Main title

A worldwide cohort study of age at symptom onset and death and disease duration in genetic frontotemporal dementia

Running title

Genetic FTD

Authors

Katrina M Moore BSc[1], Jennifer Nicholas PhD[2], Prof Murray Grossman MD PhD[3], Corey T McMillan MD PhD[3], David J Irwin MD PhD[3], Lauren Massimo PhD[3], Prof Vivianna M Van Deerlin MD PhD[3], Prof Jason D Warren FRACP PhD[1], Prof Nick C. Fox MD FRCP[1], Prof Martin N. Rossor MD FRCP[1], Prof Simon Mead FRCP PhD[4], Martina Bocchetta PhD[1], Prof Bradley F Boeve MD[5], Prof David S Knopman MD[5], Prof Neill R Graff-Radford MD PhD[6], Leah K Forsberg PhD[5], Prof Rosa Rademakers PhD[7], Prof Zbigniew K Wszolek MD[6], Prof John C van Swieten MD PhD[8], Lize C Jiskoot PhD[8], Lieke H Meeter PhD[8], Elise GP Dopper MD PhD[8], Janne M Papma PhD[8], Prof Julie S Snowden PhD[9], Jennifer Saxon PhD[9], Matthew Jones MRCP PhD[9], Prof Stuart Pickering Brown PhD[9], Isabelle Le Ber MD PhD[10], Agnès Camuzat BSc[10], Prof Alexis Brice MD[10], Paola Caroppo MD PhD[10], Prof Roberta Ghidoni PhD[11], Michela Pievani PhD[12], Luisa Benussi PhD[11], Prof Giuliano Binetti MD[11], Prof Bradford C Dickerson MD[13], Diane Lucente MS LCGC[13], Samantha Krivensky BS[13], Prof Caroline Graff MD PhD[14,15], Linn Öijerstedt MD[14,15], Marie Fallström MD[14,15], Håkan Thonberg MD[14,15], Nupur Ghoshal MD PhD[16], Prof John C Morris MD[16], Barbara Borroni MD PhD[17], Alberto Benussi MD PhD[17], Prof Alessandro Padovani MD PhD[17], Daniela Galimberti PhD[18,19], Prof Elio Scarpini MD[19,20], Giorgio G Fumagalli MD[19,20,21], Prof Ian R Mackenzie MD[22], Ging-Yuek R Hsiung MD[22], Pheth Sengdy PhD[22], Prof Adam L Boxer MD PhD[23], Prof Howie Rosen MD PhD[23], Joanne B Taylor MS LCGC [23], Prof Matthis Synofzik MD[24,25], Carlo Wilke MD[24,25], Patricia Sulzer MSc[24,25], Prof John R Hodges MD PhD[26], Prof Glenda Halliday PhD[26], John Kwok PhD[26], Raquel Sanchez-Valle MD[27], Albert Lladó MD[27], Sergi Borrego-Ecija MD[27], Isabel Santana MD PhD[28,29,30], Maria Rosário Almeida PhD[28], Miguel Tábuas-Pereira MD[29], Fermin Moreno MD PhD[31,32,33], Myriam Barandiaran PhD[31,32,33], Begoña Indakoetxea MD[31,32,33], Johannes Levin MD[34,35,36], Prof Adrian Danek MD[34], Prof James B Rowe MD PhD[37], Thomas E Cope MD PhD[37], Prof Markus Otto MD[38], Sarah Anderl-Straub PhD[38], Prof Alexandre de Mendonça MD PhD[39], Carolina Maruta PhD[39], Mario Masellis MD PhD[40], Prof Sandra E. Black MD[40], Prof Philippe Couratier MD PhD[41], Geraldine Lautrette MD[41], Edward D Huey MD[42], Prof Sandro Sorbi PhD[43,44], Benedetta Nacmias PhD[43], Robert Laforce Jr MD PhD[45], Marie-Pier L Tremblay PhD[45], Prof Rik Vandenberghe MD PhD[46], Prof Philip Van Damme MD PhD[46,47], Emily J Rogalski PhD[48], Sandra Weintraub PhD[48], Alexander Gerhard MD[49,50], Chiadi U Onyike MD MHS[51], Simon Ducharme MD MSc[52], Sokratis G Papageorgiou MD PhD[53], Adeline Su Lyn NgMD[54], Amy Brodtmann FRACP PhD[55], Elizabeth Finger MD PhD[56], Rita Guerreiro PhD[57], Jose Bras PhD[57], FTD Prevention Initiative*, Jonathan D Rohrer FRCP PhD[1]

Affiliations

[1]Dementia Research Centre, Department of Neurodegenerative Disease, Queen Square UCL Institute of Neurology, Queen Square, London, UK. [2]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK. [3]Department of Neurology, Penn Frontotemporal Degeneration Center, University of Pennsylvania, USA. [4]UCL Institute of Prion Diseases, London, UK. [5]Department of Neurology, Mayo Clinic, Rochester, MN, USA. [6]Department of Neurology, Mayo Clinic, Jacksonville, FL, USA. [7]Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA. [8]Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands. [9]Cerebral Function Unit, Salford Royal NHS Foundation Trust and Division of Neuroscience and Experimental Psychology, University of Manchester, UK. [10]Institut du Cerveau et de la Moelle épinière (ICM) & Centre de Référence des Démences Rares ou précoces, Institut de la Mémoire et de la Maladie d'Alzheimer, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital de la Pitié-Salpêtrière, Paris, France. [11]Molecular Markers Laboratory, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. [12]Lab Alzheimer's Neuroimaging & Epidemiology, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. [13]Frontotemporal Disorders Unit, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, USA. [14]Karolinska Institutet, Department NVS, Center for Alzheimer Research, Division of Neurogenetics, Bioclincum J10:20, Solna, Sweden. [15]Karolinska University Hospital, Unit for Hereditary Dementias, Theme Aging, Solna, Sweden. [16]Department of Neurology, Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA. [17]Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. [18]Dept. of Biomedical, Surgical and Dental Sciences, University of Milan, Centro Dino Ferrari, Milan, Italy. [19]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy. [20]Dept. of Pathophysiology and Transplantation, University of Milan, Centro Dino Ferrari, Milan, Italy. [21]Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy. [22]Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada. [23]Department of Neurology, Memory and Aging Center, University of California at San Francisco (UCSF), San Francisco, CA, USA. [24]Department of Neurodegenerative Diseases, Center for Neurology and Hertie-Institute for Clinical Brain Research, Tübingen, Germany. [25]German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany. [26]Brain and Mind Centre & Central Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, Australia. [27]Alzheimer's Disease and Other Cognitive Disorders Unit, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. [28]Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal. [29]Neurology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. [30]Faculty of Medicine, University of Coimbra, Portugal. [31]Cognitive Disorders Unit, Department of Neurology, Donostia Universitary Hospital, San Sebastian, Gipuzkoa, Spain. [32]Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain. [33]Center for Networked Biomedical Research on Neurodegenerative Disease (CIBERNED), Carlos III Health Institute, Spain. [34]Department of Neurology, Ludwig-Maximilians-Universität München, Munich, Germany. [35]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany. [36]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. [37]Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK.

[38]Department of Neurology, University of Ulm, Germany. [39]Faculdade de Medicina, Universidade de Lisboa, Portugal. [40]Division of Neurology, Department of Medicine, Hurvitz Brain Sciences Program, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada. [41]Centre de compétence Démences Rares, CHU Limoges, Limoges, France. [42]Departments of Psychiatry and Neurology, Columbia University, New York, USA. [43]Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy. [44]IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy. [43]Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, Hôpital de l'Enfant-Jésus, and Faculté de Médecine, Université Laval, QC, Canada. [46]Department of Neurology, University Hospitals Leuven, Leuven, Belgium. [47]Center for Brain & Disease Research, VIB, Leuven, Belgium. [48]Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Northwestern University, Chicago, USA. [49]Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK. [50]Departments of Nuclear Medicine and Geriatric Medicine, University Hospital Essen, Germany. [51]Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [52]Montreal Neurological Institute, McConnell Brain Imaging Centre, McGill University Health Centre, McGill University, 3801 University Street, Montreal, QC, Canada. [53]Cognitive Disorders/Dementia Unit, 2nd Department of Neurology, National and Kapodistrian University of Athens, Attikon University General Hospital, Athens, Greece. [54]Department of Neurology, National Neuroscience Institute, Singapore. [55]Florey Institute of Neuroscience and Mental Health, Melbourne, Australia. [56]Department of Clinical Neurological Sciences, University of Western Ontario, London, ON, Canada. [57]Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, Michigan, USA.

Corresponding author

Dr Jonathan Rohrer, Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, j.rohrer@ucl.ac.uk

*List of FPI consortium authors below

Number of words: abstract 650; main text 4451

***FTD Prevention Initiative**

Carolin Heller MSc[1,2], Rhian Convery MSc[1], Ione OC Woollacott MRCP[1], Rachelle Shafei MRCP[1], Jonathan Graff-Radford MD[3], David T Jones MD[3], Christina M Dheel BSc[3], Rodolfo Savica MD PhD[3], Maria I Lapid MD[4], Matt Baker BSc[5], Julie A Fields PhD LP[6], Ralitza Gavrilova MD[7], Kimiko Domoto-Reilly MD[8], Jackie M Poos MSc[9], Emma L van der Ende MSc[9], Jessica L Panman MSc[9], Laura Donker Kaat MD PhD[9], Harro Seelaar MD PhD[9], Anna Richardson MD[10], Giovanni Frisoni MD PhD[11], Anna Mega MSc[11], Silvia Fostinelli MSc[11], Huei-Hsin Chiang MD[12,13], Antonella Alberici MD PhD[14], Andrea Arighi, MD[15], Chiara Fenoglio,

