Author/s:
Valentino, RR;Scotton, WJ;Roemer, SF;Lashley, T;Heckman, MG;Shoai, M;Martinez-Carrasco, A;Tamvaka, N;Walton, RL;Baker, MC;Macpherson, HL;Real, R;Soto-Beasley, AI;Mok, K;Revesz, T;Christopher, EA;DeTure, M;Seeley, WW;Lee, EB;Frosch, MP;Molina-Porcel, L;Gefen, T;Redding-Ochoa, J;Ghetti, B;Robinson, AC;Kobylecki, C;Rowe, JB;Beach, TG;Teich, AF;Keith, JL;Bodi, I;Halliday, GM;Gearing, M;Arzberger, T;Morris, CM;White, CL;Mechawar, N;Boluda, S;MacKenzie, IR;McLean, C;Cykowski, MD;Wang, SHJ;Graff, C;Nagra, RM;Kovacs, GG;Giaccone, G;Neumann, M;Ang, LC;Carvalho, A;Morris, HR;Rademakers, R;Hardy, JA;Dickson, DW;Rohrer, JD;Ross, OA;Warner, TT;Jaunmuktane, Z;Boeve, BF;Duara, R;Graff-Radford, NR;Josephs, KA;Knopman, DS;Koga, S;Murray, ME;Lyons, KE;Pahwa, R;Petersen, RC;Whitwell, JL;Grinberg, LT;Miller, B;Schlereth, A;Spina, S;Grossman, M;Irwin, DJ;Suh, ER;Trojanowski, JQ;Van Deerlin, VM;Wolk, DA;Connors, TR;Dooley, PM;Oakley, DH;Aldecoa, I;Balasa, M;Gelpi, E;Borrego-Écija, S;Gascon-Bayarri, J;Sánchez-Valle, R;Sanz-Cartagena, P;Piñol-Ripoll, G;Bigio, EH;Flanagan, ME;Rogalski, EJ;Weintraub, S;Schneider, JA;Peng, L;Zhu, X;Chang, K;Troncoso, JC;Prokop, S;Newell, KL

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MAPT H2 haplotype and risk of Pick's disease in the Pick's disease International Consortium: a genetic association study

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MAPT H2 haplotype and risk of Pick's disease in the Pick's disease International Consortium: a genetic association study

Rebecca R Valentino, William J Scotton*, Shanu F Roemer, Tammaryn Lashley, Michael G Heckman, Maryam Shoai, Alejandro Martinez-Carrasco, Nicole Tamvaka, Ronald L Walton, Matthew C Baker, Hannah L Macpherson, Raquel Real, Alexandra I Soto-Beasley, Kin Mok, Tamas Revesz, Elizabeth A Christopher, Michael DeTure, William W Seeley, Edward B Lee, Matthew P Frosch, Laura Molina-Porcel, Tamar Gefen, Javier Redding-Ochoa, Bernardino Ghetti, Andrew C Robinson, Christopher Kobylecki, James B Rowe, Thomas G Beach, Andrew F Teich, Julia L Keith, Istvan Bodi, Glenda M Halliday, Marla Gearing, Thomas Arzberger, Christopher M Morris, Charles L White 3rd, Naguib Mechawar, Susana Boluda, Ian R MacKenzie, Catriona McLean, Matthew D Cykowski, Shih-Hsiu J Wang, Caroline Graff, Rashed M Nagra, Gabor G Kovacs, Giorgio Giaccone, Manuela Neumann, Lee-Cyn Ang, Agostinho Carvalho, Huw R Morris, Rosa Rademakers, John A Hardy, Dennis W Dickson, Jonathan D Rohrer*, Owen A Ross* on behalf of the Pick's disease International Consortium†*

Summary

Background Pick's disease is a rare and predominantly sporadic form of frontotemporal dementia that is classified as a primary tauopathy. Pick's disease is pathologically defined by the presence in the frontal and temporal lobes of Pick bodies, composed of hyperphosphorylated, three-repeat tau protein, encoded by the *MAPT* gene. *MAPT* has two distinct haplotypes, H1 and H2; the *MAPT* H1 haplotype is the major genetic risk factor for four-repeat tauopathies (eg, progressive supranuclear palsy and corticobasal degeneration), and the *MAPT* H2 haplotype is protective for these disorders. The primary aim of this study was to evaluate the association of *MAPT* H2 with Pick's disease risk, age at onset, and disease duration.

Methods In this genetic association study, we used data from the Pick's disease International Consortium, which we established to enable collection of data from individuals with pathologically confirmed Pick's disease worldwide. For this analysis, we collected brain samples from individuals with pathologically confirmed Pick's disease from 35 sites (brainbanks and hospitals) in North America, Europe, and Australia between Jan 1, 2020, and Jan 31, 2023. Neurologically healthy controls were recruited from the Mayo Clinic (FL, USA, or MN, USA between March 1, 1998, and Sept 1, 2019). For the primary analysis, individuals were directly genotyped for the *MAPT* H1-H2 haplotype-defining variant rs8070723. In a secondary analysis, we genotyped and constructed the six-variant-defined (rs1467967-rs242557-rs3785883-rs2471738-rs8070723-rs7521) *MAPT* H1 subhaplotypes. Associations of *MAPT* variants and *MAPT* haplotypes with Pick's disease risk, age at onset, and disease duration were examined using logistic and linear regression models; odds ratios (ORs) and β coefficients were estimated and correspond to each additional minor allele or each additional copy of the given haplotype.

Findings We obtained brain samples from 338 people with pathologically confirmed Pick's disease (205 [61%] male and 133 [39%] female; 338 [100%] White) and 1312 neurologically healthy controls (611 [47%] male and 701 [53%] female; 1312 [100%] White).The *MAPT* H2 haplotype was associated with increased risk of Pick's disease compared with the H1 haplotype (OR 1·35 [95% CI 1·12 to 1·64], p=0·0021). *MAPT* H2 was not associated with age at onset (β –0·54 [95% CI –1·94 to 0·87], p=0·45) or disease duration (β 0·05 [–0·06 to 0·16], p=0·35). Although not significant after correcting for multiple testing, associations were observed at p less than 0·05: with risk of Pick's disease for the H1f subhaplotype (OR 0·11 [0·01 to 0·99], p=0·049); with age at onset for H1b (β 2·66 [0·63 to 4·70], p=0·011), H1i (β –3·66 [–6·83 to –0·48], p=0·025), and H1u (β –5·25 [–10·42 to –0·07], p=0·048); and with disease duration for H1x (β –0·57 [–1·07 to –0·07], p=0·026).

Interpretation The Pick's disease International Consortium provides an opportunity to do large studies to enhance our understanding of the pathobiology of Pick's disease. This study shows that, in contrast to the decreased risk of four-repeat tauopathies, the *MAPT* H2 haplotype is associated with an increased risk of Pick's disease in people of European ancestry. This finding could inform development of isoform-related therapeutics for tauopathies.

