Genetic variation in APOE, GRN, and TP53 are phenotype modifiers in frontotemporal dementia

Genetic variation in *APOE, GRN and TP53* are phenotype modifiers in frontotemporal dementia

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ABSTRACT

Frontotemporal dementia (FTD) is a clinical, genetic and pathological heterogeneous group of neurodegenerative diseases. In this study, we investigated the role of *APOε4*, rs5848 in *GRN* and *rs1042522* in *TP53* gene as disease risk factors and/or phenotype modifiers in 440 frontotemporal dementia (FTD) patients, including 175 *C9orf72* expansion carriers. We found that the *C9orf72* expansion carriers showing an earlier age at onset ($p<0.001$). Among the clinical groups, the FTD-MND (motoneuron disease) showed the lowest survival (HR=4.12) and the PNFA group showed the highest onset-age ($p=0.03$). In our cohort, the rs1042522 in *TP53* was associated with disease onset ($p=0.02$) and survival (HR= 1.73) and rs5848 *GRN* with a significant shorter survival in CC homozygous patients (HR= 1.98). The frequency of *APOε4* carriers was significantly increased in the C9orf72 non carriers *($p=0.022$).* Although validation of our findings is necessary, our results suggest that *TP53,GRN a*nd *APOE* genes may act as phenotype modifiers in FTD and should be considered in future clinical trials.

1-INTRODUCTION

Frontotemporal dementia (FTD) is a group of cognitive disorders caused caused by the neurodegeneration in the frontal and temporal lobes, with variable clinical and pathological presentation. Based on behavioral and language manifestations, FTD is subdivided in behavioural FTD (bvFTD), progressive non-fluent aphasia (PNFA), and fluent progressive aphasia (semantic dementia, SD). FTD is frequently familial (up to 43% of the cases according to some studies) with 10-27% showing autosomal dominant inheritance (Rohrer et al, 2009). FTD is genetically heterogeneous and FTD-causative mutations have been identified in several genes including C*9orf72, GRN, MAPT* and *TBK1* (Van Mossevelde et al, 2018) . Some of the FTD-TDP/FUS-related mutations have also been identified in amyotrophic lateral sclerosis (ALS), suggesting a genetic overlap between the two disorders. In addition, it is fair to expect that other genetic factors would act as modifiers of the disease in FTD and motor neuron disease (MND) (Rademakers et al, 2008). A pathogenic expansion in C*9orf72* is the most common genetic cause of FTD and ALS, accounting for 29% of familial FTD cases (Van Mossevelde et al, 2018). The clinical phenotype of the C*9orf72* expansion is very heterogeneous even within the same family, with the bvFTD subtype as the most common clinical presentation, although FTD-MND, MND and PNFA are also frequent (Simón-Sánchez et al, 2012).

Both genetic and sporadic FTD showed great phenotypic variability: the clinical picture, age at onset, disease progression and survival may vary significantly. This heterogeneity makes diagnosis challenging and impacts clinical trials and therapies. A recent retrospective study involving more than 3,000 individuals with genetic FTD showed that the age at onset and age at death correlated with the genetic cause. Moreover, in FTD patients with a *MAPT* mutation the onset and age of death was influenced by the specific mutation carried and by family membership (Moore et al, 2020). From a neuropathological point of view the evidence reinforces the idea that different post-translational modifications are involved in the generation of a greater pathology in neurodegenerative diseases. For instance, significantly greater levels of phosphorylated TDP-43 were identified in the motor cortex of cases with ALS with *C9orf72* expansions, and in the spinal cord of cases with ALS with intermediate *ATXN2* expansions, while similar levels of non-phosphorylated TDP-43 were found in ALS cases with and without *ATXN2* or *C9orf72* expansions (Yang Y et al, 2019).

Different studies have tried to identify genetic modifiers of disease risk and phenotypes in FTD, such as the age at onset or survival after onset. For instance, it has been described that *ATXN-2* intermediate expansion alleles were disease modifiers in FTD *C9orf72* expansion

carriers (van Blitterswijk et al, 2014a; Rubino et al, 2019). A common polymorphism in the 3′UTR of *PGRN*, rs5848, has been related to the survival after onset in *C9orf72* expansion carriers (van Blitterswijk et al, 2014b). Also, it has been described that the *APOE*-Ɛ4 variant would lower the onset-age in patients with FTD and tauopathy independent of the existence of amyloid-β co-pathology (Koriath et al, 2019) Recently, our group described that intermediate CAG alleles (IAs) in the *ATXN1, ATXN2* and *HTT* genes might be differently presented in the different subtypes of FTD, but no association with age at onset was detected (Menéndez-González et al, 2019; Rosas et al, 2020)

In the *C9orf72* expansion carriers both, sense and antisense repeat RNA transcripts are translated into pathogenic dipeptide-repeat proteins (DPRs) which activate the DNA damage response (DDR) pathway with a subsequent increase of many proteins, including tumor protein p53 (p53), which might contribute to the neuronal death that characterize many neurodegenerative disorders. Although most investigations on p53 focused on human tumors, the regulatory function of this protein on the central nervous system has gradually attracted increasing interest (Gao and Zhao, 2018; Sun et al, 2018). Increased levels of p53 were detected in affected brain regions in different diseases, and there are regulatory pathways between p53 and the proteins that are pathological hallmarks of diseases (Szybinska and Lesniak, 2017). The overexpression of p53 has been linked to neuronal death due to the accumulation of the TAR DNA-binding protein 43 (TDP-43). TDP-43 is a key player in FTD, ALS, and other neurodegenerative processes, and reduced TDP-43 caused defects in the proliferation of neural stem/progenitor cells but not cell death, while its overexpression resulted in the induction of p53-dependent apoptosis of neural stem/progenitors and human induced pluripotent cells (iPS) derived from immature cortical neurons. Moreover, p53 inhibition rescued TDP-43 induced cell death of cortical neurons (Vogt et al, 2018).

Genetic variants in the *TP53* (such as rs1042522, Arg72Pro) have been widely associated with cancer and also studied in neurological and psychiatric disorders (Yang J et al, 2019). Interestingly, the Pro72Arg polymorphism has been associated with poor functional outcomes after either ischemic or hemorrhagic stroke, and the genotype Arg/Arg was also associated with early neurological deterioration in ischemic stroke. In primary cultured neurons, the 72-Arg isoform (but not 72-Pro) activated the intrinsic apoptotic pathway, and this would increase the vulnerability to ischemia-induced apoptotic cell death. These results suggest that the *TP53* polymorphism might influence the neuronal vulnerability to apoptosis, a finding that could be relevant for neurodegeneration beyond stroke (Gómez-Sanchez et al, 2011; Ramos-Araque et al, 2019).

In this work we investigated the role of *APOε4,* rs5848 in *GRN* gene and *rs1042522* in *TP53* as disease risk factors and/or phenotype modifiers in FTD cohort. Moreover, we took advantage of our previous results and investigated a role for *HTT, ATXN1, ATXN2* intermediate alleles in the survival probability in FTD patients.