PhD[16], Hilary Heuer PhD[17], Bruce Miller MD[17], Anna Karydas[17], Jamie Fong MSc[17], Maria João Leitão BSc[18], Beatriz Santiago MD[19], Diana Duro BSc[19], Carlos Ferreira PhD[20], Alazne Gabilondo MD[21,22,23], María de Arriba BSc[22,23,24], Mikel Tainta MD[22,23,24], Miren Zulaica BSc[22,23], Catarina B. Ferreira MSc[25], Elisa Semler MSc[26], Albert Ludolph MD[26], Bernhard Landwehrmeyer MD[26], Alexander E. Volk MD[27], Gabriel Miltenberger PhD[28], Ana Verdelho MD PhD[29], Sónia Afonso BSc[29], Maria Carmela Tartaglia MD PhD[30], Morris Freedman MD[31], Ekaterina Rogaeva PhD[30], Camilla Ferrari[32], Irene Piaceri[32], Valentina Bessi[32], Gemma Lombardi[32], Frédéric St-Onge MSc[33], Marie-Claire Doré PhD[33], Rose Bruffaerts MD PhD[34], Mathieu Vandenbulcke MD PhD[34], Jan Van den Stock PhD[34], M.Marsel Mesulam MD[35], Eileen Bigio PhD[35], Christos Koros MD[36], John Papatriantafyllou MD[36], Christos Kroupis PhD[37], Leonidas Stefanis MD[38], Christen Shoesmith MD[39], Erik Roberson MD[40], Giovanni Coppola PhD[41], Eliana Marisa Da Silva Ramos[41], Daniel Geschwind MD[41]

Affiliations

[1]Dementia Research Centre and [2]UK Dementia Research Institute, Department of Neurodegenerative Disease, Queen Square UCL Institute of Neurology, Queen Square, London, UK. [3]Department of Neurology, Mayo Clinic, Rochester, MN, USA. [4]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA. [5]Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA. [6]Department of Psychology, Mayo Clinic, Rochester, MN, USA. [7]Department of Clinical Genomics, Mayo Clinic, Rochester, MN, USA. [8]University of Washington, Seattle, WA, USA. [9]Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands. [10]Cerebral Function Unit, Salford Royal NHS Foundation Trust and Division of Neuroscience and Experimental Psychology, University of Manchester, UK. [11]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. [12]Karolinska Institutet, Department NVS, Center for Alzheimer Research, Division of Neurogenetics, Bioclincum J10:20, Solna, Sweden. [13]Karolinska University Hospital, Unit for Hereditary Dementias, Theme Aging, Solna, Sweden. [14]Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. [15]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy. [16]Dept. of Pathophysiology and Transplantation, University of Milan, Centro Dino Ferrari, Milan, Italy. [17]Department of Neurology, Memory and Aging Center, University of California at San Francisco (UCSF), San Francisco, CA, USA. [18]Neurology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. [19]Faculty of Medicine, University of Coimbra, Portugal. [20]Institute of Nuclear Sciences Applied to Health (ICNAS), Coimbra, Portugal. [21]Department of Neurology, Hospital de Bidasoa, Irun, Spain. [22]Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain. [23]Center for Networked Biomedical Research on Neurodegenerative Disease (CIBERNED), Carlos III Health Institute, Spain. [24]CITA Alzheimer, San Sebastian, Spain. [25]Laboratory of Neurosciences, Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisbon, Portugal. [26]Department of Neurology, University of Ulm, Germany. [27]Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [28]Faculty of Medicine, University of Lisbon, Lisbon, Portugal. [29]Department of Neurosciences and Mental Health, Centro Hospitalar Lisboa Norte - Hospital de Santa Maria & Faculty of Medicine, University of Lisbon, Lisbon, Portugal. [30]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada. [31]Baycrest

Health Sciences, Rotman Research Institute, University of Toronto, Toronto, Canada. [32]Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy. [33]Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, Hôpital de l'Enfant-Jésus, Université Laval, QC, Canada. [34]Department of Neurology, University Hospitals Leuven, Leuven, Belgium. [35]Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Northwestern University, Chicago, USA. [36]Cognitive Disorders/Dementia Unit, 2nd Department of Neurology, National and Kapodistrian University of Athens, Attikon University General Hospital, Athens, Greece. [37]Department of Clinical Biochemistry, National and Kapodistrian University of Athens, Attikon University General Hospital, Athens, Greece. [38]1st Department of Neurology, National and Kapodistrian University of Athens, Eginition Hospital, Athens, Greece. [39]Department of Clinical Neurological Sciences, University of Western Ontario, London, ON, Canada. [40]Departments of Neurology and Neurobiology, Center for Neurodegeneration and Experimental Therapeutics, Alzheimer's Disease Center, Evelyn F. McKnight Brain Institute, University of Alabama at Birmingham, Birmingham, AL, United States. [41]Department of Psychiatry and Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA.

Summary

Background: Frontotemporal dementia (FTD) is a heterogenous neurodegenerative disorder with around a third being accounted for by mutations in *GRN*, *MAPT*, and *C9orf72*. We aimed to complement previous phenotypic studies with a comprehensive worldwide study of age at onset (AAO), age at death (AAD), and disease duration (DD).

Methods: Data on sex, clinical phenotype, AAO, AAD and DD for patients with pathogenic mutations in the *GRN* and *MAPT* genes and pathological expansions in the *C9orf72* gene were collected through the FTD Prevention Initiative, a collaborative group of natural history genetic FTD cohort studies, as well as through published papers, between 1st January 2015 and 1st July 2017. We used mixed effects models to explore differences in AAO, AAD and DD between genetic groups and individual mutations as well across generations and by sex and clinical phenotype. We also performed a correlation of individual's AAO and AAD with the AAO and AAD of their parents and the average within other members of the same family. Lastly, we used mixed effects models to investigate the extent to which variability in AAO and AAD could be accounted by family membership and the specific mutation carried.

Findings: Data was available from 3403 symptomatic individuals from 1492 families: 1433 with *C9orf72* expansions (755 families), 1179 with *GRN* mutations (483 families, 130 different mutations), and 791 with *MAPT* mutations (254 families, 67 different mutations). Mean AAO/AAD was 49.5 (10.0)/58.5 (11.3) years for the *MAPT* group, 58.2 (9.8)/65.3 (10.9) for *C9orf72* and 61.3 (8.8)/ 68.8 (9.7) for *GRN*. Mean DD was 6.4 (4.9) years for the *C9orf72* group, 7.1 (3.9) for *GRN* and 9.3 (6.4) for *MAPT*. Individual AAO and AAD was significantly correlated with both parental AAO and AAD and mean family AAO and AAD in all three groups, but with a much stronger correlation in *MAPT* (r=0.63/0.69 for mean family AAO and AAD, and 0.45/0.58 for parental) than in either *C9orf72* (0.36/0.40, 0.32/0.38) or *GRN* (0.18/0.32, 0.22/0.22). Modelling showed that the variability in AAO and AAD was explained in part by the specific mutation (48% for AAO, 61% for AAD), and more so by family membership (66% for AAO, 74% for AAD) in the *MAPT* group. In the *GRN* group, variability was only accounted for by the specific mutation by 2% for AAO, 9% for AAD, and by family membership by 14% for AAO, 20% for AAD, whilst in the *C9orf72* group variability was only accounted for by family membership by 17% for AAO and 19% for AAD.

Interpretation: Whilst estimation of AAO will be an important factor in future presymptomatic therapeutic trials, this study suggests that data from other members of the family will only be helpful in such an estimate for the *MAPT* group. Further work in identifying both genetic and environmental factors that modify phenotype in all groups will be important to improve such estimates.

Funding: UK Medical Research Council, National Institute for Health Research, and Alzheimer's Society.

Introduction

Frontotemporal dementia (FTD) is a clinically, genetically and pathologically heterogeneous neurodegenerative disease[1]. The most common clinical subtypes are behavioural variant FTD (bvFTD), presenting with changes in personality and executive dysfunction, and primary progressive aphasia (PPA), in which people develop impairment of language processing. Three forms of PPA are described – semantic (svPPA), nonfluent/agrammatic (nfvPPA), and logopenic (lvPPA) variants – although up to 20% of people do not fit criteria for any variant (PPA-not otherwise specified, PPA-NOS)[2]. Both bvFTD and PPA overlap with amyotrophic lateral sclerosis (ALS), and the atypical parkinsonian syndromes, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP)[1].

Around a third of FTD is genetic[3], with mutations in multiple genes shown to be causative of FTD. However, the majority of the heritability of FTD is accounted for by mutations in three genes: progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) and chromosome 9 open reading frame 72 (*C9orf72*). Whilst much has been learned over the last decade about the clinical features of these genetic forms of FTD most studies exploring age at symptom onset and duration have been relatively small and geographically restricted[4-6]. In particular, although individual case series suggest that such phenotypic characteristics can be quite variable, no studies have systematically investigated these factors across all of the different genetic groups and the different mutations found within the groups. As the era of clinical trials in presymptomatic mutation carriers approaches, a better understanding of the variability in onset and duration will be important.

In this study, we therefore aimed to analyse phenotypic characteristics of the main three forms of autosomal dominant FTD including ages at onset and death and disease duration in a large cohort of individuals from across the world, examining the effect of mutation type and family membership on these factors.

Methods

Study design

Data were collected through centres that are part of the FTD Prevention Initiative (FPI), a group connecting natural history cohort studies of genetic FTD: the Genetic Frontotemporal Dementia Initiative (GENFI)[7], Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL), Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) and the Dominantly Inherited Non-Alzheimer's Dementias (DINAD) studies. These research studies account for the majority of centres investigating genetic FTD in Europe and Eastern Canada (GENFI), USA and Western Canada (ARTFL/LEFFTDS) and Australia (DINAD). In total, 33 centres across the world provided data for participants that included genetic group, individual mutation (for the *GRN* and *MAPT* groups), sex, clinical phenotype, age at symptom onset (AAO, defined by the onset of progressive behavioural, cognitive, or motor symptoms reported either by an informant, usually a family member, or for non-behavioural symptoms by the patient themselves), age at death (AAD), and relationship to other family members. Local ethics committees at each of the sites approved the study and data from participants was provided through informed consent. We also reviewed publications cited in the Alzheimer Disease & Frontotemporal Dementia Mutation Database (www.molgen.ua.ac.be/FTDmutations), and supplemented this by a detailed search of PubMed for other publications with AAO, AAD or disease duration (DD) data in people with genetic FTD: this identified 308 journal articles. To avoid potential double reporting, sites were asked to provide a list of publications relevant to their dataset. These were then manually examined for possible duplicates, which were removed where identified.