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*Joint authorship

†Members listed at the end of the Article and in the appendix (pp 8–9)

Department of Neuroscience (R R Valentino PhD, S F Roemer MD, N Tamvaka BSc, R L Walton BSc, M C Baker BSc, A I Soto-Beasley MSc, E A Christopher MBA, M DeTure PhD, Prof R Rademakers PhD, Prof D W Dickson MD, Prof O A Ross PhD), **Division of Clinical Trials and Biostatistics** (M G Heckman MSc), **and Department of Clinical Genomics** (Prof O A Ross), **Mayo Clinic, Jacksonville, FL, USA; Dementia Research Centre, Department of Neurodegenerative Disease, University College London, Queen Square Institute of Neurology, London, UK** (W J Scotton PhD MRCP, Prof J D Rohrer PhD FRCP); **Queen Square Brain Bank for Neurological Disorders** (Prof T Lashley PhD, Prof T Revesz PhD FRCPath), **Department of Neurodegenerative Disease** (Prof T Lashley, M Shoai PhD, H L Macpherson MSc, K Mok PhD FRCP, Prof T Revesz, Prof J A Hardy PhD), **Department of Clinical and Movement Neurosciences** (A Martinez-Carrasco MSc, R Real PhD, Prof H R Morris PhD FRCP), **and Reta Lila Weston Institute** (Prof J A Hardy), **University College London, Queen Square Institute of Neurology**

London, UK; UK Dementia Research Institute at UCL, London, UK (K Mok, Prof J A Hardy); Division of Life Science, State Key Laboratory of Molecular Neuroscience, Molecular Neuroscience Center, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China (K Mok); Hong Kong Center for Neurodegenerative Diseases, Hong Kong Science Park, Hong Kong, China (K Mok); Department of Neurology, Memory and Aging Center, University of California San Francisco, San Francisco, CA, USA (Prof W W Seeley MD); Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA (Prof E B Lee MD PhD); Neuropathology Service, C S Kubik Laboratory for Neuropathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA (Prof M P Frosch MD PhD); Neurological Tissue Bank, Biobanc-Hospital Clínic-Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain (L Molina-Porcel MD PhD); Alzheimer's Disease and other Cognitive Disorders Unit, Neurology Department, Hospital Clinic, Barcelona, Spain (L Molina-Porcel); Barcelona Clinical Research Foundation-August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain (L Molina-Porcel); Mesulam Center for Cognitive Neurology and Alzheimer's Disease (T Gefen PhD) and Department of Psychiatry and Behavioral Sciences (T Gefen) Northwestern University Feinberg School of Medicine, Chicago, IL, USA; Johns Hopkins School of Medicine, Baltimore, MD, USA (J Redding-Ochoa MD); Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA (Prof B Ghetti MD); Division of Neuroscience, Faculty of Biology, Medicine and Health, School of Biological Sciences, The University of Manchester, Salford Royal Hospital, Salford, UK (A C Robinson PhD);

Research in context

Evidence before this study

We searched PubMed between Jan 1, 1980, and April 1, 2023, using the terms ((Pick's disease) or (Pick disease)) and ((genetic*) or (genome wide association study) or (GWAS)), for original research articles written in English. We assessed the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach. Pick's disease is recognised as a rare frontotemporal dementia that presents with heterogenous clinical features, and no therapies are available. Given the rarity of Pick's disease, few genetic studies have been done and an association with *MAPT* H1 (observed for other primary tauopathies) or H2 haplotypes was unclear.

Added value of this study

Understanding the genetic cause of the susceptibility and progression of Pick's disease is crucial to identify potential therapeutic intervention strategies. The current study is the first from the Pick's disease International Consortium, identifying 338 individuals with pathologically defined Pick's disease across 35 brain banks. With this unique cohort, we were able to identify a disease risk association with the *MAPT* H2 haplotype, which has been nominated as protective in primary four-repeat tauopathies.

Implications of all the available evidence

The establishment of the Pick's disease International Consortium opens opportunities to gain further insight into the underlying causes and pathogenesis of Pick's disease, potentially facilitating future genetics studies and providing a resource for clinicopathological, epigenetic, transcriptomic, and proteomics studies. The association of Pick's disease risk with *MAPT* H2 suggests that the haplotype status might influence the ratio of tau three-repeat and four-repeat isoforms and might inform future therapeutic strategies targeting *MAPT*-tau expression (eg, antisense oligonucleotides or immunotherapy).

Introduction

Pick's disease is a rare and predominantly sporadic subtype of frontotemporal lobar degeneration. Frontotemporal lobar degeneration accounts for approximately 5% of cases in post-mortem analyses of people who had dementia;[1] however, given that a definite diagnosis of Pick's disease requires confirmation in post-mortem brain issue, owing to the heterogeneity of clinical presentation and the absence of a specific in-vivo biomarker, the incidence and prevalence of Pick's disease are currently unknown. Brain bank studies suggest that Pick's disease could account for up to 30% of individuals with frontotemporal lobar degeneration and tau pathology at autopsy, and 10% overall of people who have frontotemporal lobar degeneration.[2] The prevalence of frontotemporal lobar degeneration syndromes has been estimated at 10·2 per 100 000 and the incidence at 1·61 per 100 000 person-years,[3] suggesting that the prevalence of Pick's disease could be around 1 per 100 000 with an incidence of around 0·2 per 100 000 person years.

Although there are no clinical diagnostic criteria for Pick's disease, the mean age of symptom onset is 57·0 years (SD 12·5) and the disease presents with behavioural change, impaired cognition, and occasionally motor difficulties.[4–10] Pick's disease progresses relatively rapidly and patients die approximately 10 years after disease onset.[4–9] Symptomatic treatments are available, but currently no treatments can delay disease onset or progression.

Neuropathologically, Pick's disease is classified macroscopically by severe frontotemporal, knife-edge like cortical atrophy, and microscopically by the presence of ballooned neurons and argyrophilic, tau-immunoreactive inclusion Pick bodies in frontal and temporal regions.[4] Characteristic Pick bodies consist of aggregates of hyperphosphorylated three-repeat tau proteins, which are encoded by the *MAPT* gene on chromosome 17,[1,10] and therefore Pick's disease is classified as a three-repeat tauopathy. *MAPT* encodes six major tau protein isoforms in the adult human brain; these are generated by alternative splicing of exons 2, 3, and 10, which influences the number of repeat domains across the tau protein.[11] Alternative splicing leading to exclusion of exon 10 results in three-repeat units in the microtubule binding C-terminal domain, generating three-repeat tau proteins.[12]

Rare missense and duplication mutations of *MAPT* have been identified in a small number individuals with Pick's disease or with Pick's disease-like pathology;[13–17] however, these data require replication, and independent cohorts of individuals with Pick's disease have not reported common missense *MAPT* mutations.[18] *MAPT* also has two well characterised common haplotypes, H1 and H2, which developed from a 900 kb ancestral genetic inversion event.[19] *MAPT* H1 has consistently been associated with an increased risk of four-repeat primary tauopathies, such as progressive supranuclear palsy and corticobasal degeneration, and this haplotype is the strongest genetic risk factor for both diseases.[20,21] Correspondingly, the other haplotype of *MAPT,* H2, is associated with a decreased risk of these disorders. This observation has not been replicated in Pick's disease, perhaps owing to the rarity of the disease and the consequent small sample sizes in previous studies,[22,23] and thus a targeted analysis is warranted.

Owing to its low prevalence and the inability to diagnose it when the person is alive, Pick's disease is an

understudied neurodegenerative disease, and its genetic cause is unknown. Studies of *MAPT* haplotype in Pick's disease have been few, small, and underpowered. Moreover, the scarcity of samples from affected individuals has stalled advancement in understanding how *MAPT* haplotypes and isoforms influence disease risk and pathology, and has prevented progress in developing isoform-specific therapies. To address the need for larger studies, we established the Pick's disease International Consortium to collect data from individuals with pathologically confirmed Pick's disease worldwide (with current sites in North America, Europe, and Australia), to develop an in-depth consortium database of clinical, pathological, and demographic information. The primary aim of this study was to evaluate the association of the *MAPT* H2 haplotype with disease risk, age at onset, and duration of Pick's disease.

Methods

Study design

Researchers at Mayo Clinic Brain Bank in Jacksonville, FL, USA, and the UK Dementia Research Institute at University College London (UCL) Queen Square Institute of Neurology, London, UK, established the Pick's disease International Consortium. Investigators at the Mayo Clinic led efforts to identify individuals with Pick's disease and obtain their pathological samples from North America, South America, and Asia, and investigators at UCL led efforts to identify individuals with Pick's disease and obtain their pathological samples from Europe and Australia. The criteria for individuals to be included in the Pick's disease International Consortium were a neuropathological diagnosis of Pick's disease and availability of frozen brain tissue. Exclusion criteria were frontotemporal dementia with a cause other than a three-repeat-predominant tauopathy or unavailability of frozen specimens. Institutional Review Board approval was obtained for the study at both collection hubs (Mayo Clinic and UCL), and each individual brain bank had Institutional Review Board approval for collection and sharing of specimens. All individuals with Pick's disease and healthy controls gave written consent locally at their respective recruitment sites for their clinical data, brain or tissue samples, or both, to be used in research projects, including genetic studies.