2. PATIENTS AND METHODS.

2.1-Study Design

This was a multicentre study involving patients recruited from twelve centers of four countries: Hospital Universitario Central de Asturias (Spain); Hospital Santa Creu i Sant Pau (Spain); Centre for Neurodegenerative Disorders- University of Brescia (Brescia, Italy); Center for Neuroscience and Cell Biology, University of Coimbra (Coimbra, Portugal); Center for Molecular Neurology, VIB- University of Antwerp (Antwerp, Belgium), Regional Neurogenetic Centre, ASP CZ, Lamezia Terme (Catanzaro, Italy); Fondazione IRCCS Ca' Granda, Ospedale Policlinico (Milan, Italy).; RCCS Istituto Centro San Giovanni di Dio- Fatebenefratelli (Brescia, Italy), University of Florence Azienda Ospedaliero (Florence,Italy), Hospital Clínic (Barcelona, Spain); Hospital Gregorio Marañón (Madrid, Spain); Fondazione IRCCS Istituto Neurologico Carlo Besta, (Milan, Italy) and University Hospital Mutua de Terrassa, (Terrassa, Barcelona, Spain).

The anthropometric and clinical data were retrospectively collected from the medical records, and the DNA from all the participants was stored in the Institute Biobanks. We analyzed 440 FTD cases, 175 were *C9orf72* expansion-carriers. Of the C9orf72 non-expansion carriers, 258 had only clinical diagnosis and seven (6 patients with bvFTD and 1 patient with PNFA) were neuropathologically confirmed. In all the *C9orf72* non-carriers (n=265), we excluded the presence of pathogenic variants in the *GRN* and *MAPT* genes. In all the patients, we genotyped the CAG repeats in *ATXN1, ATX*N2 and *HTT* genes, *APOE* genotype (rs7412 and rs429358), rs5848 in *GRN* and rs1042522 in the *TP53* gene.

2.2-Subjects and medical records

All the patients were unrelated Caucasian, 293 from Spain, 101 from Italy, 26 from Belgium and 20 from Portugal, and were diagnosed according to the Rascovsky and Gorno-Tempini criteria as FTD (n=250), semantic dementia (n=32), progressive non-fluent aphasia (n=59), or FTD-MND (n=42) (Gorno-Tempini et al, 2011; Rascovsky et al, 2011) (***Supplementary Table 1)*** . In 57 patients FTD was classified as unspecified. Family history of dementia was present in 88.3% of the *C9orf72* expansion carriers and in 43.9% of the non-carriers.

The control group comprised 509 unrelated subjects of Spanish origin without symptoms of neurodegenerative disease. They were elderly subjects who agreed to participate and were recruited through the Health Community Service of the region of Asturias. All the patients and controls gave informed consent to participate in the study which was approved by the Ethical Committees of participating centers.

2.2 Genetic analysis

The genomic DNA was isolated from peripheral blood leukocytes. We selected two candidate SNPs (single nucleotide polymorphisms) to be tested: rs5848 and rs1042522 in *GRN* and *TP53* genes, respectively. All patients were also genotyped for the *APOE-Ɛ2/3/4* alleles (SNPs rs7412 and rs429358). The genotypes were determined by real-time PCR with Taqman commercial assays (Applied Biosystems).

The *HTT, ATXN1* and *ATXN2* CAG repeats-length were determined by polymerase chain reaction (PCR) with fluorescent-labeled primers and capillary electrophoresis using an ABI 3130XL DNA sequencer and the Gene Mapper v4.0 software (Applied Biosystems).

***C9orf72* expansion methodology**

In all patients, *C9orf72* genetic status was determined by triple repeat primed polymerase chain reaction (TP-PCR) using standard protocols (DeJesus-Hernandez et al, 2011; Gijselinck et al, 2012; Renton et al, 2011). All the *C9orf72* positive subjects in our cohort had more than 60 repeats.

2.3 Statistical analyses

To assess the influence of predictor variables in the age of onset of the disease, a multiple linear regression model was adjusted. A manual backward stepwise methodology was followed to fit the model. In the complete model only the predictors that had a p-value lesser than 0.2 in the univariate were included. Estimates, 95 % CI and p-values are reported. Survival was calculated as time from symptom onset to death from any cause (outcome= 1) or censoring date (outcome= 0). To determine the relationship between the predictors and the survival probability from symptom onset to death of any cause, a Cox proportional hazard regression model was fit using the same methodology. Hazard ratio, 95% CI and p-values are reported. In both analyses, the hypotheses were graphically corroborated, and alpha was set at 0.05. All analyses were carried out with R software version 3.5 (www.r-project.org; R-v3.5).The predictor variables were sex, family history, clinical phenotype, APOƐ4, rs5848 in *GRN* gene and rs1042522 in *TP53*. In the survival analysis, we also include the IAS in *HTT*, *ATXN*1 and *ATXN2* genes as predictor variables.

A post hoc Bonferroni correction to all pairwise comparisons was used fo the categorical variables for the sex and APOƐ4. For age at onset, factorial anova test with post hoc Bonferroni

correction was used to test all pairwise comparisons. In survival analysis, p values <0.012 were considered as statistically significant after applying Bonferroni correction for multiple testing.

2.4 Standard protocols approvals , registrations and patient consents

All the patients and controls gave informed consent to participate in the study which was approved by the Ethical Committees of the participating centers.

3. RESULTS

In ***Table 1*** we summarize the main values in the patients and controls, as well as the clinical presentation in the FTD patients.. We observed a higher frequency of men in FTD cohort and bvFTD group when compared to the control group (p=0.048 and p=0.003 , respectively).

We analyzed the effect of sex, family history, clinical phenotype, and *C9orf72, APOE, GRN* and *TP53* genotypes in the age at onset and survival among FTD patients. The presence of IAS in the *HTT, ATXN1,* and *ATXN2* genes was included as covariables in the survival. After multivariate analysis, the PNFA group had a significantly higher mean age at onset compared to the bvFTD (p=0.03; OR= 3.83, 95%CI = 0.41 to 7.26). Regarding the genetic variables, *C9orf72* carriers had a younger onset-age compared to non- carriers (57.86 vs 63.48 years; p<0.001,OR=-4.92, 95%CI=-7.44 to -2.39). No difference in the age at onset was observed between the clinical groups according to their *C9orf72* status.

When we analyzed the influence of *APOE, GRN* and *TP53* genotypes a significant association, under diverse genetic models, was found between the age at onset and the rs1042522 *TP53* with Pro carriers showing a lower mean age compared to Arg carriers ***(Table 2).***

In the survival analysis, the final multivariate model included clinical phenotype, *TP53* rs1042522 and *GRN* rs5848. For the other variants (*HTT*, *ATXN1* and *ATXN2* intermediate alleles, family history, sex, age at onset, C9orf72 status, and *APOE* genotype) a p-value higher than 0.2 in the univariate analysis was obtained and they were excluded from the final model. The multivariate Cox proportional hazard regression showed that FTD-MND patients with had a reduced survival (4.12 years) than patients with other clinical phenotypes (p<0.001, HR=4.12, 95% CI=1.97, 8.59) (***Table 3, Figure 1A***). Among the genetic factors, the carriers of Pro allele of rs1042522 *TP53* and CC homozygous of rs5848 *GRN* showed a shorter survival (***Table 3, Figures 1B and 1C***).

The *APOE*-Ɛ4 allele was significantly more frequent in the FTD compared to controls (25% vs 16%, p=0.022), and was also observed in the C9*orf72* non-carriers (27% vs 16%, p= 0.01). *APOE-Ɛ4* frequency was higher in the PNFA group compared to the controls (34% vs 16%, p=0.05) (***Table 4***). For rs1042522 *TP53* and rs5848 *GRN* , the genotypes distribution was similar between patients and controls and among the clinical groups (***Supplementary table 2***).