We aimed to include all pathogenic mutations in the *GRN, MAPT* and *C9orf72* genes within the study. 78 *GRN* and 45 *MAPT* pathogenic mutations were found in the Alzheimer Disease & Frontotemporal Dementia Mutation Database. From the PubMed search we discovered 35 *GRN* and 18 *MAPT* variants not included in the database, and centres in the study provided data additionally on another 17 *GRN*

and 4 *MAPT* variants (appendix p 2). *C9orf72* families with intermediate length expansions were not included in the study.

Statistical Analysis

All statistical analyses were performed using Stata (v.14 or later). Numbers and percentages with each mutation were calculated by geography and clinical phenotype. A chi-squared test was used to compare sex distribution in each of the genetic groups. Means and standard deviations for AAO, AAD, and DD were calculated in each genetic group and in the most common mutations in the *MAPT* and *GRN* groups (defined as those with the greatest number of individuals in the study). Mixed effects models were used to examine differences in AAO, AAD and DD: i) between genetic groups (*GRN, MAPT* and *C9orf72*), ii) between the common mutations in the *GRN* and *MAPT* groups, iii) between an earlier and later generation of family members in all genetic groups, iv) between male and female sex within each genetic group, and v) between the main clinical phenotypes within each genetic group. Analyses took account of relatedness by including family membership as a random effect. To explore the relationship between a) an individual's AAO (or AAD) and the AAO (or AAD) of their affected parent, and b) an individual's AAO (or AAD) and the average AAO (or AAD) of other members of the same family the Pearson correlation coefficient was calculated. Lastly, we also used mixed effects models to explore the extent to which variability in AAO and AAD were explained by *family membership* (exploring variability both *within* and *between* families) and the *specific mutation* carried (in *GRN* and *MAPT* groups only). Detailed statistical methods are shown in appendix pp 15-19.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author has full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

The combined dataset consisted of 3403 symptomatic individuals from 1492 families with data on one or more of AAO, AAD, DD and clinical phenotype (Tables 1 and 2): 1433 with *C9orf72* expansions (755 families), 791 with *MAPT* mutations (254 families), and 1179 with *GRN* mutations (483 families).

In total 130 *GRN* mutations and 67 *MAPT* mutations were included in the study (appendix pp 5-10). The commonest *GRN* mutations were T272fs (201 individuals, 95 families), R493X (55 individuals, 22 families), IVS7-1G>A (50 individuals, 18 families), C31fs (47 individuals, 10 families), G35fs (42 individuals, 10 families) and A9D (37 individuals, 4 families). The commonest *MAPT* mutations were: P301L (234 individuals, 59 families), IVS10+16C>T (149 individuals, 48 families), R406W (67 individuals, 9 families) and N279K (44 individuals, 17 families).

Globally, the most prevalent genetic group was the *C9orf72* expansion carriers (42.1% of all individuals), then *GRN* mutation carriers (34.6%), with *MAPT* mutation carriers the least common group (23.2%) (Figure 1). However, there was geographical variability with a different spread of frequencies amongst the three genetic groups in certain countries: *GRN* mutation carriers were more common than the other groups particularly in Italy (66% of total), and to a lesser extent in Spain (49%); and *MAPT* mutations were found more frequently in some countries than others e.g. Netherlands (40%) and parts of the US e.g. West Coast (47%). See appendix pp 20-23 for more details.

Although bvFTD was the most common diagnosis in each group, phenotypic variability was seen across the different mutations (Table 2). See appendix pp 24-32 for more details

Both the *C9orf72* and *MAPT* groups contained approximately equal numbers of men and women (52% and 49% male respectively) (Table 1, appendix pp 33-34). However, the *GRN* group had a significant

overrepresentation of women (58% female, 42% male), compared with both the *C9orf72* group (p<0.001) and the *MAPT* group (p=0.002).

The mean AAO was youngest for the *MAPT* group, 49.5 (standard deviation 10.0) years, significantly younger than both of the other groups (p<0.001 for each comparison), followed by the *C9orf72* group, 58.2 (9.8) years, which was also significantly younger than the *GRN* group (p<0.001), 61.3 (8.8) years (Table 1, appendix p 35-36). However, there was a wide range of AAO within each of the genetic groups (Figure 2, appendix p 36), from the 20's to the 90's in the *GRN* and *C9orf72* groups, and from 17 to the 80's in the *MAPT* group. Cumulative probability curves for symptom onset in each of the genetic groups are shown in Figure 3a (and data shown in appendix p 39).

A wide range of AAO was also seen in individual *GRN* and *MAPT* mutations (appendix pp 6-10). We plotted cumulative probability curves for symptom onset for the most common *GRN* (Figure 3b) and *MAPT* (Figure 3c) mutations (appendix p 39). Whilst these largely overlapped for the *GRN* mutations (and without any significant difference between groups: R493X mean (standard deviation) 60.2 (8.9) years, C31fs 60.3 (8.2), IVS7-1G>A 60.5 (7.9), G35fs 61.2 (10.9), A9D 62.1 (10.6), T272fs 62.7 (8.9)), there was a significant difference in the *MAPT* mutations with an earlier onset in the N279K mutation group (43.8 (6.7) years) in comparison to the other groups (p<0.005 for all comparisons), followed by IVS10+16C>T (50.9 (6.1)), P301L (53.0 (7.4)) and R406W (55.4 (7.5)) (appendix p 40).

The generational analysis showed a significantly younger AAO in the second (later) generation than the first (earlier generation) in all three groups: *GRN* generation 1: mean (standard deviation) 65.5 (9.1), generation 2: 60.7 (8.9), p<0.001; *C9orf72* generation 1: 62.3 (10.9) years, generation 2: 56.7 (11.0), p<0.001; *MAPT* generation 1: 51.4 (9.5), generation 2: 49.6 (10.0), p=0.011 (appendix pp 41-43).

No significant difference in AAO was seen between males and females in the *MAPT* group (appendix p 44). However, there was a significantly older age at onset in females in the *GRN* group (61.8 (9.2) years, compared with 60.5 (8.3) years in males, p=0.019), as well as in the *C9orf72* group (58.9 (9.6) years in females, compared with 57.7 (10.0) years in males, p=0.041).

No major differences in AAO were seen between *C9orf72*-bvFTD (56.7 (9.0)), *C9orf72*-ALS (57.0 (9.0)), *C9orf72*-FTD-ALS (57.8 (8.3)) or *C9orf72*-PPA (59.7 (7.4)) (appendix pp 45-46). However, *C9orf72* expansion carriers with a diagnosis of Alzheimer's disease (AD) had a significantly older AAO than the other groups (65.1 (10.6)) (p<0.001 for all comparisons except *C9orf72*-PPA vs *C9orf72*-AD, p=0.010). Similarly, there was no significant difference in AAO between *GRN*-bvFTD (59.6 (8.1)), *GRN*-PPA (60.2 (7.7)), and *GRN*-CBS (57.7 (7.3)) but those with *GRN*-AD had a significantly older AAO (66.4 (8.1)) than the other groups (p<0.001 for all comparisons). In the *MAPT* group there was no significant difference in AAO between those with *MAPT*-bvFTD (50.5 (9.0)) and *MAPT*-PPA (52.4 (12.0)) but those with *MAPT*-AD (56.7 (11.1)) had a significantly older AAO than those with *MAPT*-bvFTD (p=0.001), *MAPT*-PPA (p=0.013) and *MAPT*-CBS/PSP (44.9 (7.8), p<0.001). Furthermore, the *MAPT*-CBS/PSP had a significantly younger onset than the other groups (p=0.013 vs *MAPT*-bvFTD, p=0.037 vs *MAPT*-PPA).

The average AAD was youngest for *MAPT* mutation carriers, 58.5 (11.3) years, followed by *C9orf72* expansion carriers, 65.3 (10.9) years and oldest in *GRN* mutation carriers 68.8 (9.7) years (Table 1; p<0.001 for each comparison). AAD was variable within genetic groups (Table 1, Figure 2), and within individual mutations (appendix pp 6-10, 37).

As with AAO, there were no significant differences in AAD between males and females in the *MAPT* group (appendix p 44), but a significant difference in both the *GRN* (69.4 (10.2) females, 67.8 (8.8) males, p=0.029) and *C9orf72* groups (66.1 (11.0) females, 64.6 (10.8) males, p=0.034).

As with AAO, those with a diagnosis of AD in all groups had a significantly older AAD than all of the other groups (appendix pp 45-46). In the *C9orf72* group there was a significantly younger AAD in *C9orf72*-ALS group (59.2 (9.7)) compared to *C9orf72*-FTD-ALS (62.1 (8.9), p=0.014) and *C9orf72*-bvFTD (64.6 (9.0), p<0.001), and in turn a younger AAD in *C9orf72*-FTD-ALS compared to *C9orf72*-bvFTD (p=0.014). In the *MAPT* group there was also a significantly younger AAD in *MAPT*-CBS/PSP (52.8 (8.9)) compared with *MAPT*-bvFTD (60.6 (9.9)), p=0.030.

The average DD was shortest for *C9orf72* expansion carriers, 6.4 (4.9) years, followed by *GRN* mutation carriers, 7.1 (3.9) and then *MAPT* mutation carriers, 9.3 (6.4) (Table 1; p≤0.001 for each comparison). However, within each genetic group there were a number of people who survived for many decades (Table 1, Figure 2, appendix p 38) – the longest surviving person lived 27 years from symptom onset in the *GRN* group, 36 years in the *C9orf72* group and 45 years in the *MAPT* group.

Although there was variability within individual mutations (appendix pp 6-10, 38) mean DD was similar across the *GRN* group except for a significantly longer DD in A9D mutation carriers when compared with the majority of other common mutations (appendix p 40). There was greater variability in the mean DD across the *MAPT* group and in a subanalysis of *MAPT* mutation carriers separated by their functional consequences and underlying pathology into five groups, the exon 11-13 with paired helical filament (PHF)-tau pathology group (i.e. V337M and R406W mutations, group 5: appendix pp 47-48) had a significantly longer disease duration, 17.6 (11.8) years compared with the other groups: group 1 (exons 1,2 and 9): 8.3 (7.3), group 2 (exon/intron 10 affecting splicing): 9.3 (5.3), group 3 (exon 10 not affecting splicing): 7.9 (4.0), and group 4 (exons 11-13 with non-PHF-tau pathology): 7.8 (5.3) (p<0.005 for each comparison with group 1).