Study participants

Between Jan 1, 2020, and Jan 31, 2023, frozen brain tissue from cerebellum or prefrontal cortex were obtained for each participant with Pick's disease identified through the Pick's disease International Consortium and sent to one of the two collection hubs. Inclusion criteria for the study were that all individuals were self-reported to be unrelated to other participants in the study, White, non-Hispanic (genetically confirmed by array data in individuals with Pick's disease), and also met the Pick's disease International Consortium operational diagnostic criteria detailed in the Procedures section. Peripheral blood-derived DNA was provided from controls from the Mayo Clinic in Jacksonville, FL, or Rochester, MN. Controls were deemed as neurologically healthy by neurologists at the Mayo Clinic.

Baseline demographic information was collected for all individuals (age at onset [where available] and age at death for individuals with Pick's disease, age at blood collection for controls, and sex). Disease duration was calculated from the difference between age at death and age at onset for the subset of 309 individuals with Pick's disease for whom age at onset was available. In addition to basic demographic information, the Pick's disease International Consortium also collected information related to clinical characteristics (eg, clinical diagnosis, behavioural and language impairments, and presence or

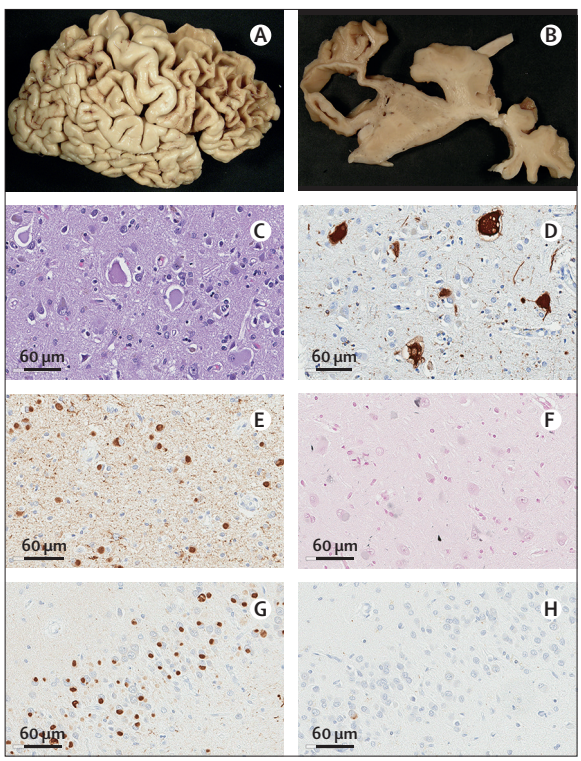


Figure 1: **Pathological assessments of brains from individuals with Pick's disease**
(A) The superior and dorsolateral surfaces of the frontal cortex and temporal lobe often show severe circumscribed knife-edge edge atrophy. (B) Coronal sections of the brain show markedly dilated ventricles, cortical atrophy, and hippocampal affection. (C) Enlarged, amorphous ballooned neurons. (D) In regions with severe astrogliosis and neuronal loss, staining against αβ-crystallin can highlight ballooned neurons. (E) Phosphorylated tau antibodies highlight dense spherical cytoplasmic neuronal inclusions and can also show marked neuropil staining, especially in individuals with concomitant Alzheimer's type pathology. (F) Gallyas silver stains can stain isolated glial lesions or neurofibrillary tangles; however, Pick bodies do not show substantial silver staining. (G) Three-repeat tau staining of the dentate fascia of the hippocampus shows strong immunoreactivity of spherical inclusions. (H) Four-repeat tau staining of the dentate fascia shows negative spherical inclusion; however, isolated neurofibrillary tangles might stain positive. Images are from individuals with Pick's disease submitted to Mayo Clinic.

Geoffrey Jefferson Brain Research Centre, Manchester Academic Health Science Centre, Manchester, UK (A C Robinson PhD); **Department of Neurology, Manchester Centre for Clinical Neurosciences, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK** (C Kobylecki PhD FRCP); **Division of Neuroscience, School of Biological Sciences, University of Manchester, Manchester, UK** (C Kobylecki); **Cambridge University Department of Clinical Neurosciences and Cambridge University Hospitals NHS Trust, Cambridge, UK** (Prof J B Rowe PhD); **Medical Research Council Cognition and Brain Sciences Unit, Cambridge, UK** (Prof J B Rowe); **Civin Laboratory of Neuropathology, Banner Sun Health Research Institute, Sun City, AZ, USA** (Prof T G Beach MD PhD); **Department of Pathology and Cell Biology, Columbia University, New York, NY, USA** (A F Teich MD PhD); **Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, USA** (A F Teich); **Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, and Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada** (J L Keith MD FRCPC); **Clinical Neuropathology Department, King's College Hospital NHS Foundation Trust, London, UK** (I Bodi FRCPath); **London Neurodegenerative Diseases Brain Bank, Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK** (I Bodi); **University of Sydney Brain and Mind Centre and Faculty of Medicine and Health School of Medical Sciences, Camperdown, NSW, Australia** (Prof G M Halliday PhD); **Department of Pathology and Laboratory Medicine** (M Gearing PhD), **Department of Neurology** (M Gearing), **and Goizueta Alzheimer's Disease Center Brain Bank** (M Gearing), **Emory University School of**

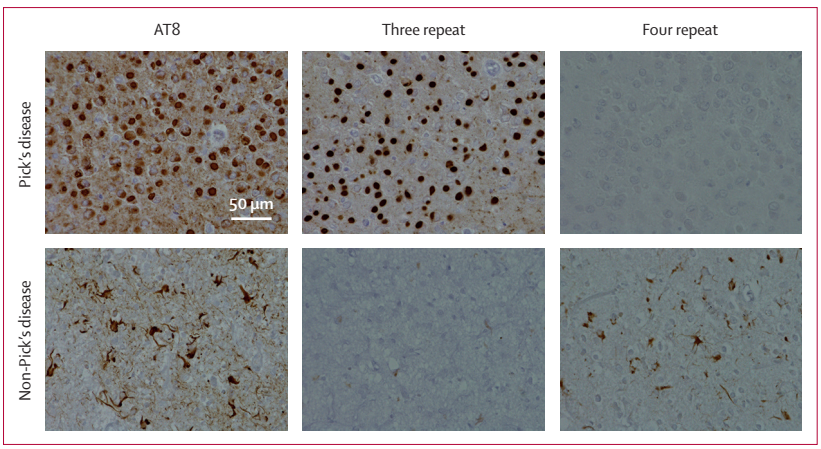


Figure 2: **Differentiation of Pick's disease from non-Pick's disease tauopathy using the Pick's disease International Consortium operational diagnostic criteria**
The top row shows a brain sample from an individual with Pick's disease that met the diagnostic criteria because it was positive for AT8 and three-repeat-tau immunoreactive Pick bodies. The bottom row shows a brain sample from an individual with a four-repeat tauopathy who had an archival diagnosis of Pick's disease; the sample was positive for AT8 and four-repeat-tau but negative for three-repeat tau immunoreactive Pick bodies. Images are from individuals with an archival neuropathological diagnosis of Pick's disease submitted to University College London Queen Square Brain Bank.

Medicine, Atlanta, GA, USA; Department of Psychiatry and Psychotherapy, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany (T Arzberger MD); **Newcastle Brain Tissue Resource, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK** (C M Morris PhD); **University of Texas Southwestern Medical Center, Dallas, TX, USA** (Prof C L White 3rd MD); **Douglas Hospital Research Centre, McGill University, Montreal, QC, Canada** (Prof N Mechawar PhD); **Laboratoire de Neuropathologie Escourolle, Hôpital de la Salpêtrière, Assistance Publique–Hôpitaux de Paris, Paris, France** (S Boluda MD); **Alzheimer Prion Team, L'Institut du Cerveau, Paris, France** (S Boluda); **Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada** (Prof I R MacKenzie MD); **Department of Anatomical Pathology Alfred Heath, Melbourne, VIC, Australia** (Prof C McLean MD PhD); **Victorian Brain Bank, The Florey Institute of Neuroscience of Mental Health, Parkville, VIC, Australia** (Prof C McLean); **Department of Pathology and Genomic**

absence of parkinsonism) and pathological information (eg, Thal phase, Braak stage, and brain weight) for each individual with Pick's disease, as well as noting whether other tissues and brain imaging data were available. Individuals were removed from this study if a rare *MAPT* missense mutation was identified by Sanger exon sequencing (primers are available on request from the corresponding authors).