4-DISCUSSION

Several studies have analyzed the role of genetic and non-genetic modifiers in FTD to ascertain their effect on clinical heterogeneity and age of onset, among other variables. In fact, some works reported an association between sex and bvFTD and between family history and survival (Chiu et al, 2010; Woolley et al, 2011). In our cohort, we observed a male predominance in the bvFTD when compared with the PNFA group, but we did not observe a significant effect of sex or family history in the age at the onset or survival probability.

We identified an effect of *C9orf72* on the onset-age, with expansion carriers showing a significant earlier mean age compared to non-carriers. This is in agreement with previous reports and could be explained by the more aggressive physio-pathology that characterizes familial monogenic neurodegenerative disorders, in which the presence of mutations results in earlier deposit of protein-aggregates compared to sporadic cases without recognized pathogenic gene variants (Yang et al, 2019). In line with this idea, it has been suggested that among patients with FTD those with autosomal dominantly inherited mutations showed the earliest onset compared to sporadic cases (Caswell et al, 2019; Moore et al 2019).

Among the clinical groups, PNFA showed a later age of onset, and the lowest survival corresponded to FTD-MND. This could be a consequence of the life-threatening symptoms caused by MND, such as dyspnea and dysphagia, which are not present in other subtypes of FTD. This was in line with a recent description of a much faster progression for FTD-MND with initial motor presentation or motor cortex atrophy, despite having similar overall cognitive impairment. This suggested that disease progression in ALS-FTD may be critically linked to physiological and motor changes (Ahmed et al, 2019). Therefore, clinical or neuroimaging involvement of the motor cortex in FTD-MND seems to be associated with speed of progression and survival.

One of the main novel findings in our study was the association between the *TP53* variant and the onset-age and survival in our FTD cohort. The p53 protein is a transcription factor that binds directly and specifically to DNA in a tissue- and cell-specific manner, and has mainly antiproliferative functions but also governs physiological functions related to brain development such as human cranial size (Haworth et al, 2019). It has been described that the Pro-carriers showed lower levels of mRNA, but the specific regulatory mechanism has not been identified (Yang et al, 2019). We can speculate that rs1042522 might affect the FTD phenotype by playing a dual role in the pathogenesis of the disease. On one hand, a neuroprotective role for p53 has been proposed because, in an in vivo model of tau-mediated neurodegeneration, this protein could be a protective molecular pathway against synaptic pathology, one of the earliest pathologic abnormalities in tauopathies (Merlo et al, 2014). On the other hand, p53 promotes neurodegeneration through its interaction with the key proteins associated with

neurodegenerative diseases. For instance, p53-null mice had increased mHtt aggregates load (Ryan et al, 2006). Thus, the lower levels of p53 protein in Pro carriers could be associated with lesser levels of neuroprotection and/or an increased aggregate load, driving to an early age at onset and/or a shorter survival after the onset.

For the rs5848 variant in *GRN* gene, we observed a significant association between the CC genotype and a shorter survival in the overall FTD cohort. The rs5848 is located in the 3′UTR within a binding site for miR-659. This miRNA binds more efficiently to the T-allele resulting in a reduction of *GRN* transcript and lower protein levels (Rademarkers et al, 2008). In opposition to our results, the rs5848 TT genotype has been associated with a shorter survival after onset in C9orf72 expansion carriers (van Blitterswijk et al, 2014b) . Regarding the effect of rs1042522 and the rs45848 in the survival probability, it has been described that the *TP53* Pro/Pro genotype increases the risk of mortality by cancer and the increased levels of pgrn (progranulin) are associated with an increased tumorigenic activity (van Heemst et al, 2005; Li et al, 2018). With the data available in our FTD cohort, we have no information on the cause of death, and we cannot thus exclude that the observed effect on survival and age at onset was related with a different risk of developing cancer between the genotypes

APOE-Ɛ4 was significantly increased in the *C9orf72* non expansion carriers and among the clinical groups, the PNFA group showed a higher frequency of *APOE*-Ɛ4 carriers. No association between *APOE* genotype and age at onset or survival were observed. PNFA is the subtype in which Tau pathology is the most common underlying proteinopathy showing in most cases mixed FTD and Alzheimer disease neuropathology (Grossman, 2010; Santos-Santo et al, 2018). In fact, across progressive aphasias, *APOE*-Ɛ4 carriers are more often amyloid-β positive than non-carriers, and the prevalence of amyloid-β positivity increases with age in PNFA and SD subtypes (Bergeron et al, 2018). Recently, it has been described that *APOE*-Ɛ4 accelerates neurodegeneration in patients with *MAPT* mutations or FTLD-tau pathology independently of Aβ (Koriath et al, 2019). Moreover, recent evidence showed that ApoE-e4 is an anatomically selective risk factor that preferentially increased the vulnerability to AD pathology of memory-related medial temporal areas rather than language-related neocortices (Weintraub et al, 2020). It has been also reported a particularly higher vulnerability to AD pathology among *APOE*-Ɛ4 carriers (Altmann et al, 2014; Buckley et al, 2019). Moreover, studies with CSF biomarkers suggested that the increased ApoE-related risk in women might be associated with tau pathology more frequently than with amyloid pathology (Buckley et al, 2019). In our cohort, the frequency of *APOE*-Ɛ4 carriers was similar in males and females in all the clinical subtypes.

Finally, our study help us to better understand the genetic factors that may influence the clinical course in FTD and the underlying proteinopathies. Further studies are needed to better determine the factors that modify the phenotype in FTD since they should be taken into account in future diagnostic criteria and in the design of clinical trials. The genetic architecture of FTD is complex and many genetic variants can modulate disease pathogenesis in different ways. These variants might have a synergistic effect in the disease onset, progression, survival after the onset, and could be also associated with the clinical phenotype. Our study has several limitations, the small sample size for some of the clinical phenotypes, the fact that the diagnosis of many cases was not neuropathologically confirmed and the absence of the cancer mortality data. Moreover, the retrospective and multicentric design might influence the genetic association results. In fact, the differences in the *APOE*-ε4 frequencies could be due to the origin patient population. Therefore, our conclusions about the clinical groups and the role of some genetic variants as phenotype modifiers require additional studies in large cohorts of FTD patients with detailed clinical data recruitment and healthy controls from the different populations.

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6- REFERENCES

Ahmed RM, Devenney EM, Strikwerda-Brown C, Hodges JR, Piguet O, Kiernan MC.COG-01 Phenotypic variation in ALS-FTD and effect on survival. Amyotroph Lateral Scler Frontotemporal Degener. 2019. doi: 10.1080/21678421.2019.1647000.