There were no significant differences in DD between males and females in any of the groups (appendix p 44).

There were no phenotypic differences in DD in the *GRN* group (*GRN*-bvFTD 7.1 (3.7), *GRN*-PPA 6.5 (2.8), *GRN*-AD 7.8 (4.9), *GRN*-CBS 8.2 (5.7)). In the *MAPT* group however, the *MAPT*-CBS/PSP group (7.2 (4.0)) had a trend to a shorter DD than the *MAPT*-bvFTD 10.2 (6.2) (p=0.072), and *MAPT*-AD 10.2 (6.2) (p=0.078) groups but not the *MAPT*-PPA 9.1 (4.1) (p=0.140) group. The *C9orf72*-ALS group had a significantly shorter duration (2.9 (2.8)) than other groups (p<0.001 for all comparisons), with *C9orf72*-FTD-ALS (5.0 (4.2)) also having a shorter DD than *C9orf72*-bvFTD (7.8 (4.4), p<0.001), *C9orf72*-PPA (7.5 (4.8), p=0.002) and *C9orf72*-AD (10.4 (4.9), p<0.001) (appendix p 45-46).

Individual AAO significantly correlated with both parental AAO and mean family AAO in all three genetic groups (p<0.001) (Figure 4), although in each group a similar or stronger correlation was seen with mean family AAO than with parental AAO. The strength of the correlation varied across the genetic groups, stronger in the *MAPT* group (r=0.63 mean family AAO, r = 0.45 parental AAO) than in the *C9orf72* group (r=0.36 mean family AAO, r = 0.32 parental AAO), and weakest in the *GRN* groups (r=0.18 mean family AAO, r = 0.22 parental AAO).

As with AAO, individual AAD significantly correlated with both parental AAD and mean family AAD in all three genetic groups (p<0.001). A similar pattern arose across the three genetic groups with the strongest correlation in the *MAPT* group (r=0.69 mean family AAD, r = 0.58 parental AAD) than in the *C9orf72* group (r=0.40 mean family AAD, r = 0.38 parental AAD), and weakest in the *GRN* groups (r=0.32 mean family AAD, r = 0.22 parental AAD).

There were significant differences between the three mutation carrier groups in the inter-family and intra-family AAO variability (both p<0.001, appendix p 49). Family membership explained 66% (95% confidence intervals: 56-75%) of the variability in AAO in *MAPT* mutation carriers but only 14 (9-22)% in *GRN* mutation carriers, and 17 (11-26)% of the variability in *C9orf72* expansion carriers.

There was a significant difference between the *GRN* and *MAPT* groups in the between mutation variability in AAO ($p<0.001$): for the *GRN* group only 2% (95% confidence intervals: 0-10%) of the variability in AAO was explained by the specific mutation, whilst for the *MAPT* group 48 (35-62)% of the variability in AAO was explained by the specific mutation.

As with AAO, there were significant differences between the three genetic groups in the inter-family and intra-family AAD variability (both $p<0.001$, appendix p 49). Family membership explained 74% (95% confidence intervals: 65-82%) of the variability in AAD in *MAPT* mutation carriers but only 20 (12-30)% in *GRN* mutation carriers, and 19 (12-29)% of the variability in *C9orf72* expansion carriers.

Also as with AAO, there was a significant difference between the *GRN* and *MAPT* groups in the between mutation variability in AAD ($p<0.001$): for the *GRN* group only 9% (95% confidence intervals: 3-21%) of the variability in AAD was explained by the specific mutation, whilst for the *MAPT* group 61 (47-73)% of the variability in AAD was explained by the specific mutation.

Discussion

We report the largest dataset of age at onset, age at death and disease duration in genetic FTD to date, incorporating data from across the world, in all the three main genetic groups, and all reported mutations within the *GRN* and *MAPT* mutation groups. The study provides evidence that an individual's age at symptom onset and death in genetic FTD varies by sex and phenotype and is modulated by both family membership and the individual mutation carried, with the strongest effect of these factors in *MAPT* mutation carriers. Our findings extend the knowledge gained from prior smaller studies in several key areas of interest to future clinical trial design of preventive therapies.

The study provides further evidence that genetic FTD is a disorder that can occur throughout adult life, with onset ranging from as young as the late teens through to the 90's. Although we did not account for unaffected mutation carriers in the analysis, the findings are also consistent with previous studies showing age-related penetrance in the *GRN*[8] and *C9orf72*[9] groups, with people developing symptoms into their 90's. There is a leftwards shift in the penetrance curve in *MAPT* carriers to a younger age, but nonetheless the oldest AAO in this group was 82. Whilst usually considered a fully penetrant disorder, there may well be occasional incomplete penetrance in some *MAPT* families (cf. previous descriptions in L315R[10], V363I[11,12], G389R[13]), which may be age-related.

Investigation of individual mutations within *GRN* reveals few differences between them in terms of AAO, AAD or DD. This is consistent with the underlying pathophysiological mechanism of progranulin haploinsufficiency being the same in the majority of mutations[14,15]. In contrast, there were much larger differences between individual *MAPT* mutations, with the mean onset in the N279K mutation group 12 years earlier than in the R406W mutation group. Along with the V337M mutation, R406W has a distinct pathological form compared with the other *MAPT* mutations, with the presence of PHF-tau similar to that seen in Alzheimer's disease; this group has a significantly longer disease duration than the other mutations, as previously described in single case reports[16].

The generational analysis revealed significant differences in all groups, consistent with previous studies[4,17], with an earlier AAO in later generations. This finding has been variably interpreted: in *C9orf72* carriers one group has suggested that this is evidence of genetic anticipation[17]. However, another group interpreted this data as likely to be related to later generations recognizing the disease earlier because of increased familiarity with symptoms, and being more likely to be alert to the presence of such symptoms due to their awareness of being at-risk[4]. At a molecular level it has been shown that whilst *C9orf72* expansions may be dynamic, they can both expand and contract across generations[17], and, furthermore, there is no clear evidence for a relationship between AAO and expansion length,

with contradictory evidence of both a positive correlation in some studies[18-20] and inverse correlation in another[21]. Evidence against anticipation being an explanation for the finding of earlier AAO in later generations also comes from the similar result in the *GRN* (found in another study as well[4]) and *MAPT* groups: these mutations are stable and do not change molecularly across generations i.e. there is no plausible mechanism for anticipation in *GRN* or *MAPT* mutations.

Few studies have compared whether AAO, AAD or DD vary by clinical phenotype within genetic groups. In this study, those with a diagnosis of AD within each group had a significantly older onset. Whilst there is a potential that those with a true amnestic presentation of genetic FTD do present at an older age (and that there is an underlying biological explanation for this), it is more likely that this is related to the misdiagnosis of those with an older onset dementia as AD. In the *MAPT* group those with an atypical parkinsonian syndrome had a younger AAO and AAD and shorter DD than other groups – this was not entirely driven by the presence of specific mutation as the phenotype was seen across multiple mutations (e.g. only 13% of this group had the N279K mutation, which as discussed above has an earlier mean AAO). In the *C9orf72* group the presence of ALS was associated with a shorter DD (with pure ALS shorter than combined FTD-ALS), as previously reported[22]. Previous studies have compared an all 'FTD' group with ALS in *C9orf72* carriers and found an earlier onset in the ALS group[9]. In the cohort studied here, combining 'cognitive' presentations of *C9orf72* expansions also finds a significantly earlier onset in the ALS group (mean 57.0, standard deviation 9.0, versus cognitive *C9orf72* group 58.6 (10.2) (adjusted mean difference -1.8, 95% confidence intervals -3.4, -0.2, p=0.024)), but this is in part driven by the 'AD' group, and no differences were found between the ALS group and either the bvFTD or PPA groups individually.

Individual AAO (and AAD) were significantly correlated with both parental AAO (and AAD) and mean family AAO (and AAD) in all three genetic groups. However, there was a stronger correlation in the *MAPT* group compared with the other two groups, similar to that found in familial AD[23]. Modelling

revealed that the variability in AAO and AAD for *MAPT* mutation carriers was explained in part by the specific mutation (48% for AAO, 61% for AAD), and more so by family membership (66% for AAO, 74% for AAD). Unlike the other genetic groups, in *MAPT* mutation carriers, prediction of likely AAO (and AAD) is therefore highly related to the presence of the *MAPT* mutation itself. Other genetic or environmental factors affecting AAO and AAD in *MAPT* mutation carriers have not yet been well studied[24].

Despite being statistically significant, the correlation coefficient was only 0.18/0.22 for the mean family/parental AAO comparison with individual AAO in *GRN* carriers (and 0.32/0.22 for AAD). Modelling revealed that the variability in AAO and AAD for *GRN* mutation carriers was not accounted for particularly by either the individual mutation (2% for AAO, 9% for AAD), or family membership (14% for AAO, 20% for AAD). This is consistent with previous reports of large variability within families (and specific mutations), even within the same generation[25-27]. Genetic factors affecting AAO include polymorphisms in *TMEM106B*[28,29], and potentially also *PRNP*[30], but multiple studies now suggest that environmental factors related to an altered neuroinflammatory response may also be important[31-34].

The *C9orf72* group sits between the *GRN* and *MAPT* groups in terms of the strength of correlation of individual AAO and AAD with mean family/parental AAO and AAD (0.36/0.32 for AAO, 0.40/0.38 for AAD). However, similar to *GRN* mutations, modelling revealed that the variability in AAO and AAD was not accounted for particularly by family membership (17% for AAO, 19% for AAD). Whilst there is conflicting evidence about whether expansion length is relevant[18-21], recent studies have identified DNA methylation[21,35-36] and a locus on chromosome 6[37] as important factors in AAO, AAD and DD in *C9orf72* expansion carriers.

See appendix pp 49-50 for further discussion of potential modifiers of AAO and AAD in genetic FTD.