Procedures

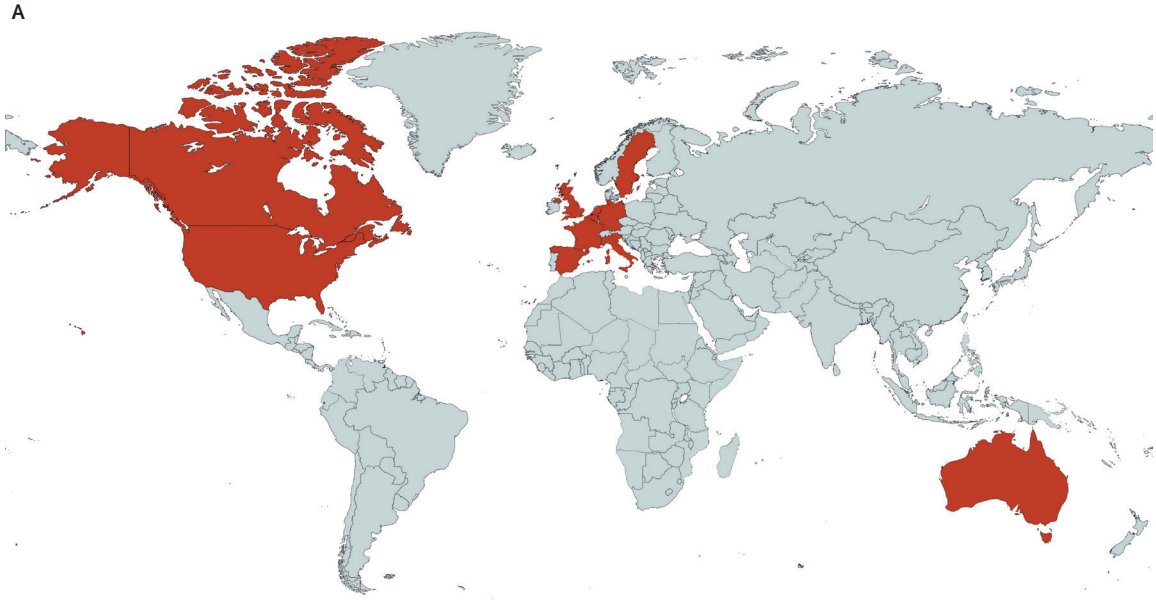
Currently, consensus diagnostic criteria for the neuropathological diagnosis of Pick's disease do not exist. In many diagnostic centres, a neuropathological diagnosis of Pick's disease relies on a characteristic pattern of atrophy and the presence of argyrophilic, spherical neuronal inclusions using traditional silver staining methods, such as Bielschowsky's or Gallyas-Braak silver staining (figure 1). Both methods stain Alzheimer's disease neurofibrillary tangles, yet spherical inclusions in Pick's disease are positive with Bielschowsky and negative with the Gallyas-Braak silver staining.[24] This differentiation is helpful especially for centres that rely on immunohistochemistry against phosphorylated tau and do not have isotype-specific tau antibodies incorporated in diagnostic tests, because Alzheimer's disease and Pick's disease neuropathological changes can coexist in the same patient. Immunohistochemistry against epitope-specific tau antibodies further helps to distinguish between Alzheimer's disease and Pick's disease features. Because both spherical inclusions and neurofibrillary tangles stain positive with antibodies against phosphorylated tau, epitope-specific antibodies highlight selective three-repeat tau spherical inclusions in Pick's disease, which is further validated by antibodies to four-repeat tau if these spherical inclusions stain negative (figure 1). This distinction is particularly obvious in the granule cell neurons of the hippocampal dentate fascia, which can be used solely to diagnose Pick's disease.

Because a harmonised neuropathological diagnostic scheme does not exist, it was pivotal to the aims of the Pick's disease International Consortium to define operational diagnostic criteria for three-repeat-predominant tauopathy. All individuals considered for inclusion in the Pick's disease International Consortium had an archival neuropathological diagnosis of Pick's disease (ie, the presence of argyrophilic or phosphorylated tau positive spherical inclusions) and underwent neuropathological assessments at their respective brain banks. Owing to the multisite nature of the Consortium, each participating centre was requested to report three-repeat and four-repeat tau staining results for each individual. To fulfil our criteria, Pick bodies had to be confirmed to be present in each individual and in addition each individual had to have three-repeat tau-positive and four-repeat tau-negative inclusions. The additional presence of ballooned neurons and negative Gallyas staining of inclusions was preferred (but not necessary) to confirm diagnosis. If three-repeat and four-repeat tau immunohistochemistry had not been done, routinely cut sections (up to 7 µm) of unstained, formalin-fixed paraffin-embedded tissue from hippocampal, frontal, or temporal lobe regions were submitted to either the Mayo Clinic Brain Bank for Neurodegenerative Diseases or UCL for three-repeat and four-repeat tau immunohistochemistry assessments, as per the operational diagnostic criteria (figure 2). Brain samples from individuals with Pick's disease were examined by Pick's disease International Consortium investigators: by two neuropathologists (DWD and SFR) at Mayo Clinic Brain Bank for Neurodegenerative Diseases or by a neuropathologist (TL) and a neurologist (WJS, under the supervision of TL) at UCL Queen Square Brain Bank, all using the Pick's disease International Consortium operational diagnostic criteria. All sections were stained using standard immunohistochemical methods (figure 2).[25]

DNA was extracted from samples from each participant at either the Mayo Clinic (North American Pick's disease cohort and all controls) or the UCL Queen Square Brain Bank for Neurological Disorders (European or Australian Pick's disease cohort). At the Mayo Clinic, genomic DNA was extracted from frozen brain tissue from individuals with Pick's disease and from peripheral blood lymphocytes from controls using an automated or manual method. Automated DNA extractions were carried out using Autogen Tissue Kit reagents (Autogen, Holliston, MA, USA) according to manufacturer protocols and were processed on the Autogen FlexSTAR+ instrument (Autogen, Holliston, MA, USA). At the UCL Queen Square Brain Bank for

Neurological Disorders, total genomic DNA was extracted from frozen brain tissue using the Kleargene XL Nucleic Acid Purification kit (LGC, Hoddesdon, UK). DNA quality was assessed with a NanoDrop 8000 spectrophotometer (ThermoFisher Scientific, Waltham, Massachusetts, USA) and absorbance ratios for 260/280 nm were between 1·7 and 2·2, and for 260/230 nm were between 2·0 and 2·2.