Altmann, A., Tian, L., Henderson, V.W., Greicius, M.D., 2014. Sex modifies the APOE-related risk of developing Alzheimer disease. Ann. Neurol. https://doi.org/10.1002/ana.24135

Bergeron, D., Gorno-Tempini, M.L., Rabinovici, G.D., Santos-Santos, M.A., Seeley, W., Miller, B.L., Pijnenburg, Y., Keulen, M.A., Groot, C., van Berckel, B.N.M., van der Flier, W.M., Scheltens, P., Rohrer, J.D., Warren, J.D., Schott, J.M., Fox, N.C., Sanchez-Valle, R., Grau-Rivera, O., Gelpi, E., Seelaar, H., Papma, J.M., van Swieten, J.C., Hodges, J.R., Leyton, C.E., Piguet, O., Rogalski, E.J., Mesulam, M.M., Koric, L., Nora, K., Pariente, J., Dickerson, B., Mackenzie, I.R., Hsiung, G.Y.R., Belliard, S., Irwin, D.J., Wolk, D.A., Grossman, M., Jones, M., Harris, J., Mann, D., Snowden, J.S., Chrem-Mendez, P., Calandri, I.L., Amengual, A.A., Miguet-Alfonsi, C., Magnin, E., Magnani, G., Santangelo, R., Deramecourt, V., Pasquier, F., Mattsson, N., Nilsson, C., Hansson, O., Keith, J., Masellis, M., Black, S.E., Matías-Guiu, J.A., Cabrera-Martin, M.N., Paquet, C., Dumurgier, J., Teichmann, M., Sarazin, M., Bottlaender, M., Dubois, B., Rowe, C.C., Villemagne, V.L., Vandenberghe, R., Granadillo, E., Teng, E., Mendez, M., Meyer, P.T., Frings, L., Lleó, A., Blesa, R., Fortea, J., Seo, S.W., Diehl-Schmid, J., Grimmer, T., Frederiksen, K.S., Sánchez-Juan, P., Chételat, G., Jansen, W., Bouchard, R.W., Laforce, R.J., Visser, P.J., Ossenkoppele, R., 2018. Prevalence of amyloid-β pathology in distinct variants of primary progressive aphasia. Ann. Neurol. https://doi.org/10.1002/ana.25333

Buckley, R.F., Mormino, E.C., Chhatwal, J., Schultz, A.P., Rabin, J.S., Rentz, D.M., Acar, D., Properzi, M.J., Dumurgier, J., Jacobs, H., Gomez-Isla, T., Johnson, K.A., Sperling, R.A., Hanseeuw, B.J., 2019. Associations between baseline amyloid, sex, and APOE on subsequent tau accumulation in cerebrospinal fluid. Neurobiol. Aging. https://doi.org/10.1016/j.neurobiolaging.2019.02.019

Caswell, C., McMillan, C.T., Xie, S.X., Van Deerlin, V.M., Suh, E.R., Lee, E.B., Trojanowski, J.Q., Lee, V.M.Y., Irwin, D.J., Grossman, M., Massimo, L.M., 2019. Genetic predictors of survival in behavioral variant frontotemporal degeneration. Neurology. https://doi.org/10.1212/WNL.0000000000008387

Chiu, W.Z., Kaat, L.D., Seelaar, H., Rosso, S.M., Boon, A.J.W., Kamphorst, W., Van Swieten, J.C., 2010. Survival in progressive supranuclear palsy and frontotemporal dementia. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp.2009.195719

DeJesus-Hernandez, M., Mackenzie, I.R., Boeve, B.F., Boxer, A.L., Baker, M., Rutherford, N.J., Nicholson, A.M., Finch, N.C.A., Flynn, H., Adamson, J., Kouri, N., Wojtas, A., Sengdy, P., Hsiung, G.Y.R., Karydas, A., Seeley, W.W., Josephs, K.A., Coppola, G., Geschwind, D.H., Wszolek, Z.K., Feldman, H., Knopman, D.S., Petersen, R.C., Miller, B.L., Dickson, D.W., Boylan, K.B., Graff-Radford, N.R., Rademakers, R., 2011. Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. Neuron. https://doi.org/10.1016/j.neuron.2011.09.011

Gao, M., Zhao, L.R., 2018. Turning Death to Growth: Hematopoietic Growth Factors Promote Neurite Outgrowth through MEK/ERK/p53 Pathway. Mol. Neurobiol. https://doi.org/10.1007/s12035-017-0814-x

Gijselinck, I., Van Langenhove, T., van der Zee, J., Sleegers, K., Philtjens, S., Kleinberger, G., Janssens, J., Bettens, K., Van Cauwenberghe, C., Pereson, S., Engelborghs, S., Sieben, A., De Jonghe, P., Vandenberghe, R., Santens, P., De Bleecker, J., Maes, G., Bäumer, V., Dillen, L., Joris, G., Cuijt, I., Corsmit, E., Elinck, E., Van Dongen, J., Vermeulen, S., Van den Broeck, M., Vaerenberg, C., Mattheijssens, M., Peeters, K., Robberecht, W., Cras, P., Martin, J.J., De Deyn, P.P., Cruts, M., Van Broeckhoven, C., 2012. A C9orf72 promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: A gene identification study. Lancet Neurol. https://doi.org/10.1016/S1474-4422(11)70261-7

Gomez-Sanchez, J.C., Delgado-Esteban, M., Rodriguez-Hernandez, I., Sobrino, T., De La Ossa, N.P., Reverte, S., Bolaños, J.P., Gonzalez-Sarmiento, R., Castillo, J., Almeida, A., 2011. The human Tp53 Arg72Pro polymorphism explains different functional prognosis in stroke. J. Exp. Med. https://doi.org/10.1084/jem.20101523

Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., Ogar, J.M., Rohrer, J.D., Black, S., Boeve, B.F., Manes, F., Dronkers, N.F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B.L., Knopman, D.S., Hodges, J.R., Mesulam, M.M., Grossman, M., 2011. Classification of primary progressive aphasia and its variants. Neurology. https://doi.org/10.1212/WNL.0b013e31821103e6

Grossman, M., 2010. Primary progressive aphasia: Clinicopathological correlations. Nat. Rev. Neurol. https://doi.org/10.1038/nrneurol.2009.216

Haworth, S., Shapland, C.Y., Hayward, C., Prins, B.P., Felix, J.F., Medina-Gomez, C., Rivadeneira, F., Wang, C., Ahluwalia, T.S., Vrijheid, M., Guxens, M., Sunyer, J., Tachmazidou, I., Walter, K., Iotchkova, V., Jackson, A., Cleal, L., Huffmann, J., Min, J.L., Sass, L., Timmers,