The study is limited by its focus on mainly retrospective data collection, with AAO recorded as the age at which an individual was determined to have progressive cognitive, behavioural or motor symptoms, and as such our data may be confounded by factors such as individual differences in interpreting symptom onset. This is a major issue in FTD, with objective measures of symptom onset lacking. A 'grey' zone in proximity to symptom onset exists where subtle cognitive and behavioural deficits are present[7], but have not yet been identified by the patient themselves or family members as symptoms. Work within the FPI aims to identify such 'proximity markers', which will be important for future stratification in disease trials, particularly, as identified in this study, for *GRN* and *C9orf72* mutation carriers where prediction by age itself is poor.

Another limitation of the study is that we did not record data on known mutation carriers who did not develop symptoms of FTD. This is particularly important when assessing age-related penetrance in the *GRN* and *C9orf72* groups, although we did identify people into their 90's developing symptoms of FTD in both of these groups. Attainment of data from long-living mutation carriers will be important to better understand modifiers of AAO, and this is more likely in large, well-characterized longitudinal cohort studies such as those in the FPI.

Whilst many of the centres saw patients and families with all phenotypes of FTD, ALS and movement disorders within their clinics, the focus on genetic FTD within the study may have led to an underrepresentation of ALS or parkinsonian disorders. However, many of the families had members with multiple different phenotypes (including cognitive, behavioural and motor), and there were few families with only a single phenotype, suggesting the data in the study is unlikely to lead to a major discrepancy in phenotypic frequency.

Lastly, we did not have any data on *TMEM106B* genotype nor on other genetic modifiers, in order to investigate their effect further. However, such data, along with a variety of environmental and lifestyle factors, is now being collected within the FPI and will be able to be combined in future studies to further investigate the effects of these modifiers.

In summary, we show that *MAPT* mutation carriers are associated with a younger AAO and AAD than the other groups, with the observed variance largely accounted for by family membership and the specific mutation carried. *GRN* mutation carriers have the weakest association of individual AAO/AAD with other members of the family, and the majority of the observed variance in AAO/AAD is accounted for by neither family membership nor mutation. However there was a sex effect, with increased prevalence and older age at onset in women, probably driven by the age-related penetrance seen in *GRN* mutation carriers. *C9orf72* expansions are the most common cause of genetic FTD across the world. Phenotypic differences in DD exist, with the presence of ALS leading to a shortened DD. Like *GRN*, little of the variance in AAO/AAD is accounted for by family membership with other genetic and environmental factors likely to be involved.

This study highlights the strength of collaborative studies in rare diseases, bringing together data from across the world to better understand genetic FTD, and providing important data relevant to future trial design. The prospective cohort studies within the FPI will hopefully be able to provide more solutions to some of the unanswered questions over the forthcoming years.

Panel: Research in context

Evidence before this study

We searched Pubmed for articles on genetic frontotemporal dementia (FTD) up to Jul 1, 2017, using the following terms: "frontotemporal dementia AND genetics", "progranulin OR *GRN*", "tau OR *MAPT*" and "chromosome 9 open reading frame 72 OR *C9orf72*", focusing on those studies that reported age at symptom onset (AAO), age at death (AAD) or disease duration (DD) of symptomatic individuals. Evidence from group studies and individual case series suggested that the AAO, AAD and DD were highly variable across the FTD-causing genes. Age-related penetrance was described in both *GRN* and *C9orf72* mutation carriers with *MAPT* mutations usually being fully penetrant. A generational difference in AAO was found with an earlier onset in more recent generations in *GRN* and *C9orf72* mutation carriers. Interpretation of this finding differed in the two studies, with one interpreting the result in the *C9orf72* group as evidence of anticipation, but the other arguing that this was unlikely given the similar result in *GRN* mutation carriers, where there is no molecular basis for anticipation. Phenotypic differences in AAO have not been studied in detail, but one study showed a shorter disease duration (DD) in people with an ALS diagnosis in the *C9orf72* group, and another study showed an earlier AAO in this group. No studies were found which had systematically investigated AAO, AAD or DD across all the different genetic groups and the different mutations found within the groups.

Added value of this study

This is the largest international study to date investigating individual AAO, AAD and DD in genetic FTD, incorporating data from across the world, across all the three main genetic groups (*C9orf72, GRN, MAPT*) and all mutations within the *GRN* and *MAPT* groups. The study provides important evidence about the factors underlying AAO, AAD and DD in the different groups, showing that only in the *MAPT* mutation group are AAO (and AAD) highly correlated with both parental AAO (and AAD) and mean family AAO (and AAD), with variability in AAO (and AAD) explained in part by the specific mutation, and more so by family membership. Such correlations are lower in the other two groups, with the specific mutation in the *GRN* group and family membership in both *GRN* and *C9orf72* groups only accounting for a small percentage of the variability in AAO and AAD. This is the first time that such key differences between genetic FTD groups have been shown.

Implications of all the available evidence

Optimal therapeutic trial design will be important in genetic FTD and in particular, many trials will aim to include presymptomatic mutation carriers who are expected to be in proximity to symptom onset. The evidence here suggests that only in *MAPT* mutation carriers will data from other family members be helpful in estimating the individual time from symptom onset. Further work is needed to understand the variability in the other groups, and it is likely that other proximity markers either individually or in combination will be required to refine the estimation of time to onset in those with *GRN* or *C9orf72* mutations. In the meantime, the current data will allow clinicians and family members a better understanding of the individual risk of likely symptom onset and time to death in each genetic group and within individual mutations.

Contributors

KMM and JDR drafted the initial version and figures. JN and JDR performed the statistical analysis. All authors were involved in data collection, interpretation and drafting of the manuscript. KMM, JDR, MG, BFB, JCvS, BCD, CG, NG, BB, DGa, IRM, ALB, HR, JL, JBR, MO, MM, RL, CUO and JN contributed to the study design. All authors critically reviewed the manuscript and approved the final draft.

Conflict of interest statement

KMM reports grants from Alzheimer's Society, during the conduct of the study. JN reports grants from Medical Research Council, during the conduct of the study. MG and CTM report grants from NIH (AG017586, AG010124), during the conduct of the study. DJI reports grants from NIH, during the conduct of the study. JDW reports grants from Alzheimer's Society, and NIHR UCLH Biomedical Research Centre, during the conduct of the study. NCF reports grants from Leonard Wolfson Experimental Neurology Centre, and UK Dementia Research Institute, during the conduct of the study; and personal fees from Biogen, GE healthcare, Lilly, and Roche outside the submitted work. MNR reports fees paid to Institution from Servier and Merck, outside the submitted work. BFB reports grants from Mayo Alzheimer's Disease Research Center (P50 AG016574), NIH (AG045390 [Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects study], NS092089, AG038791, AG052943, AG041797, AG016574, AG006786; NS100620, AG056639, AG054256, AG0503260), during the conduct of the study; and personal fees from Scientific Advisory Board - Tau Consortium, grants from Biogen, Mangurian Foundation, Alector, and Little Family Foundation outside the submitted work. DSK reports personal fees from DIAN study, grants from Lilly Pharmaceuticals, and grants from Biogen, outside the submitted work. NRG-R reports grants from Novartis, AbbVie, Lilly, and Biogen, outside the submitted work. JCvS reports grants from Dioraphte Foundation grant 09-02-03-00, the Bluefield project, Alzheimer Nederland, ZonMw Memorabel (Deltaplan Dementie, project number 733 051 042), The Netherlands Organization for Scientific Research (NWO) grant HCMI 056-13-018, The Association for Frontotemporal Dementias Research Grant 2009, during the conduct of the study. LHM reports grants from Deltaplan Dementie (The Netherlands Organisation for Health Research and Development, and Alzheimer Nederland), Alzheimer Nederland, European Joint Programme - Neurodegenerative Disease Research and the Netherlands Organisation for Health Research and Development (PreFrontALS: 733051042, RiMod-FTD 733051024), and the Bluefield Project, during the conduct of the study; and grants from Alector, outside the submitted work. ABri reports grants from France Parkinson + FRC, ANR - EPIG - Agence nationale de recherche, ANR - JPND - Agence nationale de recherche, RDS (Roger de Spoelberch Foundation), France Alzheimer, ENP -Ecole des neurosciences Paris, Institut de France, CHU de Nimes, ERA NET, ANR - EPIG, APHP, outside the submitted work. RGh reports grants from Italian Ministry of Health: Ricerca Corrente, and from Italian Ministry of Health grant RF-2016-02361492, during the conduct of the study. BCD reports grants from National Institute of Neurological Disorders and Stroke R21 NS084156, R21 NS085487, during the conduct of the study. CG and LÖ report grants from JPND Prefrontals Swedish Research council (VR) 529-2014-7504, Swedish research council (VR) 2015-02926, Swedish