The *MAPT* H2 haplotype-tagging variant rs8070723 was genotyped in all individuals with Pick's disease and controls; the minor allele of rs8070723 corresponds to the *MAPT* H2 haplotype, and the major allele corresponds to the *MAPT* H1 haplotype. Additionally, the five common *MAPT* variants (rs1467967, rs242557 [the H1c haplotype-tagging variant], rs3785883, rs2471738, and rs7521), which along with rs8070723 define H1 subhaplotypes, were genotyped to assess *MAPT* subhaplotype structure.[26,27] North American individuals with Pick's disease and all controls were genotyped using TaqMan single-nucleotide polymorphism (SNP) genotyping assays on an ABI 7900HT Fast Real-Time PCR system (Applied Bio-systems, Foster City, CA, USA).[28] *MAPT* variants were genotyped according to manufacturer instructions (primer sequences available upon request from the corresponding authors). Genotypes were called using TaqMan Genotyper Software v1.3 (Applied Bio-systems, Foster City, CA, USA). European and Australian



B

UCL Queen Square Institute of Neurology cohort (Europe or Australia; n=138)
Netherlands Brainbank, Amsterdam, Netherlands (n=29)
UCL Queen Square Brain Bank, London, UK (n=16)
Neurological Tissue Bank, Biobanc-Hospital Clínic-IDIBAPS, Barcelona, Spain (n=12)
Cambridge Brain Bank, Cambridge, UK (n=10)
Manchester Brain Bank, Manchester, UK (n=9)
London Neurodegenerative Diseases Brain Bank, London, UK (n=8)
South West Dementia Brain Bank, University of Bristol, Bristol, UK (n=8)
Sydney Brain Bank, Sydney, NSW, Australia (n=7)
Neurobiobank München, Munich, Germany (n=7)
Oxford Brain Bank, Oxford, UK (n=7)
Newcastle Brain Tissue Resource, Newcastle-upon-Tyne, UK (n=7)
Neuro-CEB Biobank France, Paris, France (n=5)
Victorian Brain Bank, Florey Institute, Parkville, VIC, Australia (n=5)
Douglas-Bell Canada Brain Bank, Montreal, QC, Canada* (n=3)
The Brain Bank at Karolinska Institutet, Stockholm, Sweeden (n=2)
Fondazione IRCCS Instituto Neurologico Carlo, Milan, Italy (n=2)
DZNE Standort Tübingen, Germany (n=1)

Mayo Clinic, Jacksonville cohort (North America; n=200)
Mayo Clinic, Jacksonville, FL, or Rochester, MN, USA (n=55)
University of Pennsylvania, Philadelphia, PA, USA (n=18)
University of California, San Francisco, CA, USA (n=16)
Massachusetts General Hospital, Boston, MA, USA (n=15)
Northwestern University, Chicago, IL, USA (n=14)
John Hopkins University, Baltimore, MD, USA (n=13)
Indiana University, Bloomington, IN, USA (n=12)
Banner Sun Health Research, Sun City, AZ, USA (n=9)
Sunnybrook Health Research, Toronto, ON, Canada (n=9)
Columbia University, New York City, NY, USA (n=9)
Emory University, Atlanta, GA, USA (n=7)
University of Texas Southwestern Medical Center, Dallas, TX, USA (n=7)
University of British Columbia Hospital, Vancouver, BC, Canada (n=5)
Houston Methodist Hospital, Houston, TX, USA (n=4)
Duke University, Durham, NC, USA (n=3)
Krembil Research Institute, University of Toronto, Toronto, ON, Canada (n=2)
University of California, Los Angeles, CA, USA (n=1)
Parkwood Institute, University of Toronto, Toronto, ON, Canada (n=1)

Figure 3: **Countries that have contributed samples to the Pick's disease International Consortium and sites that contributed to this study**
(A) Countries (red) that have contributed Pick's disease tissues to the Pick's disease International Consortium to date. Samples from Belgium were included in the Pick's disease International Consortium but not in the present study (B) Recruitment sites that contributed samples to this study. The number of samples from each site are listed. Map created from https://www.mapchart.net/. CEB=Collection d'Echantillons Biologiques. DZNE=Deutsches Zentrum für Neurodegenerative Erkrankungen. IDIBAPS=Institut d'Investigacions Biomèdiques August Pi i Sunyer. IRCCS=Istituto di Ricovero e Cura a Carattere Scientifico. UCL=University College London. *These samples were processed and genotyped at UCL and therefore were included in the UCL cohort.

Medicine, Houston Methodist Research Institute and Weill Cornell Medicine, Houston, TX, USA (M D Cykowski MD); **Department of Neurology, Duke University Medical Center, Durham, NC, USA** (S-H J Wang MD PhD); **Division for Neurogeriatrics, Centre for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden** (Prof C Graff PhD); **Unit for Hereditary Dementias, Karolinska University Hospital Solna, Stockholm, Sweden** (Prof C Graff); **Human Brain and Spinal Fluid Resource Center, Brentwood Biomedical Research Institute, Los Angeles, CA, USA** (R M Nagra PhD); **Tanz Centre for Research in Neurodegenerative Disease** (Prof G G Kovacs MD PhD) **and Department of Laboratory Medicine and Pathobiology** (Prof G G Kovacs), **University of Toronto, Toronto, ON, Canada; Laboratory Medicine Program and Krembil Brain Institute, University Health Network, Toronto, ON, Canada** (Prof G G Kovacs); **Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Neurologico Carlo Besta, Milan, Italy** (G Giaccone MD); **Molecular Neuropathology of Neurodegenerative Diseases, German Center for Neurodegenerative Diseases, Tübingen, Germany** (Prof M Neumann MD); **Department of Neuropathology, University Hospital of Tübingen, Tübingen, Germany** (Prof M Neumann); **Department of Pathology and Laboratory Medicine, London Health Sciences Centre, London, ON, Canada** (Prof L-C Ang MD); **Schulich School of Medicine and Dentistry, Western University, London, ON, Canada** (Prof L-C Ang); **Life and Health Sciences Research Institute, School of Medicine, University of Minho, Braga, Portugal** (A Carvalho PhD); **ICVS/3B's-PT Government Associate Laboratory, Braga/Guimarães, Portugal** (A Carvalho); **Vlaams Instituut voor Biotechnologie-Universiteit Antwerpen, Center for Molecular Neurology, University of Antwerp,**

Antwerp, Belgium (Prof R Rademakers)**; Institute for Advanced Study, The Hong Kong University of Science and Technology, Hong Kong, China** (Prof J A Hardy)

Correspondence to: Prof Owen A Ross, Department of Neuroscience, Mayo Clinic, Jacksonville, FL 32224, USA **ross.owen@mayo.edu**

or

Dr William J Scotton, Dementia Research Centre, Department of Neurodegenerative Disease, University College London, Queen Square Institute of Neurology, London WC1N 3BG, UK **w.scotton@ucl.ac.uk**

See Online for appendix

For more on the **Pick's disease International Consortium** see https://www.picksdisease.net/

For more on **GnomAD** see http://gnomad.broadinstitute.org/

individuals with Pick's disease were genotyped using KASP SNP genotyping assays on the Hydrocyler2 system (LGC Genomics, Hoddesdon, UK) according to manufacturer instructions and were read on a PHERAStar FSX plate reader (BMG Labtech, Cary, NC, USA). Genotypes were called using Kraken KlusterKaller software (LGC Genomics, Hoddesdon, UK). Genotype call rates for all individuals were 100% for each variant. There was no evidence of a departure from Hardy-Weinberg equilibrium in controls for any of the six variants (all p>0·01 after Bonferroni correction). All individuals with Pick's disease, but not controls, were assessed for European ancestry using genome wide SNP genotyping data. Specifically, after standard genotyping data quality control steps, we did a principal components analysis, merged all individuals with Pick's disease with the European (CEU population code, which refers to Utah residents with northern and western European ancestry from the Centre d'Etude du Polymorphism Humain collection) HapMap reference dataset,[29] and identified any individuals with non-White European ancestry (individuals with Pick's disease who deviated more than six standard deviations from the mean of the first 10 principal components of the HapMap3 CEU population); individuals with known Hispanic or non-European ancestry were excluded from our analysis as the frequencies of genetic variants can vary substantially based on ethnic background,[30] and there were too few non-European individuals in our study to analyse such individuals separately or adjust for this factor in regression models. For controls for whom genome-wide SNP genotyping data were not available to confirm the self-reported White, non-Hispanic ethnicity, we also compared the control allele frequencies with the population-level allele frequencies on GnomAD, and the allele frequencies of controls (n=980) from the Global Parkinson's Genetics Program.[31]

