Creating the Pick's disease International Consortium: Association study of *MAPT* H2 haplotype with risk of Pick's disease

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Abstract

Background: Pick's disease (PiD) is a rare and predominantly sporadic form of frontotemporal dementia that is classified as a primary tauopathy. PiD is pathologically defined by argyrophilic inclusion Pick bodies and ballooned neurons in the frontal and temporal brain lobes. PiD is characterised by the presence of Pick bodies which are formed from aggregated, hyperphosphorylated, 3-repeat tau proteins, encoded by the *MAPT* gene. The *MAPT* H2 haplotype has consistently been associated with a decreased disease risk of the 4-repeat tauopathies of progressive supranuclear palsy and corticobasal degeneration, however its role in susceptibility to PiD is unclear. The primary aim of this study was to evaluate the association between *MAPT* H2 and risk of PiD.

Methods: We established the Pick's disease International Consortium (PIC) and collected 338 (60.7% male) pathologically confirmed PiD brains from 39 sites worldwide. 1,312 neurologically healthy clinical controls were recruited from Mayo Clinic Jacksonville, FL (N=881) or Rochester, MN (N=431). For the primary analysis, subjects were directly genotyped for *MAPT* H1-H2 haplotype-defining variant rs8070723. In secondary analysis, we genotyped and constructed the six-variant *MAPT* H1 subhaplotypes (rs1467967, rs242557, rs3785883, rs2471738, rs8070723, and rs7521).

Findings: Our primary analysis found that the *MAPT* H2 haplotype was associated with increased risk of PiD (OR: 1.35, 95% CI: 1.12-1.64 P=0.002). In secondary analysis involving H1 subhaplotypes, a protective association with PiD was observed for the H1f haplotype (0.0% vs. 1.2%, P=0.049), with a similar trend noted for H1b (OR: 0.76, 95% CI: 0.58-1.00, P=0.051). The 4-repeat tauopathy risk haplotype *MAPT* H1c was not associated with PiD susceptibility (OR: 0.93, 95% CI: 0.70-1.25, P=0.65).

Interpretation: The PIC represents the first opportunity to perform relatively large-scale studies to enhance our understanding of the pathobiology of PiD. This study demonstrates that in contrast to its protective role in 4R tauopathies, the *MAPT* H2 haplotype is associated with an increased risk of PiD. This finding is critical in directing isoform-related therapeutics for tauopathies.

Funding: See funding section

Introduction

Pick's disease (PiD) is a rare and predominantly sporadic subtype of frontotemporal lobar degeneration (FTLD) which represents approximately 5% of all dementias worldwide. Although there are no clinical diagnostic criteria for PiD, it typically develops in individuals approximately 55 years of age and presents with behavioral change, impaired cognition and occasionally motor difficulties (1-7). PiD is a relatively rapidly progressive disease and patients die approximately 10 years after disease onset (1-6). Symptomatic treatments are available, but currently no treatments exist that can delay disease onset or progression. A definite diagnosis of PiD requires autopsy confirmation.

Neuropathologically, PiD is classified by severe frontotemporal, knife-edge like cortical atrophy macroscopically, and microscopically the presence of ballooned neurons and argyrophilic, tau-immunoreactive inclusion "Pick bodies" in frontal and temporal regions (1). Characteristic Pick bodies consist of hyperphosphorylated 3-repeat (3R) tau aggregate proteins which are encoded by the *MAPT* gene on chromosome 17 (7, 8), and therefore PiD is classified as a 3R tauopathy. *MAPT* codes for six major tau isoforms in the adult human brain, and this is determined by alternative splicing of exons 2, 3, and 10 influencing the number of repeat domains in the N-terminus and C-terminus (9). More specifically, alternative splicing leading to exon 10 exclusion results in 3-repeat units in the microtubule binding C-terminal domain, generating 3R tau proteins (10).