Research Council (VR) 2018-02754, Swedish FTD Initiative Schörling Foundation, Swedish Alzheimer foundation, Swedish Brain Foundation, Stockholm County Council ALF, during the conduct of the study. LÖ also reports grants from Karolinska Institutet Doctoral Funding and StratNeuro, and from Swedish Demensfonden, during the conduct of the study. NG reports grants from Tau Consortium/ Rainwater Foundation, NIH/ NICHD/ OD K12 HD001459, NIH/ NIA/ NINDS U01AG045390, NIH/ NCATS/ NINDS U54NS092089, during the conduct of the study. JCM reports grants from NIH grant P50AG005681, NIH grant P01AG003991, NIH grant P01AG026276, NIH grant UF1AG032438, during the conduct of the study. DGa and ESc report grants from EU Joint Programme – Neurodegenerative Disease Research (JPND), and Italian Ministry of Health (PreFrontALS) grant 733051042, during the conduct of the study. GGF reports grants from Associazione Italiana Ricerca Alzheimer ONLUS (AIRAlzh Onlus)-COOP Italia, during the conduct of the study. IRM reports personal fees from Prevail Therapeutics, grants from CIHR, NIH/NIA, Brain Canada, and Weston Brain Institute, outside the submitted work; and has a patent "Detecting and treating dementia" issued. G-YRH reports grants from CIHR, Brain Canada, and NIH/NIA. ALB reports grants from NIH/NIA grant (AG038791) and NIH/NINDS grant (NS092089 [Advancement of Research and Treatment in Frontotemporal Lobar Degeneration study]), during the conduct of the study; and stock/options from Aeton Therapeutics and Alector, personal fees from Abbvie, Amgen, Arkuda, Arvinas, Denali, Ionis, Janssen, Lundbeck, Merck, Pinteon, Passage BIO, Neurogenetics. Samumed, Toyama and UCB; and grants from C2N, Cortice, Eli Lilly, Forum, Genentech, Roche, TauRx, NIH, AFTD, Bluefield Project, Tau Consortium, outside the submitted work. GH reports grants from National Health and Medical Research Council of Australia, during the conduct of the study. RS-V reports grants from Fundació Marató de TV3, Spain (grant no. 20143810).during the conduct of the study. SB-E reports grants from the Instituto de Salud Carlos III, Spain (Rio-Hortega post-residency grant), during the conduct of the study. FM reports grants from Tau Consortium, during the conduct of the study. JBR reports grants from National Institute for Health Research, Wellcome Trust, Medical Research Council, during the conduct of the study; travel funds from Guarantors of Brain, personal fees from Asceneuron, Astex, and Biogen, and grants from Janssen, AZ Medimmune, and Lilly, outside the submitted work. MO and SA-S report grants from Federal ministry of education and research (BMBF/FTLDc), during the conduct of the study. MM reports grants from Canadian Institutes of Health Research, during the conduct of the study; Board Membership of Current Pharmacogenomics and Personalized Medicine, personal fees from Arkuda Therapeutics, and Ionis, grants from Canadian Institutes of Health Research, Early Researcher Award, Ministry of Economic Development and Innovation of Ontario, Ontario Brain Institute, Sunnybrook AFP Innovation Fund, Alzheimer's Drug Discovery Foundation (ADDF), Brain Canada, Heart and Stroke Foundation Centre for Stroke Recovery, Weston Brain Institute, Roche, Washington University, Axovant, Novartis, Alector, and royalties from Henry Stewart Talks, outside the submitted work. SB reports grants and personal fees from Eli Lilly, Novartis, Biogen Idec, and Roche, and grants from GE Healthcare, Genentech, and Optina, outside the submitted work. EDH reports grants from NIH / NINDS grant NS076837, outside the submitted work. RV reports grants from Mady Browaeys Fund for Research into Frontotemporal Dementia, during the conduct of the study. PVD reports membership of advisory board for Pfizer, Cytokinetics, and Alexion Pharmaceuticals, outside the submitted work. EJR reports

grants from NIH, during the conduct of the study. SW reports grants from NIH, during the conduct of the study; and consulting fees from Bracket Global, outside the submitted work. CUO reports grants from National Institutes of Health, and support for research from the Jane Tanger Black Scholarship, the Nancy H. Hall Memorial Fund, and the Joseph Trovato Fund, during the conduct of the study; and reports a grant from Biogen Inc. outside the submitted work. ASLN reports grants from National Medical Research Council Singapore, during the conduct of the study. EF reports grants from CIHR, during the conduct of the study. JDR reports grants from MRC Clinician Scientist (MR/M008525/1), NIHR Rare Diseases Translational Research Collaboration (BRC149/NS/MH), the Bluefield Project, the Association for Frontotemporal Degeneration, MRC (MR/M023664/1) GENFI study, during the conduct of the study; and Medical Advisory Boards for Ionis, Alector, and Prevail, outside the submitted work. DTJ reports grants from NIH, during the conduct of the study. KD-R reports grants from National Institutes of Health, during the conduct of the study; grants and personal fees from Biogen, grants from Avid Radiopharmaceuticals, outside the submitted work. ELvdE reports grants from Deltaplan Dementie (The Netherlands Organisation for Health Research and Development, and Alzheimer Nederland), grant numbers 733050103 and 733050813, and The Bluefield Project to Cure Frontotemporal Dementia, during the conduct of the study. BM reports grants from National Institute of Health/National Institute of Aging grants: P30AG062422, P01AG019724,T32 AG023481, University of California Berkeley Subcontract (Miller): 2R56AG041762-06A1, UCSF/Quest Diagnostics Dementia Pathway Collaboration Research Grant, Cornell University Subcontract (Grinberg):1U54NS100717-01, during the conduct of the study. BL reports personal fees from AOP Orphan Pharmaceuticals, affiris, Hoffmann-La Roche, Teva, Ionis Pharma and Lundbeck; and grants from CHDI Foundation, European Commission, and Deutsche Forschungsgemeinschaft; and non-financial support from Wave Life, and NeuraMetrix, outside the submitted work. MFr reports the patents: International Patent Application No. PCT/CA2009/000346 and Israeli Patent Application No.208134 pending. ERob reports grants from NIH, during the conduct of the study; personal fees from Novartis, Biogen, AVROBIO, AGTC, and grants from Alector, outside the submitted work. GC reports grants from NIH, during the conduct of the study; personal fees from Regeneron Pharmaceuticals, and grants from NIH, Tau Consortium, French Foundation, Takeda Pharmaceuticals, outside the submitted work. LM, VMVD, SM, MBo, LKF, RR, ZKW, LCJ, EGPD, JMP, JSS, JS, MJ, SPB, ILB, AC, PCa, MP, LB, GB, DL, SK, MFa, HT, BB, ABe, AP, PSe, HR, JBT, MS, CW, PSu, JRH, JK, ALl, SB-E, IS, MRA, MT-P, MBar, BI, JL, AD, TEC, AdM, CM, PCo, GLa, SS, BN, RL, M-PLT, AGe, SD, SP, ABro, RGu, JB, CH, RC, IOCW, RSh, JG-R, CMD, RSa, MIL, MBak, JAF, RGa, JMP, JLP, LDK, HS, AR, GF, AM, SF, H-HC, AAl, AAr, CFen, HH, AK, JF, MJL, BS, DD, CFerre, AGa, MdA, MT, MZ, CBF, ESe, ALu, AEV, GM, AV, SA, MCT, ERog, CFerra, IP, VB, GLo, FS-O, M-CD, RB, MV, JVdS, MMM, EB, CKo, JP, CKr, LS, CS, EMDSR, and DGe declare no competing interests.

Acknowledgments

We particularly extend our appreciation to the members of these kindreds who have been active participants in familial FTLD research for over three decades.

References

1. Warren JD, Rohrer JD, Rossor MN. Clinical review. Frontotemporal dementia. BMJ. 2013 Aug 6;347:f4827.
2. Harris JM, Gall C, Thompson JC, Richardson AM, Neary D, du Plessis D, Pal P, Mann DM, Snowden JS, Jones M. Classification and pathology of primary progressive aphasia. Neurology. 2013 Nov 19;81(21):1832-9.
3. Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, Isaacs AM, Authier A, Ferrari R, Fox NC, Mackenzie IR, Warren JD, de Silva R, Holton J, Revesz T, Hardy J, Mead S, Rossor MN. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009 Nov 3;73(18):1451-6.
4. Barbier M, Camuzat A, Houot M, Clot F, Caroppo P, Fournier C, Rinaldi D, Pasquier F, Hannequin D, Pariente J, Larcher K; French Clinical and Genetic Research Network on FTD/FTD-ALS*; Predict-PGRN & PrevDemAls Study Groups†, Brice A, Génin E, Sabbagh A, Le Ber I. Factors influencing the age at onset in familial frontotemporal lobar dementia: Important weight of genetics. Neurol Genet. 2017 Dec 13;3(6):e203.
5. Cosseddu M, Benussi A, Gazzina S, Turrone R, Archetti S, Bonomi E, Biasiotto G, Zanella I, Ferrari R, Cotelli MS, Alberici A, Padovani A, Borroni B. Mendelian forms of disease and age at onset affect survival in frontotemporal dementia. Amyotroph Lateral Scler Frontotemporal Degener. 2018 Feb;19(1-2):87-92.
6. Ferrari R, Grassi M, Graziano F, Palluzzi F, Archetti S, Bonomi E, Bruni AC, Maletta RG, Bernardi L, Cupidi C, Colao R, Rainero I, Rubino E, Pinessi L, Galimberti D, Scarpini E, Serpente M, Nacmias B, Piaceri I, Bagnoli S, Rossi G, Giaccone G, Tagliavini F, Benussi L, Binetti G, Ghidoni R, Singleton A, Hardy J, Momeni P, Padovani A, Borroni B. Effects of Multiple Genetic Loci on Age at Onset in Frontotemporal Dementia. J Alzheimers Dis. 2017;56(4):1271-1278.
7. Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, van Minkelen R, Rombouts SA, Cardoso MJ, Clegg S, Espak M, Mead S, Thomas DL, De Vita E, Masellis M, Black SE, Freedman

M, Keren R, MacIntosh BJ, Rogaeva E, Tang-Wai D, Tartaglia MC, Laforce R Jr, Tagliavini F, Tiraboschi P, Redaelli V, Prioni S, Grisoli M, Borroni B, Padovani A, Galimberti D, Scarpini E, Arighi A, Fumagalli G, Rowe JB, Coyle-Gilchrist I, Graff C, Fallström M, Jelic V, Ståhlbom AK, Andersson C, Thonberg H, Lilius L, Frisoni GB, Pievani M, Bocchetta M, Benussi L, Ghidoni R, Finger E, Sorbi S, Nacmias B, Lombardi G, Polito C, Warren JD, Ourselin S, Fox NC, Rossor MN, Binetti G. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. Lancet Neurol. 2015 Mar;14(3):253-62. doi: 10.1016/S1474-4422(14)70324-2.