	Participants
Pick's disease (N=338)	
Age at death, years	69 (65–74); 338
Age of disease onset, years	58 (54–65); 309
Disease duration, years	10 (8–13); 309
Sex (N=338)	
Male	205 (61%)
Female	133 (39%)
Clinical diagnosis (N=328)	
Frontotemporal dementia	262 (80%)
Alzheimer's disease	40 (12%)
Corticobasal syndrome	15 (5%)
Progressive supranuclear palsy	2 (<1%)
Dementia not otherwise specified	8 (2%)
Vascular dementia	1 (<1%)
Behavioural impairment during illness (N=232)	188 (81%)
Language impairment during illness (N=221)	153 (69%)
Parkinsonism during illness (N=206)	56 (27%)
Braak neurofibrillary tangle stage (N=176)	
Stage 0	87 (49%)
Stage I	29 (16%)
Stage II	28 (16%)
Stage III	11 (6%)
Stage IV	10 (6%)
Stage V	4 (2%)
Stage VI	7 (4%)
Thal amyloid phase (N=177)	
Phase 0	100 (56%)
Phase 1	32 (18%)
Phase 2	18 (10%)
Phase 3	15 (8%)
Phase 4	7 (4%)
Phase 5	5 (3%)
Brain weight, g	980 (880–1083); 296
Healthy controls (N=1312)	
Age at blood draw, years	69 (61–75); 1312
Sex	
Male	611 (47%); 1312
Female	701 (53%); 1312

Data are median (IQR); N or n (%). All participants with Pick's disease and healthy controls were White and non-Hispanic. Sex was determined by self-report.

Table 1: **Summary of characteristics of the individuals with Pick's disease and controls**

Statistical analysis

Statistical analyses were done using R Statistical Software (version 4.1.2). Associations between individual *MAPT* variants and risk of Pick's disease were evaluated using logistic regression models that were adjusted for age (age at death in Pick's disease and age at blood draw in controls) and sex; each variant was assessed as number of minor alleles (ie, under an additive model) in all regression analysis. Odds ratios (ORs) and 95% CIs were estimated and correspond to each additional minor allele. In individuals with Pick's disease, associations of individual variants with age at onset were examined using linear regression models that were adjusted for sex and cohort (Europe or Australia, or North America), and associations between individual variants with disease duration were assessed using linear regression models that were adjusted for sex, age at onset, and cohort. Disease duration was considered on the square root scale in all regression analyses owing to its skewed distribution. Regression coefficients (referred to as β) and 95% CIs were estimated and are interpreted as the increase in the mean age at onset or disease duration (on the square root scale for disease duration) corresponding to each additional copy of the minor allele. For all associations between individual *MAPT* variants and outcomes, analysis involving rs8070723 (the H2-tagging variant) was considered as the primary analysis, with results for the five remaining variants considered as secondary and presented for

completeness. In exploratory analysis, associations of rs8070723 with other clinical and neuropathological factors were also assessed; these analyses are described in the appendix (p 1).

Associations between the six-variant-defined (rs1467967-rs242557-rs3785883-rs2471738-rs8070723-rs7521) *MAPT* haplotypes and risk of Pick's disease were assessed using the R haplo.stats package (version 1.9.5.1).[32] Specifically, based on estimated haplotype probabilities, the expected number of copies of the given haplotype was first estimated for each individual, and subsequently logistic regression models that were adjusted for age (age at death in Pick's disease and age at blood draw in controls) and sex were used to assess the association between the expected number of copies of the given haplotype and risk of Pick's disease.[32] ORs and 95% CIs were estimated and correspond to each additional copy of the given haplotype. In analysis of individuals with Pick's disease, associations of six-variant-defined *MAPT* haplotypes with age at onset were assessed in the same way, based on the expected number of copies of the given haplotype,[32] except that linear regression models were adjusted for sex and cohort. Finally, associations of six-variant-defined *MAPT* haplotypes with disease duration were evaluated in this same manner[32] using linear regression models that were adjusted for sex, age at onset, and cohort. β-coefficients and 95% CIs were estimated and are interpreted as the increase in the mean age at onset or disease duration (on the square root scale for disease duration) corresponding to each additional copy of the given haplotype. Haplotypes occurring in less than 1% of individuals in a specific analysis were excluded from that analysis.

We adjusted for multiple testing separately for each outcome measure that was examined (presence of Pick's disease, age at onset, or disease duration). p values less than 0·05 were considered as statistically significant in the primary analysis involving the *MAPT* rs8070723 variant. In secondary analysis assessing associations between *MAPT* haplotypes and outcomes, p values less than 0·0028 (18 tests, corresponding to 18 different haplotypes with 1% or more frequency in this specific analysis) were considered as statistically significant after Bonferroni correction in the disease-association analysis, and p values less than 0·0031 (16 tests, corresponding to 16 different haplotypes with ≥1% frequency in this specific analysis) were considered as statistically significant in the age at onset and disease duration analyses. p values less than or equal to 0·05 were considered as significant in all remaining analysis. All statistical tests were two-sided. Examples of R code for

	MAPT variant						Haplotype frequency		Association with Pick's disease	
	rs1467967	rs242557	rs3785883	rs2471738	rs8070723	rs7521	Individuals with Pick's disease (N=338)	Healthy controls (N=1312)	OR (95% CI)	p value
H1b	G	G	G	C	A	A	13·1%	16·0%	0·76 (0·58–1·00)	0·051
H1c	A	A	G	T	A	G	10·2%	11·3%	0·93 (0·70–1·25)	0·65
H1d	A	A	G	C	A	A	7·4%	7·1%	0·99 (0·68–1·42)	0·94
H1e	A	G	G	C	A	A	9·8%	9·0%	1·03 (0·74–1·42)	0·87
H1f	G	G	A	C	A	A	0·0%	1·2%	0·11 (0·01–0·99)	0·049
H1g	G	A	A	C	A	A	0·7%	1·1%	0·43 (0·11–1·65)	0·22
H1h	A	G	A	C	A	A	4·0%	4·1%	0·95 (0·57–1·57)	0·85
H1i	G	A	G	C	A	A	3·9%	4·4%	0·98 (0·60–1·61)	0·95
H1l	A	G	A	C	A	G	3·6%	3·0%	1·11 (0·67–1·84)	0·69
H1m	G	A	G	C	A	G	2·9%	2·9%	1·00 (0·56–1·78)	0·99
H1o	A	A	A	C	A	A	1·1%	2·3%	0·53 (0·23–1·26)	0·15
H1p	G	G	G	T	A	G	1·1%	1·5%	0·82 (0·33–2·04)	0·66
H1r	A	G	G	T	A	G	0·7%	1·1%	0·63 (0·20–2·01)	0·44
H1u	A	A	G	C	A	G	2·4%	2·4%	1·11 (0·58–2·11)	0·75
H1v	G	G	A	T	A	G	2·2%	1·2%	1·50 (0·70–3·21)	0·30
H1x	G	A	A	T	A	G	1·3%	1·3%	1·06 (0·44–2·56)	0·91
H1y	A	A	A	T	A	G	1·4%	1·6%	0·85 (0·34–2·07)	0·71
H2	A	G	G	C	G	G	28·5%	22·7%	1·34 (1·11–1·63)	0·0028

ORs, 95% CIs, and p values were calculated using the R haplo.stats package; based on estimated haplotype probabilities, the expected number of copies of the given haplotype was first estimated for each individual. Subsequently, logistic regression models that were adjusted for age (age at death in individuals with Pick's disease and age at blood draw in healthy controls) and sex were used to assess the association between the expected number of copies of the given haplotype and risk of Pick's disease. ORs and 95% CIs correspond to each additional copy of the given haplotype. p values of less than 0·0028 are considered as statistically significant after applying a Bonferroni correction for multiple testing for the 18 different haplotypes that were assessed for association with risk of Pick's disease. Haplotypes occurring in less than 1% of individuals were excluded from the analysis. OR=odds ratio.

Table 2: **Associations between *MAPT* haplotypes and risk of Pick's disease**

the association analysis involving individual variants as well as six-variant-defined haplotypes are in the appendix (pp 1–2).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report or decision to publish.