P.R.H.J., Turki, S. Al, Anderson, C.A., Anney, R., Antony, D., Artigas, M.S., Ayub, M., Bala, S., Barrett, J.C., Barroso, I., Beales, P., Bentham, J., Bhattacharya, S., Birney, E., Blackwood, D., Bobrow, M., Bochukova, E., Bolton, P.F., Bounds, R., Boustred, C., Breen, G., Calissano, M., Carss, K., Charlton, R., Chatterjee, K., Chen, L., Ciampi, A., Cirak, S., Clapham, P., Clement, G., Coates, G., Cocca, M., Collier, D.A., Cosgrove, C., Cox, T., Craddock, N., Crooks, L., Curran, S., Curtis, D., Daly, A., Danecek, P., Day, I.N.M., Day-Williams, A., Dominiczak, A., Down, T., Du, Y., Dunham, I., Durbin, R., Edkins, S., Ekong, R., Ellis, P., Evans, D.M., Farooqi, I.S., Fitzpatrick, D.R., Flicek, P., Floyd, J., Foley, A.R., Franklin, C.S., Futema, M., Gallagher, L., Gaunt, T.R., Geihs, M., Geschwind, D., Greenwood, C.M.T., Griffin, H., Grozeva, D., Guo, Xiaosen, Guo, Xueqin, Gurling, H., Hart, D., Hendricks, A.E., Holmans, P., Howie, B., Huang, J., Huang, L., Hubbard, T., Humphries, S.E., Hurles, M.E., Hysi, P., Jackson, D.K., Jamshidi, Y., Joyce, C., Karczewski, K.J., Kaye, J., Keane, T., Kemp, J.P., Kennedy, K., Kent, A., Keogh, J., Khawaja, F., van Kogelenberg, M., Kolb-Kokocinski, A., Lachance, G., Langford, C., Lawson, D., Lee, I., Lek, M., Li, R., Li, Y., Liang, J., Lin, H., Liu, R., Lönnqvist, J., Lopes, L.R., Lopes, M., MacArthur, D.G., Mangino, M., Marchini, J., Marenne, G., Maslen, J., Mathieson, I., McCarthy, S., McGuffin, P., McIntosh, A.M., McKechanie, A.G., McQuillin, A., Memari, Y., Metrustry, S., Migone, N., Mitchison, H.M., Moayyeri, A., Morris, A., Morris, J., Muddyman, D., Muntoni, F., Northstone, K., O'Donovan, M.C., O'Rahilly, S., Onoufriadis, A., Oualkacha, K., Owen, M.J., Palotie, A., Panoutsopoulou, K., Parker, V., Parr, J.R., Paternoster, L., Paunio, T., Payne, F., Payne, S.J., Perry, J.R.B., Pietilainen, O., Plagnol, V., Pollitt, R.C., Porteous, D.J., Povey, S., Quail, M.A., Quaye, L., Raymond, F.L., Rehnström, K., Richards, J.B., Ridout, C.K., Ring, S., Ritchie, G.R.S., Roberts, N., Robinson, R.L., Savage, D.B., Scambler, P., Schiffels, S., Schmidts, M., Schoenmakers, N., Scott, R.H., Semple, R.K., Serra, E., Sharp, S.I., Shaw, A., Shihab, H.A., Shin, S.Y., Skuse, D., Small, K.S., Smee, C., Smith, B.H., Soranzo, N., Southam, L., Spasic-Boskovic, O., Spector, T.D., St Clair, D., Stalker, J., Stevens, E., Sun, J., Surdulescu, G., Suvisaari, J., Syrris, P., Taylor, R., Tian, J., Tobin, M.D., Valdes, A.M., Vandersteen, A.M., Vijayarangakannan, P., Visscher, P.M., Wain, L. V., Walters, J.T.R., Wang, G., Wang, J., Wang, Y., Ward, K., Wheeler, E., Whyte, T., Williams, H.J., Williamson, K.A., Wilson, C., Wilson, S.G., Wong, K., Xu, C.J., Yang, J., Zhang, F., Zhang, P., Zheng, H.F., Davey Smith, G., Fisher, S.E., Wilson, J.F., Cole, T.J., Fernandez-Orth, D., Bønnelykke, K., Bisgaard, H., Pennell, C.E., Jaddoe, V.W.V., Dedoussis, G., Timpson, N., Zeggini, E., Vitart, V., St Pourcain, B., 2019. Low-frequency variation in TP53 has large effects on head circumference and intracranial volume. Nat. Commun. https://doi.org/10.1038/s41467-018-07863-x

Koriath, C., Lashley, T., Taylor, W., Druyeh, R., Dimitriadis, A., Denning, N., Williams, J., Warren, J.D., Fox, N.C., Schott, J.M., Rowe, J.B., Collinge, J., Rohrer, J.D., Mead, S., 2019.

ApoE4 lowers age at onset in patients with frontotemporal dementia and tauopathy independent of amyloid-β copathology. Alzheimer's Dement. Diagnosis, Assess. Dis. Monit. https://doi.org/10.1016/j.dadm.2019.01.010

Li, G., Dong, T., Yang, D., Gao, A., Luo, J., Yang, H., Wang, L., 2018. Progranulin promotes lymphangiogenesis through VEGF-C and is an independent risk factor in human esophageal cancers. Hum. Pathol. https://doi.org/10.1016/j.humpath.2018.02.008

Menéndez-González, M., Clarimón, J., Rosas-Allende, I., Blázquez, M., San Martín, E.S., García-Fernández, C., Lleó, A., Dols-Icardo, O., Illán-Gala, I., Morís, G., Ribacoba, R., Álvarez, V., Martínez, C., 2019. HTT gene intermediate alleles in neurodegeneration: evidence for association with Alzheimer's disease. Neurobiol. Aging. https://doi.org/10.1016/j.neurobiolaging.2018.11.014

Merlo, P., Frost, B., Peng, S., Yang, Y.J., Park, P.J., Feany, M., 2014. P53 prevents neurodegeneration by regulating synaptic genes. Proc. Natl. Acad. Sci. U. S. A. https://doi.org/10.1073/pnas.1419083111

Moore, K.M., Nicholas, J., Grossman, M., McMillan, C.T., Irwin, D.J., Massimo, L., Van Deerlin, V.M., Warren, J.D., Fox, N.C., Rossor, M.N., Mead, S., Bocchetta, M., Boeve, B.F., Knopman, D.S., Graff-Radford, N.R., Forsberg, L.K., Rademakers, R., Wszolek, Z.K., van Swieten, J.C., Jiskoot, L.C., Meeter, L.H., Dopper, E.G., Papma, J.M., Snowden, J.S., Saxon, J., Jones, M., Pickering-Brown, S., Le Ber, I., Camuzat, A., Brice, A., Caroppo, P., Ghidoni, R., Pievani, M., Benussi, L., Binetti, G., Dickerson, B.C., Lucente, D., Krivensky, S., Graff, C., Öijerstedt, L., Fallström, M., Thonberg, H., Ghoshal, N., Morris, J.C., Borroni, B., Benussi, A., Padovani, A., Galimberti, D., Scarpini, E., Fumagalli, G.G., Mackenzie, I.R., Hsiung, G.Y.R., Sengdy, P., Boxer, A.L., Rosen, H., Taylor, J.B., Synofzik, M., Wilke, C., Sulzer, P., Hodges, J.R., Halliday, G., Kwok, J., Sanchez-Valle, R., Lladó, A., Borrego-Ecija, S., Santana, I., Almeida, M.R., Tábuas-Pereira, M., Moreno, F., Barandiaran, M., Indakoetxea, B., Levin, J., Danek, A., Rowe, J.B., Cope, T.E., Otto, M., Anderl-Straub, S., de Mendonça, A., Maruta, C., Masellis, M., Black, S.E., Couratier, P., Lautrette, G., Huey, E.D., Sorbi, S., Nacmias, B., Laforce, R., Tremblay, M.P.L., Vandenberghe, R., Damme, P. Van, Rogalski, E.J., Weintraub, S., Gerhard, A., Onyike, C.U., Ducharme, S., Papageorgiou, S.G., Ng, A.S.L., Brodtmann, A., Finger, E., Guerreiro, R., Bras, J., Rohrer, J.D., Heller, C., Convery, R.S., Woollacott, I.O., Shafei, R.M., Graff-Radford, J., Jones, D.T., Dheel, C.M., Savica, R., Lapid, M.I., Baker, M., Fields, J.A., Gavrilova, R., Domoto-Reilly, K., Poos, J.M., Van der Ende, E.L., Panman, J.L., Donker Kaat, L., Seelaar, H., Richardson, A., Frisoni, G., Mega, A., Fostinelli, S., Chiang, H.H., Alberici, A., Arighi, A., Fenoglio, C., Heuer, H., Miller, B., Karydas, A., Fong, J., João

