Glutamatergic dysfunctioning in Alzheimer's disease and related therapeutic targets. J. Alzheimers Dis. 42 (Suppl 3), S177–S187.

Zaganas, I., Kanavouras, K., Mastorodemos, V., Latsoudis, H., Spanaki, C., Plaitakis, A., 2009. The human GLUD2 glutamate dehydrogenase: localization and functional aspects. Neurochem. Int. 55 (1-3), 52–63.

Zaganas, I., Mastorodemos, V., Spilioti, M., Mathioudakis, L., Latsoudis, H., Michaelidou, K., Kotzamani, D., Notas, K., Dimitrakopoulos, K., Skoula, I., Ioannidis, S., Klothaki, E., Erimaki, S., Stavropoulos, G., Vassilikos, V., Amoiridis, G., Efthimiadis, G., Evangeliou, A., Mitsias, P., 2020. Genetic cause of heterogeneous inherited myopathies in a cohort of Greek patients. Mol. Genet. Metab. Rep. 25, 100682.

Zaganas, I., Spanaki, C., Plaitakis, A., 2012. Expression of human GLUD2 glutamate dehydrogenase in human tissues: functional implications. Neurochem. Int. 61 (4), 455–462.

Zaganas, I., Vorgia, P., Spilioti, M., Mathioudakis, L., Raissaki, M., Ilia, S., Giorgi, M., Skoula, I., Chinitrakis, G., Michaelidou, K., Paraskevoulakos, E., Grafakou, O., Kariniotaki, C., Psyllou, T., Zafeiris, S., Tzardi, M., Briassoulis, G., Dinopoulos, A., Mitsias, P., Evangeliou, A., 2021. Genetic cause of epilepsy in a Greek cohort of children and young adults with heterogeneous epilepsy syndromes. Epilepsy Behav. Rep. 16, 100477.

Zaganas, I.V., Kanavouras, K., Borompokas, N., Arianoglou, G., Dimovasili, C., Latsoudis, H., Vlassi, M., Mastorodemos, V., 2014. The odyssey of a young gene: structure-function studies in human glutamate dehydrogenases reveal evolutionary-acquired complex allosteric regulation mechanisms. Neurochem. Res. 39 (3), 471–486.

Zaganas, I.V., Simos, P., Basta, M., Kapetanaki, S., Panagiotakis, S., Koutentaki, I., Fountoulakis, N., Bertsias, A., Duijker, G., Tziraki, C., Scarmeas, N., Plaitakis, A., Boumpas, D., Lionis, C., Vgontzas, A.N., 2019. The Cretan Aging Cohort: cohort description and burden of dementia and mild cognitive impairment. Am. J. Alzheimers Dis. Other Demen. 34 (1), 23–33.

Zekanowski, C., Pepłońska, B., Styczyńska, M., Religa, D., Pfeffer, A., Czyzewski, K., Gabryelewicz, T., Szybińska, A., Kijanowska-Haładyna, B., Kotapka-Minc, S., Łuczywek, E., Barczak, A., Wasiak, B., Chodakowska-Zebrowska, M., Przekop, I., Kuźnicki, J., Barcikowska, M., 2004. The E318G substitution in PSEN1 gene is not connected with Alzheimer's disease in a large Polish cohort. Neurosci. Lett. 357 (3), 167–170.

Zhang, W., Gong, J., Ding, L., Zhang, Z., Pan, X., Chen, X., Guo, W., Zhang, X., Yang, X., Peng, G., Lin, Y., Gao, F., Li, Y., Zhu, X., Xuan, A., Wang, S., Sun, X., Zhang, Y., Xu, P., 2020. Functional validation of a human GLUD2 variant in a murine model of Parkinson's disease. Cell Death. Dis. 11 (10), 897.

Zou, Z.Y., Zhou, Z.R., Che, C.H., Liu, C.Y., He, R.L., Huang, H.P., 2017. Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry 88 (7), 540–549.