Results

338 individuals with pathologically defined Pick's disease were identified from the Pick's disease International Consortium across 35 independent recruitment sites and included in this study (205 [61%] male and 133 [39%] female; 338 [100%] White; figure 3; table 1). 1312 neurologically healthy controls were identified from the Mayo Clinic in Jacksonville, FL (N=881) or Rochester, MN (N=431; 611 [47%] male and 701 [53%] female; 1312 [100%] White; table 1), from March 1, 1998, to Sept 1, 2019. Allele and genotype frequencies for each variant are in the appendix (p 3). The *MAPT* rs8070723 H2 allele was significantly associated with an increased risk (in comparison with the H1 allele) of Pick's disease in the overall cohort (OR 1·35 [95% CI 1·12 to 1·64], p=0·0021), with minor allele frequencies of 29·0% in the 338 individuals with Pick's disease and 23·0% in the 1312 controls. *MAPT* rs8070723 was not associated with age at onset (β –0·54 [95% CI –1·94 to 0·87], p=0·45) or disease duration (β 0·05 [–0·06 to 0·16], p=0·35). Single-variant associations with risk of Pick's disease, age at onset, and disease duration are shown for all six *MAPT* variants used to define *MAPT* haplotypes in the appendix (pp 4–5). rs242557 was not associated with risk of Pick's disease (OR 0·94 [0·79 to 1·12], p=0·51; appendix p 4). We found no significant associations of *MAPT* H2 with the available clinical and neuropathological data (appendix p 6).

Results of the secondary analysis, an evaluation of associations between the six-variant-defined *MAPT* haplotypes and risk of Pick's disease, are in table 2. As with the single-variant analysis, the H2 haplotype was associated with an increased risk of Pick's disease (OR 1·34 [95% CI 1·11 to 1·63], p=0·0028); the slight difference between the two numerical estimates is due to the two different analysis approaches. Additionally, although not significant after correcting for multiple testing, weak evidence of an association was observed at the p less than 0·05 significance level for the rare H1f haplotype (OR 0·11 [0·01 to 0·99], p=0·049), with a slightly weaker finding noted for H1b (OR 0·76 [0·58 to 1·00], p=0·051). We found no other associations between *MAPT* haplotypes and risk of Pick's disease (all p≥0·15; table 2).

Associations of *MAPT* haplotypes with age at onset and disease duration in individuals with Pick's disease are shown in table 3. None of the six-variant-defined *MAPT* haplotypes was significantly associated with age at onset or disease duration after correcting for multiple testing (p<0·0031 considered significant). However, associations at the p less than 0·05 significance level were observed with age at onset for H1b (β 2·66 [95% CI 0·63 to 4·70], p=0·011), H1i (β –3·66 [–6·83 to –0·48], p=0·025), and H1u (β –5·25 [–10·42 to –0·07], p=0·048), and with a shorter disease duration for H1x (β –0·57 [–1·07 to –0·07], p=0·026).

	Association with age of disease onset			Association with disease duration	
	Haplotype frequency (N=309)	β (95% CI)	p value	β (95% CI)	p value
H1b	13·3%	2·66 (0·63 to 4·70)	0·011	–0·01 (–0·17 to 0·15)	0·91
H1c	10·0%	1·63 (–0·61 to 3·86)	0·15	0·01 (–0·16 to 0·19)	0·89
H1d	7·2%	0·79 (–1·79 to 3·38)	0·55	–0·15 (–0·35 to 0·05)	0·15
H1e	9·3%	0·52 (–1·94 to 2·98)	0·68	0·05 (–0·14 to 0·24)	0·60
H1h	4·0%	2·03 (–1·57 to 5·64)	0·27	–0·10 (–0·38 to 0·18)	0·50
H1i	4·1%	–3·66 (–6·83 to –0·48)	0·025	–0·12 (–0·37 to 0·13)	0·36
H1l	3·5%	–1·75 (–5·42 to 1·92)	0·35	0·07 (–0·22 to 0·35)	0·65
H1m	3·1%	–1·25 (–5·33 to 2·84)	0·55	0·14 (–0·18 to 0·46)	0·38
H1o	1·2%	0·05 (–6·91 to 7·00)	0·99	0·01 (–0·52 to 0·55)	0·96
H1p	1·0%	–5·65 (–12·60 to 1·30)	0·11	0·01 (–0·53 to 0·55)	0·96
H1u	2·2%	–5·25 (–10·42 to –0·07)	0·048	–0·38 (–0·78 to 0·02)	0·066
H1v	2·1%	–1·74 (–6·61 to 3·13)	0·48	0·30 (–0·07 to 0·68)	0·11
H1x	1·4%	–5·39 (–11·84 to 1·07)	0·10	–0·57 (–1·07 to –0·07)	0·026
H1y	1·5%	–0·70 (–6·93 to 5·54)	0·83	0·31 (–0·17 to 0·79)	0·21
H1z	1·6%	–1·81 (–8·02 to 4·40)	0·57	–0·01 (–0·49 to 0·47)	0·98
H2	29·4%	–0·62 (–2·03 to 0·79)	0·39	0·05 (–0·06 to 0·16)	0·39

β values, 95% CIs, and p values were calculated using the R haplo.stats package; based on estimated haplotype probabilities, the expected number of copies of the given haplotype was first estimated for each individual. Subsequently, linear regression models that were adjusted for sex and cohort (Europe or Australia, or North America) were used to assess the association between the expected number of copies of the given haplotype and age of disease onset, and linear regression models that were adjusted for sex, age of disease onset, and cohort were used to examine the association between the expected number of copies of the given haplotype and disease duration. β values are interpreted as the change in the mean value of the given outcome (age of disease onset or disease duration) corresponding to each additional copy of the given haplotype. p values of less than 0·0031 are considered as statistically significant after applying a Bonferroni correction for multiple testing for the 16 different haplotypes that were assessed for association with age of disease onset and disease duration. Haplotypes occurring in less than 1% of individuals were excluded from the analysis.

Table 3: **Associations of *MAPT* haplotype with age of disease onset and disease duration in individuals with Pick's disease**

Discussion

Pick's disease is a rare, predominantly sporadic three-repeat tauopathy that presents primarily as a behavioural or language variant of frontotemporal dementia.[4–9] Little is known regarding its causes or underlying pathobiology. To date, no genetic variation has been shown to associate with disease risk, although in a small number of individuals with Pick's disease, or Pick's disease-like pathology, rare *MAPT* mutations or duplications have been suggested to be causative.[13–17] Thus, given the rare nature of Pick's disease, a comprehensive screening of rare variants across tau-related genes including copy number changes is warranted, and the creation of the Pick's disease International Consortium will facilitate such studies. In the present study, we have shown that the

common *MAPT* H2 haplotype, which reduces the risk of four-repeat-tauopathy, is associated with an increased risk of the three-repeat tauopathy Pick's disease. This finding was possible only by establishing a global consortium to increase the number of available pathologically defined individuals. Previous genetic studies were underpowered with only 34 and 33 individuals with Pick's disease;[22,23] a ten times increase in sample size was needed to establish *MAPT* H2 as a risk factor.

Previous research in frontotemporal dementia linked to chromosome 17 with tau pathology has clearly shown that mutations in the 5□ splice site of *MAPT* exon 10 can increase the expression of the four-repeat tau isoform, emphasising how important exon 10 splicing regulation is in tangle formation and neurodegeneration.[19,33] Given the association of *MAPT* H2 with a three-repeat-tauopathy, and its protection in four-repeat-tauopathy, the *MAPT* H1 haplotype might increase the expression of four-repeat tau and the H2 might increase the expression of three-repeat tau. Previous studies have attempted to investigate the haplotype risk in related neurodegenerative disorders (eg, progressive supranuclear palsy and corticobasal degeneration; appendix p 7) and the subsequent influence on *MAPT*-tau expression, although results have been inconclusive; given the presence of six different isoforms in human brain, defining specific isoform expression remains complex.[34–36] The genetic predisposition we describe supports the hypothesis that the pathological effects of the H1-H2 haplotypes occur via isoform-specific expression differences, which might have implications in the determination of therapeutic strategies that have focused either on overall lowering of tau expression or on lowering specifically of four-repeat-tau or increasing three-repeat-tau isoforms. The overall balance of tau isoforms seems to be important for the primary tauopathies but does not in itself explain the mixed pathology observed in individuals with Alzheimer's disease; however, an overall increased expression of total tau might underly the mixed pathology. Studies on haplotype-specific or isoform-specific *MAPT* expression are urgently needed. In addition to providing evidence that the *MAPT* H2 haplotype is associated with an increased risk of Pick's disease, we observed associations at the p less than 0·05 significance level of H1 subhaplotypes with risk of Pick's disease, age at onset, and disease duration; however, these associations will require validation.