Leitão, M., Santiago, B., Duro, D., Ferreira, Carlos, Gabilondo, A., De Arriba, M., Tainta, M., Zulaica, M., Ferreira, Catarina, Semler, E., Ludolph, A., Landwehrmeyer, B., Volk, A.E., Miltenberger, G., Verdelho, A., Afonso, S., Tartaglia, M.C., Freedman, M., Rogaeva, E., Ferrari, C., Piaceri, I., Bessi, V., Lombardi, G., St-Onge, F., Doré, M.C., Bruffaerts, R., Vandenbulcke, M., Van den Stock, J., Mesulam, M.M., Bigio, E., Koros, C., Papatriantafyllou, J., Kroupis, C., Stefanis, L., Shoesmith, C., Robertson, E., Coppola, G., Da Silva Ramos, E.M., Geschwind, D., 2020. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. Lancet Neurol. https://doi.org/10.1016/S1474-4422(19)30394-1

Rademakers, R., Eriksen, J.L., Baker, M., Robinson, T., Ahmed, Z., Lincoln, S.J., Finch, N., Rutherford, N.J., Crook, R.J., Josephs, K.A., Boeve, B.F., Knopman, D.S., Petersen, R.C., Parisi, J.E., Caselli, R.J., Wszolek, Z.K., Uitti, R.J., Feldman, H., Hutton, M.L., Mackenzie, I.R., Graff-Radford, N.R., Dickson, D.W., 2008. Common variation in the miR-659 binding-site of GRN is a major risk factor for TDP43-positive frontotemporal dementia. Hum. Mol. Genet. https://doi.org/10.1093/hmg/ddn257

Ramos-Araque, M.E., Rodriguez, C., Vecino, R., Cortijo Garcia, E., de Lera Alfonso, M., Sanchez Barba, M., Colàs-Campàs, L., Purroy, F., Arenillas, J.F., Almeida, A., Delgado-Esteban, M., 2019. The Neuronal Ischemic Tolerance Is Conditioned by the Tp53 Arg72Pro Polymorphism. Transl. Stroke Res. https://doi.org/10.1007/s12975-018-0631-1

Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., Van Swieten, J.C., Seelaar, H., Dopper, E.G.P., 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. https://doi.org/10.1093/brain/awr179

Renton, A.E., Majounie, E., Waite, A., Simón-Sánchez, J., Rollinson, S., Gibbs, J.R., Schymick, J.C., Laaksovirta, H., van Swieten, J.C., Myllykangas, L., Kalimo, H., Paetau, A., Abramzon, Y., Remes, A.M., Kaganovich, A., Scholz, S.W., Duckworth, J., Ding, J., Harmer, D.W., Hernandez, D.G., Johnson, J.O., Mok, K., Ryten, M., Trabzuni, D., Guerreiro, R.J., Orrell, R.W., Neal, J., Murray, A., Pearson, J., Jansen, I.E., Sondervan, D., Seelaar, H., Blake, D., Young, K., Halliwell, N., Callister, J.B., Toulson, G., Richardson, A., Gerhard, A., Snowden, J.,

Mann, D., Neary, D., Nalls, M.A., Peuralinna, T., Jansson, L., Isoviita, V.M., Kaivorinne, A.L., Hölttä-Vuori, M., Ikonen, E., Sulkava, R., Benatar, M., Wuu, J., Chiò, A., Restagno, G., Borghero, G., Sabatelli, M., Heckerman, D., Rogaeva, E., Zinman, L., Rothstein, J.D., Sendtner, M., Drepper, C., Eichler, E.E., Alkan, C., Abdullaev, Z., Pack, S.D., Dutra, A., Pak, E., Hardy, J., Singleton, A., Williams, N.M., Heutink, P., Pickering-Brown, S., Morris, H.R., Tienari, P.J., Traynor, B.J., 2011. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. https://doi.org/10.1016/j.neuron.2011.09.010

Rohrer, J.D., Guerreiro, R., Vandrovcova, J., Uphill, J., Reiman, D., Beck, J., Isaacs, A.M., Authier, A., Ferrari, R., Fox, N.C., MacKenzie, I.R.A., Warren, J.D., De Silva, R., Holton, J., Revesz, T., Hardy, J., Mead, S., Rossor, M.N., 2009. The heritability and genetics of frontotemporal lobar degeneration. Neurology. https://doi.org/10.1212/WNL.0b013e3181bf997a

Rosas, I., Martínez, C., Clarimón, J., Lleó, A., Illán-Gala, I., Dols-Icardo, O., Borroni, B., Almeida, M.R., van der Zee, J., Van Broeckhoven, C., Bruni, A.C., Anfossi, M., Bernardi, L., Maletta, R., Serpente, M., Galimberti, D., Scarpini, E., Rossi, G., Caroppo, P., Benussi, L., Ghidoni, R., Binetti, G., Nacmias, B., Sorbi, S., Piaceri, I., Bagnoli, S., Antonell, A., Sánchez-Valle, R., De la Casa-Fages, B., Grandas, F., Diez-Fairen, M., Pastor, P., Ferrari, R., Álvarez, V., Menéndez-González, M., 2020. Role for ATXN1, ATXN2, and HTT intermediate repeats in frontotemporal dementia and Alzheimer's disease. Neurobiol. Aging. https://doi.org/10.1016/j.neurobiolaging.2019.10.017

Rubino, E., Mancini, C., Boschi, S., Ferrero, P., Ferrone, M., Bianca, S., Zucca, M., Orsi, L., Pinessi, L., Govone, F., Vacca, A., Gai, A., Giordana, M.T., Brusco, A., Rainero, I., 2019. ATXN2 intermediate repeat expansions influence the clinical phenotype in frontotemporal dementia. Neurobiol. Aging. https://doi.org/10.1016/j.neurobiolaging.2018.09.009

Ryan, A.B., Zeitlin, S.O., Scrable, H., 2006. Genetic interaction between expanded murine Hdh alleles and p53 reveal deleterious effects of p53 on Huntington's disease pathogenesis. Neurobiol. Dis. https://doi.org/10.1016/j.nbd.2006.08.002

Santos-Santos, M.A., Rabinovici, G.D., Iaccarino, L., Ayakta, N., Tammewar, G., Lobach, I., Henry, M.L., Hubbard, I., Mandelli, M.L., Spinelli, E., Miller, Z.A., Pressman, P.S., O'Neil, J.P., Ghosh, P., Lazaris, A., Meyer, M., Watson, C., Yoon, S.J., Rosen, H.J., Grinberg, L., Seeley, W.W., Miller, B.L., Jagust, W.J., Gorno-Tempini, M.L., 2018. Rates of amyloid imaging positivity in patients with primary progressive aphasia. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2017.4309

Simón-Sánchez, J., Dopper, E.G.P., Cohn-Hokke, P.E., Hukema, R.K., Nicolaou, N., Seelaar, H., De Graaf, J.R.A., De Koning, I., Van Schoor, N.M., Deeg, D.J.H., Smits, M., Raaphorst, J., Van Den Berg, L.H., Schelhaas, H.J., De Die-Smulders, C.E.M., Majoor-Krakauer, D., Rozemuller, A.J.M., Willemsen, R., Pijnenburg, Y.A.L., Heutink, P., Van Swieten, J.C., 2012. The clinical and pathological phenotype of C9ORF72 hexanucleotide repeat expansions. Brain. https://doi.org/10.1093/brain/awr353