8. Gass J, Cannon A, Mackenzie IR, Boeve B, Baker M, Adamson J, Crook R, Melquist S, Kuntz K, Petersen R, Josephs K, Pickering-Brown SM, Graff-Radford N, Uitti R, Dickson D, Wszolek Z, Gonzalez J, Beach TG, Bigio E, Johnson N, Weintraub S, Mesulam M, White CL 3rd, Woodruff B, Caselli R, Hsiung GY, Feldman H, Knopman D, Hutton M, Rademakers R. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. Hum Mol Genet. 2006; 15(20):2988-3001.
9. Murphy NA, Arthur KC, Tienari PJ, Houlden H, Chiò A, Traynor BJ. Age-related penetrance of the C9orf72 repeat expansion. Sci Rep. 2017; 7(1):2116.
10. van Herpen E, Rosso SM, Serverijnen LA, Yoshida H, Breedveld G, van de Graaf R, Kamphorst W, Ravid R, Willemsen R, Dooijes D, Majoor-Krakauer D, Kros JM, Crowther RA, Goedert M, Heutink P, van Swieten JC. Variable phenotypic expression and extensive tau pathology in two families with the novel tau mutation L315R. Ann Neurol. 2003 Nov;54(5):573-81.
11. Anfossi M, Bernardi L, Gallo M, Geracitano S, Colao R, Puccio G, Curcio SA, Frangipane F, Mirabelli M, Tomaino C, Smirne N, Maletta R, Bruni AC. MAPT V363I variation in a sporadic case of frontotemporal dementia: variable penetrant mutation or rare polymorphism? Alzheimer Dis Assoc Disord. 2011 Jan-Mar;25(1):96-9.

12. Munoz DG, Ros R, Fatas M, Bermejo F, de Yebenes JG. Progressive nonfluent aphasia associated with a new mutation V363I in tau gene. Am J Alzheimers Dis Other Demen. 2007 Aug-Sep;22(4):294-9.
13. Rossi G, Marelli C, Farina L, Laurà M, Maria Basile A, Ciano C, Tagliavini F, Pareyson D. The G389R mutation in the MAPT gene presenting as sporadic corticobasal syndrome. Mov Disord. 2008 Apr 30;23(6):892-5.
14. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boeve B, Feldman H, Hutton M. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature. 2006 Aug 24;442(7105):916-9.
15. Cruts M, Gijselinck I, van der Zee J, Engelborghs S, Wils H, Pirici D, Rademakers R, Vandenberghe R, Dermaut B, Martin JJ, van Duijn C, Peeters K, Sciot R, Santens P, De Pooter T, Mattheijssens M, Van den Broeck M, Cuijt I, Vennekens K, De Deyn PP, Kumar-Singh S, Van Broeckhoven C. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature. 2006 Aug 24;442(7105):920-4.
16. Ygland E, van Westen D, Englund E, Rademakers R, Wszolek ZK, Nilsson K, Nilsson C, Landqvist Waldö M, Alafuzoff I, Hansson O, Gustafson L, Puschmann A. Slowly progressive dementia caused by MAPT R406W mutations: longitudinal report on a new kindred and systematic review. Alzheimers Res Ther. 2018 Jan 9;10(1):2.
17. Van Mossevelde S, van der Zee J, Gijselinck I, Sleegers K, De Bleecker J, Sieben A, Vandenberghe R, Van Langenhove T, Baets J, Deryck O, Santens P, Ivanoiu A, Willems C, Bäumer V, Van den Broeck M, Peeters K, Mattheijssens M, De Jonghe P, Cras P, Martin JJ, Cruts M, De Deyn PP, Engelborghs S, Van Broeckhoven C; Belgian Neurology (BELNEU) Consortium. Clinical Evidence of Disease Anticipation in Families Segregating a C9orf72 Repeat Expansion. JAMA Neurol. 2017 Apr 1;74(4):445-452.

18. van Blitterswijk M, DeJesus-Hernandez M, Niemantsverdriet E, Murray ME, Heckman MG, Diehl NN, Brown PH, Baker MC, Finch NA, Bauer PO, Serrano G, Beach TG, Josephs KA, Knopman DS, Petersen RC, Boeve BF, Graff-Radford NR, Boylan KB, Petrucelli L, Dickson DW, Rademakers R. Association between repeat sizes and clinical and pathological characteristics in carriers of C9ORF72repeat expansions (Xpansize-72): a cross-sectional cohort study. Lancet Neurol. 2013 Oct;12(10):978-88.

19. Nordin A, Akimoto C, Wuolikainen A, Alstermark H, Jonsson P, Birve A, Marklund SL, Graffmo KS, Forsberg K, Brännström T, Andersen PM. Extensive size variability of the GGGGCC expansion in C9orf72 in both neuronal and non-neuronal tissues in 18 patients with ALS or FTD.Hum Mol Genet. 2015 Jun 1;24(11):3133-42

20. Fournier C, Barbier M, Camuzat A, Anquetil V, Lattante S, Clot F, Cazeneuve C, Rinaldi D, Couratier P, Deramecourt V, Sabatelli M, Belliard S, Vercelletto M, Forlani S, Jornea L; French Clinical and Genetic Research Network on FTLD/FTLD-ALS; PREVDEMALS and FTLD-Exome Study Groups, Leguern E, Brice A, Le Ber I. Relations between C9orf72 expansion size in blood, age at onset, age at collection and transmission across generations in patients and presymptomatic carriers. Neurobiol Aging. 2019 Feb;74:234.e1-234.e8.

21. Gijselinck I, Van Mossevelde S, van der Zee J, Sieben A, Engelborghs S, De Bleecker J, Ivanoiu A, Deryck O, Edbauer D, Zhang M, Heeman B, Bäumer V, Van den Broeck M, Mattheijssens M, Peeters K, Rogaeva E, De Jonghe P, Cras P, Martin JJ, de Deyn PP, Cruts M, Van Broeckhoven C. The C9orf72 repeat size correlates with onset age of disease, DNA methylation and transcriptional downregulation of the promoter. Mol Psychiatry. 2016 Aug;21(8):1112-24.

22. Irwin DJ, McMillan CT, Brettschneider J, Libon DJ, Powers J, Rascovsky K, Toledo JB, Boller A, Bekisz J, Chandrasekaran K, Wood EM, Shaw LM, Woo JH, Cook PA, Wolk DA, Arnold SE, Van Deerlin VM, McCluskey LF, Elman L, Lee VM, Trojanowski JQ, Grossman M. Cognitive decline and reduced survival in C9orf72 expansion frontotemporal degeneration and amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2013 Feb;84(2):163-9.

23. Ryman DC, Acosta-Baena N, Aisen PS, Bird T, Danek A, Fox NC, Goate A, Frommelt P, Ghetti B, Langbaum JB, Lopera F, Martins R, Masters CL, Mayeux RP, McDade E, Moreno S, Reiman EM, Ringman JM, Salloway S, Schofield PR, Sperling R, Tariot PN, Xiong C, Morris JC, Bateman RJ; Dominantly Inherited Alzheimer Network. Symptom onset in autosomal dominant Alzheimer disease: a systematic review and meta-analysis. Neurology. 2014 Jul 15;83(3):253-60.

24. Koriath C, Lashley T, Taylor W, Druyeh R, Dimitriadis, A, Denning N, Williams J, Warren JD, Fox NC, Schott JM, Rowe JB, Collinge J, Rohrer JD, Mead S. ApoE4 lowers age at onset in patients with frontotemporal dementia and tauopathy independent of amyloid-β copathology. Alzheimers Dement (Amst). 2019;11:277-280.

25. Kelley BJ, Haidar W, Boeve BF, Baker M, Graff-Radford NR, Krefft T, Frank AR, Jack CR Jr, Shiung M, Knopman DS, Josephs KA, Parashos SA, Rademakers R, Hutton M, Pickering-Brown S, Adamson J, Kuntz KM, Dickson DW, Parisi JE, Smith GE, Ivnik RJ, Petersen RC. Prominent phenotypic variability associated with mutations in Progranulin. Neurobiol Aging. 2009 May;30(5):739-51.

26. Beck J, Rohrer JD, Campbell T, Isaacs A, Morrison KE, Goodall EF, Warrington EK, Stevens J, Revesz T, Holton J, Al-Sarraj S, King A, Scahill R, Warren JD, Fox NC, Rossor MN, Collinge J, Mead S. A distinct clinical, neuropsychological and radiological phenotype is associated with progranulin gene mutations in a large UK series. Brain. 2008 Mar;131(Pt 3):706-20.

27. Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet-Lecrux A, Hahn-Barma V, van der Zee J, Clot F, Bakchine S, Puel M, Ghanim M, Lacomblez L, Mikol J, Deramecourt V, Lejeune P, de la Sayette V, Belliard S, Vercelletto M, Meyrignac C, Van Broeckhoven C, Lambert JC, Verpillat P, Campion D, Habert MO, Dubois B, Brice A; French research network on FTD/FTD-MND. Phenotype variability in progranulin mutation carriers: a clinical, neuropsychological, imaging and genetic study. Brain. 2008 Mar;131(Pt 3):732-46.

28. Nicholson AM, Rademakers R. What we know about TMEM106B in neurodegeneration. Acta Neuropathol. 2016; 132(5):639-651.

29. Pottier C, Zhou X, Perkerson RB 3rd, Baker M, Jenkins GD, Serie DJ, Ghidoni R, Benussi L, Binetti G, López de Munain A, Zulaica M, Moreno F, Le Ber I, Pasquier F, Hannequin D, Sánchez-Valle R, Antonell A, Lladó A, Parsons TM, Finch NA, Finger EC, Lippa CF, Huey ED, Neumann M, Heutink P, Synofzik M, Wilke C, Rissman RA, Slawek J, Sitek E, Johannsen P, Nielsen JE, Ren Y, van Blitterswijk M, DeJesus-Hernandez M, Christopher E, Murray ME, Bieniek KF, Evers BM, Ferrari C, Rollinson S, Richardson A, Scarpini E, Fumagalli GG, Padovani A, Hardy J, Momeni P, Ferrari R, Frangipane F, Maletta R, Anfossi M, Gallo M, Petrucelli L, Suh E, Lopez OL, Wong TH, van Rooij JGJ, Seelaar H, Mead S, Caselli RJ, Reiman EM, Noel Sabbagh M, Kjolby M, Nykjaer A, Karydas AM, Boxer AL, Grinberg LT, Grafman J, Spina S, Oblak A, Mesulam MM, Weintraub S, Geula C, Hodges JR, Piguet O, Brooks WS, Irwin DJ, Trojanowski JQ, Lee EB, Josephs KA, Parisi JE, Ertekin-Taner N, Knopman DS, Nacmias B, Piaceri I, Bagnoli S, Sorbi S, Gearing M, Glass J, Beach TG, Black SE, Masellis M, Rogaeva E, Vonsattel JP, Honig LS, Kofler J, Bruni AC, Snowden J, Mann D, Pickering-Brown S, Diehl-Schmid J, Winkelmann J, Galimberti D, Graff C, Öijerstedt L, Troakes C, Al-Sarraj S, Cruchaga C, Cairns NJ, Rohrer JD, Halliday GM, Kwok JB, van Swieten JC, White CL 3rd, Ghetti B, Murell JR, Mackenzie IRA, Hsiung GR, Borroni B, Rossi G, Tagliavini F, Wszolek ZK, Petersen RC, Bigio EH, Grossman M, Van Deerlin VM, Seeley WW, Miller BL, Graff-Radford NR, Boeve BF, Dickson DW, Biernacka JM, Rademakers R. Potential genetic modifiers of disease risk and age at onset in patients with frontotemporal lobar degeneration and GRN mutations: a genome-wide association study. Lancet Neurol. 2018; 17(6):548-558.