This study has strengths, in the large cohort of patients with Pick's disease and the direct genotyping of the *MAPT* H1-H2 haplotype, but there also several limitations. Our study did not include a replication cohort, as such a cohort does not currently exist, given the rare nature of Pick's disease; future replication of our reported risk association between *MAPT* H2 and Pick's disease will be important. A type 2 error (ie, false-negative finding) is possible, and we cannot conclude that there is no true association between a given haplotype and risk of Pick's disease simply owing to a non-significant p value in this study. Therefore, our OR of 1·35 and p value of 0·002 for the association of *MAPT* H2 with risk of Pick's disease are noteworthy when considering the importance and previous knowledge of *MAPT* in tauopathies, even though this p value does not approach the threshold of 5×10^{-8} that would be considered statistically significant in a genome-wide association study. Additionally, without available genome-wide SNP data for controls, we were unable to regress out genetic principal components or genetically confirm the self-reported White or non-Hispanic ethnicity, and population stratification could have affected our results. However, we used the case genetic principal components to exclude any individuals with non-European ancestry, and our control *MAPT* H1-H2 frequencies (rs8070723 minor allele frequency 23%) were in keeping with published data[37,38] and the general population frequency (19·7% in non-Finnish Europeans on GnomAD). The highest population frequency for rs8070723 in gnomAD is 23·8%, which is very similar to the control frequency of 23% in this study. Additionally, we checked the allele frequency for rs8070723 in a subset of 980 neurologically healthy European controls from the Global Parkinson's Genetics Program cohort, which gave a frequency of 23%, giving further confidence that population stratification was not confounding our results. Because our study included only individuals of European descent, we cannot extrapolate our findings to individuals of other racial and ethnic backgrounds; indeed, we hope that we can establish further collaboration to create a truly worldwide Pick's disease International Consortium to address this limitation. Finally, unfortunately the inclusion of age-matched and sex-matched controls from each site, to allow for site-specific adjustment in our analysis, was not possible.

In summary, Pick's disease is a rare and understudied disease with a devastating effect on both patients and their families. Through collaboration and building of the Pick's disease International Consortium, we have a rare opportunity to engage in studies that might tease out the underlying pathobiology in Pick's disease. As a primary tauopathy, the identification of genetic variants, such as *MAPT* H2, involved in Pick's disease, might inform the study of more common tau-related disorders, such as progressive supranuclear palsy, corticobasal degeneration, and potentially Alzheimer's disease. Larger unbiased studies to explore genome-wide or structural genetic variation in Pick's disease are now warranted. Furthermore, resolving the genetic determinants of Pick's disease might help in establishing diagnostic criteria and elucidating dysfunctional pathways to direct future therapeutic strategies.

Pick's disease International Consortium members
Thomas T Warner, Zane Jaunmuktane, Bradley F Boeve, Ranjan Duara, Neill R Graff-Radford, Keith A Josephs, David S Knopman,

Shunsuke Koga, Melissa E Murray, Kelly E Lyons, Rajesh Pahwa, Ronald C Petersen, Jennifer L Whitwell, Lea T Grinberg, Bruce Miller, Athena Schlereth, Salvatore Spina, Murray Grossman, David J Irwin, EunRan Suh, John Q Trojanowski, Vivianna M Van Deerlin, David A Wolk, Theresa R Connors, Patrick M Dooley, Derek H Oakley, Iban Aldecoa, Mircea Balasa, Ellen Gelpi, Sergi Borrego-Écija, Rosa Maria de Eugenio Huélamo, Jordi Gascon-Bayarri, Raquel Sánchez-Valle, Pilar Sanz-Cartagena, Gerard Piñol-Ripoll, Eileen H Bigio, Margaret E Flanagan, Emily J Rogalski, Sandra Weintraub, Julie A Schneider, Lihua Peng, Xiongwei Zhu, Koping Chang, Juan C Troncoso, Stefan Prokop, Kathy L Newell, Matthew Jones, Anna Richardson, Federico Roncaroli, Julie Snowden, Kieren Allinson, Poonam Singh, Geidy E Serrano, Xena E Flowers, James E Goldman, Allison C Heaps, Sandra P Leskinen, Sandra E Black, Mario Masellis, Andrew King, Safa-Al Sarraj, Claire Troakes, John R Hodges, Jillian J Kril, John B Kwok, Olivier Piguet, Sigrun Roeber, Johannes Attems, Alan J Thomas, Bret M Evers, Kevin F Bieniek, Anne A Sieben, Patrick P Cras, Bart B De Vil, Thomas Bird, Rudolph J Castellani, Ann Chaffee, Erin Franklin, Vahram Haroutunian, Max Jacobsen, Dirk Keene, Caitlin S Latimer, Richard J Perrin, Jeff Metcalf, Dushyant P Purohit, Robert A Rissman, Aimee Schantz, Jamie Walker, Peter P De Deyn, Charles Duyckaerts, Isabelle Le Ber, Danielle Seilhean, Sabrina Turbant-Leclere, John F Ervin, Inger Nennesmo, James Riehl, Benedetta Nacmias, Elizabeth C Finger, Cornelis Blauwendraat, Mike A Nalls, Andrew B Singleton, Dan Vitale, Cristina Cunha, and Zbigniew K Wszolek.

Contributors

RRV and WJS: equal contribution as first authors, conceptualisation, data curation, formal analysis, methodology, investigation, project administration, visualisation, and writing (original draft, review, and editing). SFR and TL: original draft, data collection, investigation, and writing (review and editing). MGH: original draft, formal analysis, methodology, visualisation, and writing (review and editing). MS and AM-C: investigation, methodology, and writing (review and editing). NT: project administration, investigation, and writing (review and editing). RLW, MCB, HLM, RRe, AIS-B, and KM: investigation, and writing (review and editing). TR, EAC, MD, WWS, EBL, MPF, LM-P, TG, JR-O, BG, ACR, CK, JBR, TGB, AFT, JLK, IB, GMH, MG, TA, CMM, CLW, NM, SB, IRM, CM, MDC, S-HJW, CG, RMN, GGK, GG, MN, L-CA, and AC: resources, data curation, and writing (review and editing). HRM and RRa: conceptualisation, resources, and writing (review and editing). JAH, DWD, JDR, and OAR: conceptualisation, original draft, funding acquisition, supervision, resources, and writing (review and editing). All Pick's disease International Consortium members listed in the appendix (p 8–9) were involved in funding acquisition, resources, validation, critically reviewing, and approving final version of manuscript. All authors confirm that they had full access to all the data in this study and accept responsibility of publication submission. WJS, RRV, MGH, and OAR verified the data.

Declarations of interest

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Data sharing

The Pick's disease International Consortium has built a database that contains detailed demographic, clinical, and pathological information for deidentified participants with Pick's disease (https://www.picksdisease.net/). Basic demographic information (eg, age at onset, age at death, disease duration, sex, and ethnicity), family history, clinical history (eg, behavioural and language impairments, presence of parkinsonism, and upper and lower motor deficits), and pathological observations (eg, immunohistochemical staining records, Thal phase, Braak stage, TDP-43 type, post-mortem intervals, brain weight, and vascular pathology), other available tissues, genetic data, and clinical imaging data are available for each participant upon request. All requests must be submitted to Owen A Ross (ross.owen@mayo.edu), William J Scotton (w.scotton@ucl.ac.uk), and Jonathan D Rohrer (j.rohrer@ucl.ac.uk).

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