Sun, G., Wang, Y., Zhang, J., Lin, N., You, Y., 2018. MiR-15b/HOTAIR/p53 form a regulatory loop that affects the growth of glioma cells. J. Cell. Biochem. https://doi.org/10.1002/jcb.26591

Szybinska, A., Lesniak, W., 2017. P53 dysfunction in neurodegenerative diseases - The cause or effect of pathological changes? Aging Dis. https://doi.org/10.14336/AD.2016.1120

van Blitterswijk, M., Mullen, B., Heckman, M.G., Baker, M.C., DeJesus-Hernandez, M., Brown, P.H., Murray, M.E., Hsiung, G.Y.R., Stewart, H., Karydas, A.M., Finger, E., Kertesz, A., Bigio, E.H., Weintraub, S., Mesulam, M., Hatanpaa, K.J., White, C.L., Neumann, M., Strong, M.J., Beach, T.G., Wszolek, Z.K., Lippa, C., Caselli, R., Petrucelli, L., Josephs, K.A., Parisi, J.E., Knopman, D.S., Petersen, R.C., Mackenzie, I.R., Seeley, W.W., Grinberg, L.T., Miller, B.L., Boylan, K.B., Graff-Radford, N.R., Boeve, B.F., Dickson, D.W., Rademakers, R., 2014a. Ataxin-2 as potential disease modifier in C9ORF72 expansion carriers. Neurobiol. Aging. https://doi.org/10.1016/j.neurobiolaging.2014.04.016

van Blitterswijk, M., Mullen, B., Wojtas, A., Heckman, M.G., Diehl, N.N., Baker, M.C., DeJesus-Hernandez, M., Brown, P.H., Murray, M.E., Hsiung, G.Y.R., Stewart, H., Karydas, A.M., Finger, E., Kertesz, A., Bigio, E.H., Weintraub, S., Mesulam, M., Hatanpaa, K.J., White, C.L., Neumann, M., Strong, M.J., Beach, T.G., Wszolek, Z.K., Lippa, C., Caselli, R., Petrucelli, L., Josephs, K.A., Parisi, J.E., Knopman, D.S., Petersen, R.C., Mackenzie, I.R., Seeley, W.W., Grinberg, L.T., Miller, B.L., Boylan, K.B., Graff-Radford, N.R., Boeve, B.F., Dickson, D.W., Rademakers, R., 2014b. Genetic modifiers in carriers of repeat expansions in the C9ORF72 gene. Mol. Neurodegener. https://doi.org/10.1186/1750-1326-9-38

Van Heemst, D., Mooijaart, S.P., Beekman, M., Schreuder, J., De Craen, A.J.M., Brandt, B.W., Eline Slagboom, P., Westendorp, R.G.J., 2005. Variation in the human TP53 gene affects old age survival and cancer mortality. Exp. Gerontol. https://doi.org/10.1016/j.exger.2004.10.001

Van Mossevelde, S., Engelborghs, S., Van Der Zee, J., Van Broeckhoven, C., 2018. Genotype-phenotype links in frontotemporal lobar degeneration. Nat. Rev. Neurol. https://doi.org/10.1038/s41582-018-0009-8

Vogt, M.A., Ehsaei, Z., Knuckles, P., Higginbottom, A., Helmbrecht, M.S., Kunath, T., Eggan, K., Williams, L.A., Shaw, P.J., Wurst, W., Floss, T., Huber, A.B., Taylor, V., 2018. TDP-43 induces p53-mediated cell death of cortical progenitors and immature neurons. Sci. Rep. https://doi.org/10.1038/s41598-018-26397-2

Weintraub, S., Teylan, M., Rader, B., Chan, K.C.G., Bollenbeck, M., Kukull, W.A., Coventry, C., Rogalski, E., Bigio, E., Mesulam, M.M., 2020. APOE is a correlate of phenotypic heterogeneity in Alzheimer disease in a national cohort. Neurology. https://doi.org/10.1212/WNL.0000000000008666

Woolley, J.D., Khan, B.K., Murthy, N.K., Miller, B.L., Rankin, K.P., 2011. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: Rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. J. Clin. Psychiatry. https://doi.org/10.4088/JCP.10m06382oli

Yang, J., Wu, X., Huang, J., Chen, Z., Huang, G., Guo, X., Zhu, L., Su, L., 2019. TP53 Polymorphism Contributes to the Susceptibility to Bipolar Disorder but Not to Schizophrenia in the Chinese Han Population. J. Mol. Neurosci. https://doi.org/10.1007/s12031-019-01330-y

Yang, Y., Halliday, G.M., Kiernan, M.C., Tan, R.H., 2019. TDP-43 levels in the brain tissue of ALS cases with and without C9ORF72 or ATXN2 gene expansions. Neurology. https://doi.org/10.1212/WNL.0000000000008439

Table 1 - Demographic and clinic characteristics of patient and control groups.

Group	**N**	**Male (%)**	**Family history N%**	**Age at examination (controls) / Age at onset (patients)** mean±StD	**Disease duration (years)** mean±Std
Controls	509	234 (46)		71.14±6.42	
FTD	440	241 (54.8)*	270(61)	61.42±9.90	5.98±4.79
***C9orf72 expansion-* non carrier**	265	143(54)	116(43)	63.48±9.43	7.9 ±9.18
***C9orf72* expansion carriers**	175	98(56)	154(88)	57.86±9.43	4.22 ±4.80
bvFTD	250	149(59.6)*	170(68)	60.15±9.70	6.55±5.29
PNFA	59	24(40.7)	32(55)	66.21±8.14	5.54±3.26
SD	32	16(50)	15(47)	63.08±9.21	6.01±3.87
FTD-MND	42	28(66.7)	28(67)	59.32±10.35	3.29±3.32
Unspecified	57	24(42.1)	27(48)	62.21±11.04	5.78±4.69

**p<0.05 Post hoc Bonferroni correction. FTD vs control ; bvFTD vs control *. post hoc Bonferroni correction was applied for the global number of tests FTD- frontotemporal dementia; bvFTD behavioural frontotemporal dementia; PNFA- progressive non fluent aphasia; SD- semantic dementia; FTD-MND- frontotemporal dementia and motoneuron disease;FTD unspecified - Frontotemporal dementia with no specified phenotype; StD- standard deviation*

Table 2- Variants associated with age at onset after multivariate regression analysis.

Variable	**Allele**	**OR (95%CI)**	**p value**
***TP53* rs1042522**	***Pro***		
	Dominant Model	- 2.51(-4.47,-0.55)	p=0.012
	Additive model	-2.34(-3.89,-0.79)	p=0.003
	Recessive model	-4.87(-9.08,-066)	p=0.02
	Alelic	-2.42 (-2.42,-0.84)	p=0.003
C9orf72			
Non carriers		**Reference**	
Carriers		-4.99(-7.52,-2.46)	p<0.001
Clinical phenotype			
bvFTD		**Reference**	
FTD_MND PNFA SD Unspecified		2.28(-1.31,5.87) 3.83(0.41,7,26) 2.66(-1.88,7.20) 1.41(-1.76,4.59)	0.21 0.03* 0.25 0.38

p<0.05 factorial anova with post hoc bonferroni correction. bvFTD behavioural frontotemporal dementia; PNFA- progressive non fluent aphasia; SD- semantic dementia; FTD-MND- frontotemporal dementia and motoneuron disease;FTD unspecified - Frontotemporal dementia with no specified phenotype. 95% CI = 95% confidence interval

T*able 3* - Multivariate Cox proportional-hazard regression analysis.