30. Moreno F, Alzualde A, Camblor PM, Barandiaran M, Van Deerlin VM, Gabilondo A, Martí Massó JF, López de Munain A, Indakoetxea B. Prion protein codon 129 polymorphism modifies age at onset of frontotemporal dementia with the C.709-1G>A progranulin mutation. Alzheimer Dis Assoc Disord. 2011 Jan-Mar;25(1):93-5.

31. Bossù P, Salani F, Alberici A, Archetti S, Bellelli G, Galimberti D, Scarpini E, Spalletta G, Caltagirone C, Padovani A, Borroni B. Loss of function mutations in the progranulin gene are related to pro-

inflammatory cytokine dysregulation in frontotemporal lobar degeneration patients. J Neuroinflammation. 2011 Jun 6;8:65.

32. Martens LH, Zhang J, Barmada SJ, Zhou P, Kamiya S, Sun B, Min SW, Gan L, Finkbeiner S, Huang EJ, Farese RV Jr. Progranulin deficiency promotes neuroinflammation and neuron loss following toxin-induced injury. J Clin Invest. 2012 Nov;122(11):3955-9.
33. Miller ZA, Rankin KP, Graff-Radford NR, Takada LT, Sturm VE, Cleveland CM, Criswell LA, Jaeger PA, Stan T, Heggeli KA, Hsu SC, Karydas A, Khan BK, Grinberg LT, Gorno-Tempini ML, Boxer AL, Rosen HJ, Kramer JH, Coppola G, Geschwind DH, Rademakers R, Seeley WW, Wyss-Coray T, Miller BL. TDP-43 frontotemporal lobar degeneration and autoimmune disease. J Neurol Neurosurg Psychiatry. 2013 Sep;84(9):956-62
34. Menzel L, Kleber L, Friedrich C, Hummel R, Dangel L, Winter J, Schmitz K, Tegeder I, Schäfer MK. Progranulin protects against exaggerated axonal injury and astrogliosis following traumatic brain injury. Glia. 2017 Feb;65(2):278-292.
35. Russ J, Liu EY, Wu K, Neal D, Suh E, Irwin DJ, McMillan CT, Harms MB, Cairns NJ, Wood EM, Xie SX, Elman L, McCluskey L, Grossman M, Van Deerlin VM, Lee EB. Hypermethylation of repeat expanded C9orf72 is a clinical and molecular disease modifier. Acta Neuropathol. 2015 Jan;129(1):39-52.
36. Zhang M, Tartaglia MC, Moreno D, Sato C, McKeever P, Weichert A, Keith J, Robertson J, Zinman L, Rogaeva E. DNA methylation age-acceleration is associated with disease duration and age at onset in C9orf72patients. Acta Neuropathol. 2017 Aug;134(2):271-279.
37. Zhang M, Ferrari R, Tartaglia MC, Keith J, Surace EI, Wolf U, Sato C, Grinberg M, Liang Y, Xi Z, Dupont K, McGoldrick P, Weichert A, McKeever PM, Schneider R, McCorkindale MD, Manzoni C, Rademakers R, Graff-Radford NR, Dickson DW, Parisi JE, Boeve BF, Petersen RC, Miller BL, Seeley WW, van Swieten JC, van Rooij J, Pijnenburg Y, van der Zee J, Van Broeckhoven C, Le Ber I, Van Deerlin V, Suh E, Rohrer JD, Mead S, Graff C, Oijerstedt L, Pickering-Brown S, Rollinson S, Rossi G, Tagliavini F, Brooks WS, Dobson-Stone C, Halliday GM, Hodges JR, Piguet O, Binetti G, Benussi

L, Ghidoni R, Nacmias B, Sorbi S, Bruni AC, Galimberti D, Scarpini E, Rainero I, Rubino E, Clarimon J, Lleo A, Ruiz A, Hernandez I, Pastor P, Diez-Fairen M, Borroni B, Pasquier F, Deramecourt V, Lebouvier T, Perneczky R, Diehl-Schmid J, Grafman J, Huey ED, Mayeux R, Nalls MA, Hernandez D, Singleton A, Momeni P, Zeng Z, Hardy J, Robertson J, Zinman L, Rogaeva E, International FTDGC A C6orf10/LOC101929163 locus is associated with age of onset in C9orf72 carriers. Brain 2018;141:2895-2907.

Table 1. Patient demographics and mean age at onset, age at death and disease duration in each of the mutation groups. For gender differences, p values from a chi-squared test are shown. For age at onset, age at death and disease duration the last column shows the adjusted mean difference (natural log values for disease duration), 95% confidence interval in parentheses, and p-value when groups are compared with mixed effects models.

	GRN	***MAPT***	***C9orf72***	
N	1179	791	1433	
Sex (male, N [%])	490 [42%]	386 [49%]	742 [52%]	*MAPT vs GRN, 0.002* *C9orf72 vs GRN, <0.001* *C9orf72 vs MAPT, 0.178*
Number of families	483	254	755	
Age at onset (years)				
N	967	609	1076	*MAPT vs GRN -11.8 (-13.0, -10.6), <0.001*
Mean (SD)	61.3 (8.8)	49.5 (10.0)	58.2 (9.8)	*C9orf72 vs GRN -2.8 (-3.8, -1.9), <0.001*
Range (min-max)	25-90	17-82	20-91	*C9orf72 vs MAPT 9.0 (7.8, 10.1), <0.001*
Age at death (years)				
N	656	485	839	*MAPT vs GRN -10.7 (-12.3, -9.1), <0.001*
Mean (SD)	68.8 (9.7)	58.5 (11.3)	65.3 (10.9)	*C9orf72 vs GRN -3.5 (-4.9, -2.2), <0.001*
Range (min-max)	42-98	24-93	26-97	*C9orf72 vs MAPT 7.2 (5.7, 8.6), <0.001*
Disease duration (years)				
N	548	394	618	*MAPT vs GRN 0.18 (0.08, 0.29), 0.001*
Mean (SD)	7.1 (3.9)	9.3 (6.4)	6.4 (4.9)	*C9orf72 vs GRN -0.26 (-0.35, -0.17), <0.001*
Range (min-max)	0-27	0-45	0-36	*C9orf72 vs MAPT -0.44 (-0.54, -0.34), <0.001*

Table 2. Primary clinical diagnosis for each mutation group. Diagnoses within the frontotemporal dementia (FTD) spectrum include behavioural variant FTD (bvFTD), the primary progressive aphasia (PPA) subtypes [nfv = nonfluent variant, sv = semantic variant, lv = logopenic variant, PPA-NOS = PPA not otherwise specified i.e. does not meet criteria for a specific subtype], FTD with amyotrophic lateral sclerosis (ALS), ALS, corticobasal syndrome (CBS) and progressive supranuclear palsy – Richardson's syndrome (PSP). Diagnoses outside the FTD spectrum include Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), VaD (vascular dementia) and a dementia diagnosis not otherwise specific (Dementia-NOS).

	GRN	***MAPT***	***C9orf72***
Diagnoses within the FTD spectrum			
bvFTD	446 (38%)	354 (45%)	450 (31%)
nfvPPA	107 (9%)	14 (2%)	26 (2%)
svPPA	13 (1%)	14 (2%)	13 (1%)
lvPPA	4 (<1%)	0 (<1%)	3 (<1%)
PPA-NOS	36 (3%)	2 (<1%)	4 (<1%)
FTD-ALS	7 (1%)	2 (<1%)	157 (11%)
ALS	7 (1%)	1 (<1%)	276 (19%)
CBS	47 (4%)	14 (2%)	2 (<1%)
PSP	0 (0%)	33 (4%)	1 (<1%)
Diagnoses outside of the FTD spectrum			
AD	97 (8%)	24 (3%)	84 (6%)
HD	0 (0%)	1 (<1%)	4 (<1%)
PD	16 (1%)	39 (5%)	15 (1%)
DLB	4 (<1%)	1 (<1%)	5 (<1%)
VaD	9 (1%)	1 (<1%)	7 (<1%)
Dementia-NOS	361 (31%)	274 (35%)	362 (25%)
Other	25 (2%)	17 (2%)	24 (2%)

Figure legends:

Figure 1. Map showing countries with data included in the study (shown in dark turquoise). Individual centres are represented by a red dot on the map. Pie charts show relative frequency of each of the three genetic groups within a geographical area (yellow, *C9orf72*, pink *GRN*, blue *MAPT*); the number in the centre of the pie chart represents the number of cases included within that area.

Figure 2. Violin plots of median and interquartile range of ages at onset (AAO) and death (AAD) for each of the three genetic groups.

Figure 3. Cumulative probability of symptom onset in a) each individual genetic group, and in the common b) *GRN* and c) *MAPT* mutations. Note that data includes only cases who have become symptomatic and does not account for non-symptomatic family members.

Figure 4. Correlation of individual ages at onset with A) parental age at onset and B) mean familial age at onset for *GRN*, *MAPT*, and *C9orf72* genetic groups. Pearson's correlation coefficient is shown on each graph.