Rare mutations in *MAPT* have been identified in a handful of PiD cases or individuals with PiD-like pathology (11-14); however, these data are inconsistent as larger, independent cohorts of PiD cases do not report *MAPT* mutations (15).The *MAPT* gene also has two well characterized common haplotypes, H1 and H2, which developed from a 900kb ancestral genetic inversion event (16). Not only has *MAPT* H1 consistently been associated with an increased risk of 4-repeat (4R) primary tauopathies such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), but the H1 haplotype is also the strongest genetic risk factor for both diseases (17, 18). To date, this observation has not been replicated in 3R tauopathy of PiD which may be due to the limited available sample size (19, 20).

Due to its rare prevalence and the inability to diagnose it clinically in life, PiD is an understudied neurodegenerative disease, and its genetic etiology is unknown. As previously mentioned, the few studies of *MAPT* haplotype in PiD that have been conducted were small and underpowered. Moreover, limited access to 3R tauopathy samples has stalled research advancement in understanding how *MAPT* haplotypes and isoforms influence disease risk/pathology and has prevented progress in developing isoform-specific therapies. To address this, we established the Pick's disease International Consortium (PIC) and are collecting data from pathologically confirmed PiD cases from sites worldwide. Whilst also developing an in-depth consortium database of clinical, pathological, and demographic

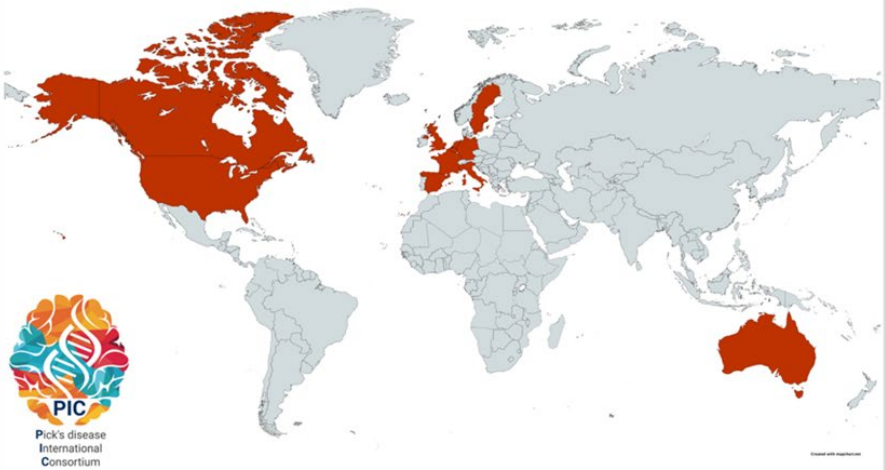
information, the primary aim of the PIC was to evaluate the association of the *MAPT* H1/H2 haplotype with disease risk, age of onset (AAO), and disease duration (DD) in PiD.

Methods

Pick's disease International Consortium (PIC)

Due to the rare and understudied landscape of PiD, researchers at Mayo Clinic Brain Bank in Jacksonville, FL, USA (MC) and the UK Dementia Research Institute at University College London Queen Square Institute of Neurology (UCL) led efforts to establish the world's first international consortium for Pick's disease (PIC). MC led the effort for identifying and sourcing PiD cases from North American regions and UCL was responsible for collecting PiD cases from European and Australasian territories. Inclusion criteria were a neuropathologic diagnosis of PiD with Pick bodies and available frozen brain tissue. Exclusion criteria were frontotemporal dementia due to etiology other than a 3R predominant tauopathy or lack of frozen specimens. IRB approval was obtained for the studies at both collection hubs (MC and UCL) and each individual brain bank had institutional IRB approval for collection and sharing of specimens.

