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


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) 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

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 [–0.16 to 0.36], p=0.53). 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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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; however, given that a definite diagnosis of Pick’s disease requires confirmation in post-mortem brain tissue, 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. 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, 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. Pick’s disease progresses relatively rapidly and patients die approximately 10 years after disease onset. 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. Characteristic Pick bodies consist of aggregates of hyperphosphorylated three-repeat tau proteins, which are encoded by the MAPT gene on chromosome 17, 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. 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.

Rare missense and duplication mutations of MAPT have been identified in a small number of individuals with Pick’s disease or with Pick’s disease-like pathology, however, these data require replication, and independent cohorts of individuals with Pick’s disease have not reported common missense MAPT mutations. MAPT also has two well characterised common haplotypes, H1 and H2, which developed from a 900 kb ancestral genetic inversion event. 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. 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, and thus a targeted analysis is warranted.
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 absence of dementia).
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 staining. This differentiation is particularly obvious in the granule cell layer of the 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 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, 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 FlexSTAR+ instrument (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

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.

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<th>AT8</th>
<th>Three repeat</th>
<th>Four repeat</th>
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<td>Pick's disease</td>
<td><img src="image" alt="Pick's disease" /></td>
<td><img src="image" alt="Three repeat" /></td>
<td><img src="image" alt="Four repeat" /></td>
</tr>
<tr>
<td>Non-Pick's disease</td>
<td><img src="image" alt="Non-Pick's disease" /></td>
<td><img src="image" alt="Non-Pick's disease" /></td>
<td><img src="image" alt="Non-Pick's disease" /></td>
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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 aNanoDrop 8000 spectrophotometer (Thermo Fisher 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], rs7521), which along with rs8070723 define H1 subhaplotypes, were genotyped to assess MAPT subhaplotype structure.26–29 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). 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

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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. Recruitment sites that contributed samples to this study. The number of samples from each site are listed. Map created from https://www.mapchart.net/. CEBI=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.

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=13) 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 (1) Parkwood Institute, University of Toronto, Toronto, ON, Canada (n=1)
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, 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, 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 Disease Database.

**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 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
Articles

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). 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. ORs and 95% CIs were estimated and correspond to each additional copy of the given haplotype. ORs and 95% CIs 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 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

<table>
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<tr>
<th>MAPT variant</th>
<th>n1467967</th>
<th>n242557</th>
<th>n3785883</th>
<th>n2471738</th>
<th>n8070723</th>
<th>n7521</th>
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<td>H1b G G G C A A</td>
<td>13.1%</td>
<td>16.0%</td>
<td>0.76 (0.58–1.00)</td>
<td>0.051</td>
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<tr>
<td>H1c A A G T A G</td>
<td>10.2%</td>
<td>11.3%</td>
<td>0.93 (0.70–1.25)</td>
<td>0.65</td>
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<tr>
<td>H1d A A G C A A</td>
<td>7.4%</td>
<td>7.1%</td>
<td>0.99 (0.68–1.42)</td>
<td>0.94</td>
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<td>H1e A G G C A A</td>
<td>9.8%</td>
<td>9.0%</td>
<td>1.03 (0.74–1.42)</td>
<td>0.87</td>
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<tr>
<td>H1f G G A C A A</td>
<td>0.0%</td>
<td>1.2%</td>
<td>0.11 (0.01–0.99)</td>
<td>0.049</td>
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<tr>
<td>H1g G A A C A A</td>
<td>0.7%</td>
<td>1.1%</td>
<td>0.43 (0.11–1.65)</td>
<td>0.22</td>
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<tr>
<td>H1h A G A C A A</td>
<td>4.0%</td>
<td>4.1%</td>
<td>0.95 (0.57–1.57)</td>
<td>0.85</td>
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<tr>
<td>H1i G A G C A A</td>
<td>3.9%</td>
<td>4.4%</td>
<td>0.98 (0.60–1.61)</td>
<td>0.95</td>
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<tr>
<td>H1j A G A C A G</td>
<td>3.6%</td>
<td>3.0%</td>
<td>1.11 (0.67–1.84)</td>
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<tr>
<td>H1m A G C C A A</td>
<td>2.9%</td>
<td>2.9%</td>
<td>1.00 (0.56–1.78)</td>
<td>0.99</td>
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<tr>
<td>H1n A A A C A A</td>
<td>1.1%</td>
<td>2.3%</td>
<td>0.53 (0.23–1.26)</td>
<td>0.35</td>
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<tr>
<td>H1p G G C T A G</td>
<td>1.1%</td>
<td>1.5%</td>
<td>0.82 (0.33–2.04)</td>
<td>0.66</td>
<td></td>
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<tr>
<td>H1q A G G T A G</td>
<td>0.7%</td>
<td>1.1%</td>
<td>0.83 (0.20–3.21)</td>
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<tr>
<td>H1r A A G C A G</td>
<td>2.4%</td>
<td>2.4%</td>
<td>0.11 (0.58–2.11)</td>
<td>0.75</td>
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<tr>
<td>H1s G A A T A G</td>
<td>2.2%</td>
<td>1.2%</td>
<td>1.05 (0.44–2.56)</td>
<td>0.91</td>
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<tr>
<td>H1t A G A T A G</td>
<td>1.3%</td>
<td>1.3%</td>
<td>0.85 (0.34–2.07)</td>
<td>0.71</td>
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<tr>
<td>H1u A G G C G G</td>
<td>28.5%</td>
<td>22.7%</td>
<td>1.34 (1.11–1.63)</td>
<td>0.0028</td>
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</table>