Variable	**Allele**	**HR (95%CI)**	**p value**
***TP53* rs1042522**	***Pro***		
	Dominant model	1.73(1.07,2.86)	P=0.03
	Additive model	1.56 (1.06,2.3)	p=0.02
	Recessive model	1.63 (0.55, 1.14)	p=0.09
	Alelic model	1.72(1.17-2.53)	p=0.007
GRN rs5848	**C**		
	Dominant model	0.51 (0.19,1.15)	p=0.25
	Additive model	2.83 (0.96,8,31)	p=0.058
	Recessive model	1.98(1.16,3.35)	p=0.011
	Alelic model	1.80 (1.19,2.72)	p=0.005
Clinical phenotype			
	bvFTD	**Reference**	
	FTD_MND PNFA SD Unspecified	4.12(1.97,859) 1.88(0.95,3.69) 1.10(0.45,2.68) 0.65(0.23,1.85)	p<0.001* p=0.07 p=0.83 p=0.42

** p<0.012 was significant after Bonferroni correction . bvFTD behavioural frontotemporal dementia; PNFA- progressive non fluent aphasia; SD- semantic dementia; FTD-MND- frontotemporal dementia and motoneuron disease;FTD unspecified - Frontotemporal dementia with no specified phenotype. 95% CI = 95% confidence interva*l.

Table 4- *APOE* distribution in patients and controls.

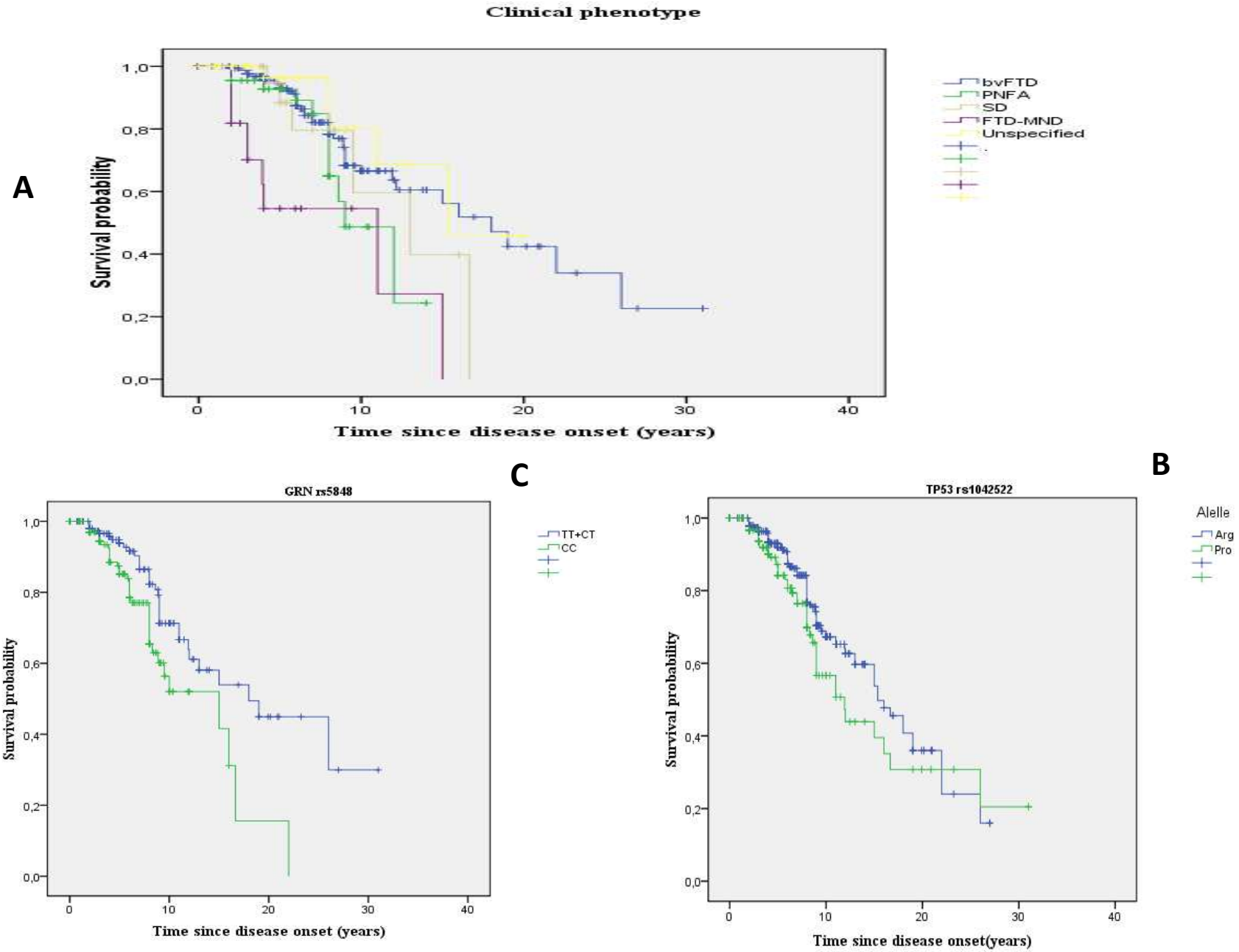
	Ɛ4- **N(%)**	**Ɛ4+** **N(%)**	**p Bonferroni**
Control	429(84.3)	80(15.7)	
FTD	330(75)	110(25)	0.022*
FTD C9+	137(78.3)	38(21.7)	1
FTD C9-	193(72.8)	72(27.2)	0.01**
bvFTD	189(75.6)	61(24.4)	0.246
PNFA	39(66.1)	20(33.9)	0.05***
SD	24(75)	8(25)	1
FTD-MND	35(83.3)	7(16.7)	1
FTD unspecified	43(75.4)	14(26.4)	1

*Post hoc Bonferroni correction was applied for the global number of tests*Ɛ4+ carrier frequency FTD vs controls ;**E4+ carrier frequency C9 negative FTD vs controls ;*** E4+ carrier frequency PNFA vs controls. FTD- frontotemporal dementia; bvFTD behavioural frontotemporal dementia; PNFA- progressive non fluent aphasia; SD- semantic dementia; FTD-MND- frontotemporal dementia and motoneuron disease;FTD unspecified - Frontotemporal dementia with no specified phenotype*

Figure´s footnotes

Figure 1- Survival curves for clinical phenotype, *rs5848 and rs1042522-*. *FTD- bvFTD behavioural frontotemporal dementia; PNFA- progressive non fluent aphasia; SD- semantic dementia; FTD-MND- frontotemporal dementia and motoneuron disease;FTD unspecified - Frontotemporal dementia witht no specified phenotype*

Figure 1


A
Clinical phenotype
Survival probability
1,0
0,8
0,6
0,4
0,2
0,0
0
10
20
30
40
Time since disease onset (years)
bvFTD
PNFA
SD
FTD-MND
Unspecified
B
TP53 rs1042522
Survival probability
Time since disease onset(years)
Alelle
Arg
Pro
C
GRN rs5848
Survival probability
Time since disease onset (years)
TT+CT
CC

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