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). 3312 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; 3312 [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 3312 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 1·21], 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 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 −0·70 [−1·24 to −0·16], p=0·0021), with minor allele frequencies of 29·0% in the 338 individuals with Pick’s disease and 23·0% in the 3312 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 1·21], p=0·51; appendix p 4). We found no significant associations of MAPT H2 with the available clinical and neuropathological data (appendix p 6).

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

<table>
<thead>
<tr>
<th>Association with age of disease onset</th>
<th>Association with disease duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haplotype frequency</td>
<td>p value</td>
</tr>
<tr>
<td>H1b 33·3%</td>
<td>2·66 (0·63 to 4·70)</td>
</tr>
<tr>
<td>H1c 10·0%</td>
<td>1·63 (0·61 to 3·86)</td>
</tr>
<tr>
<td>H1d 7·2%</td>
<td>0·79 (−1·79 to 3·38)</td>
</tr>
<tr>
<td>H1e 9·3%</td>
<td>0·52 (−1·94 to 2·98)</td>
</tr>
<tr>
<td>H1f 4·0%</td>
<td>0·03 (−5·57 to 5·54)</td>
</tr>
<tr>
<td>H1i 4·1%</td>
<td>−3·66 (−6·83 to −0·48)</td>
</tr>
<tr>
<td>H1l 3·5%</td>
<td>−1·75 (−5·42 to 1·92)</td>
</tr>
<tr>
<td>H1m 3·1%</td>
<td>−1·25 (−5·33 to 2·84)</td>
</tr>
<tr>
<td>H1o 1·2%</td>
<td>0·05 (−6·91 to 7·00)</td>
</tr>
<tr>
<td>H1p 1·0%</td>
<td>−5·65 (−12·60 to 1·30)</td>
</tr>
<tr>
<td>H1q 2·2%</td>
<td>−2·52 (−10·42 to 5·37)</td>
</tr>
<tr>
<td>H1r 2·1%</td>
<td>−1·74 (−6·61 to 3·13)</td>
</tr>
<tr>
<td>H1s 1·4%</td>
<td>−5·39 (−11·84 to 0·07)</td>
</tr>
<tr>
<td>H1t 1·5%</td>
<td>−0·70 (−6·93 to 5·54)</td>
</tr>
<tr>
<td>H1u 1·6%</td>
<td>−1·81 (−9·02 to 4·40)</td>
</tr>
<tr>
<td>H1v 2·9%</td>
<td>−0·62 (−2·02 to 0·79)</td>
</tr>
</tbody>
</table>

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.

Discussion
Pick’s disease is a rare, predominantly sporadic three-repeat tauopathy that presents primarily as a behavioural or language variant of frontotemporal dementia.*+ 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.*+ 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; 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 5κ 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. 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. 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 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 Jaumumukane, Bradley F Boeve, Ranjan Duara, Neill R Graff-Radford, Keith A Josephs, David S Knopman,

Contributors
RRV and WJS: equal contribution as first authors, conceptualisation, data curation, formal analysis, methodology, investigation, project administration, supervision, and writing (review and editing). GMH: original draft, formal analysis, methodology, visualisation, and writing (review and editing). SFR and TL: original draft, data collection, investigation, and writing (review and editing). MHG: 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). RIW, MCB, HLM, RRe, AIS-B, and KM: investigation, writing (review and editing). TR, EAC, MD, WWS, EBL, MPF, LM-P, TG, JRO, BG, ACR, CK, JBR, TGB, AFT, JLB, GMH, MG, TA, CMM, CIW, NM, SB, IRM, CM, MDC, S-HJW, CG, RMN, GGG, GC, MN, L-CA, and AC: resources, data curation, and writing (review and editing). HRM and RR: 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, GMH, and OAR verified the data.

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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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