A



B

Contributing Site	Country	# samples
UCL Institute of Neurology cohort (Europe / Australia)		**138**
Netherlands Brainbank, Amsterdam	Netherlands	29
UCL Queen Square Brain Bank, London	UK	16
Neurological Tissue Bank, Biobanc-Hospital Clinic-IDIBAPS, Barcelona	Spain	12
Cambridge Brain Bank, Cambridge	UK	10
Manchester Brain Bank, Manchester	UK	9
London Neurodegenerative Diseases Brain Bank, London	UK	8
South West Dementia Brain Bank, University of Bristol	UK	8
Sydney Brain Bank, Sydney	Australia	7
Neurobiobank München, Munich	Germany	7
Oxford Brain Bank, Oxford	UK	7
Newcastle Brain Tissue Resource, Newcastle-upon-Tyne	UK	7
GIE-Neuro-CEB Biobank France, Paris	France	5
Victorian Brain Bank, Florey Institute, Parkville, VIC	Australia	5
Douglas-Bell Canada Brain Bank, Montreal, QC	Canada	3
The Brain Bank at Karolinska Institutet, Stockholm	Sweden	2
Fondazione IRCCS Instituto Neurologico Carlo, Milan	Italy	2
DZNE e.V. Standort Tübingen	Germany	1
Mayo Clinic, Jacksonville cohort (North America)		**200**
Mayo Clinic, Jacksonville, FL/Rochester, MN	USA	55
University of Pennsylvania, Philadelphia, PA	USA	18
University of California, San Francisco, CA	USA	16
Massachusetts General Hospital, Boston, MA	USA	15
Northwestern University, Chicago, IL	USA	14
John Hopkins University, Baltimore, MD	USA	13
Indiana University, Bloomington, IN	USA	12
Banner Sun Health Research, Sun City, AZ	USA	9
Sunnybrook Health Research, Toronto, ON	Canada	9
Columbia University, New York City, NY	USA	9
Emory University, Atlanta, GA	USA	7
UT Southwestern Medical Center, Dallas, TX	USA	7
University of British Columbia Hospital, Vancouver. BC	Canada	5
Houston Methodist Hospital, Houston. TX	USA	4
Duke University, Durham, NC	USA	3
Krembil Research Institute, University of Toronto, Toronto, ON	Canada	2
UCLA - Sepulveda, Los Angeles, CA	USA	1
Parkwood Institute, University of Toronto, Toronto, ON	Canada	1
Total PIC samples		**338**

Figure 1: Global map and table reporting countries and recruitment sites that have contributed Pick's disease tissues to the Pick's disease International Consortium (PIC) to date. Dark red= countries that have collected and donated Pick's disease tissues.

Study Subjects

In the current study, 338 neuropathologically confirmed PiD cases were recruited from 39 sites worldwide (**Figure 1**), at the two major collection hubs in North America (MC) and Europe (UCL). Frozen brain tissue from cerebellum or prefrontal cortex were obtained from each case. All subjects were self-reported unrelated and Caucasian, non-Hispanic (genetically confirmed by array data). Baseline demographic information was collected for all subjects (AAO and age at death (AAD) for PiD patients, age at blood collection for controls, and sex). DD was calculated from the difference between AAD and AAO for a subset of 309 PiD cases. Subject characteristics are summarized in **Table 1**. In addition to basic demographic information, the PIC also collected information related to family histories, clinical outcomes (e.g. behavioral and language impairments, presence/absence of parkinsonism, upper and lower motor neurone deficits, Mini-Mental State Examination and Clinical Dementia Rating), and pathological information (e.g. Thal phase, Braak stage, and brain weight,) for each individual case, as well as noting whether other tissues and brain imaging data were available. Cases were removed if a rare *MAPT* mutation was identified. Peripheral blood-derived DNA was provided from 1,312 controls from Mayo Clinic in Jacksonville, FL (N=881) or Rochester, MN (N=431). Control subjects were deemed neurologically healthy by neurologists at Mayo Clinic.

Variable	Pick's disease series (N=338)	Controls (N=1,312)
Age (years)	69 (40, 100)	69 (45, 92)
Age of disease onset (years)	58 (33, 80)	N/A
Disease duration (years)	10 (2, 25)	N/A
Sex		
Male	205 (60.7%)	611 (46.6%)
Female	133 (39.3%)	701 (53.4%)

Table 1: Summary of subject characteristics.

The sample median (minimum, maximum) is given for age. Age represents age at death in Pick's disease cases and age at blood draw in controls. Age at disease onset and disease duration information was unavailable for N=29 Pick's disease cases.

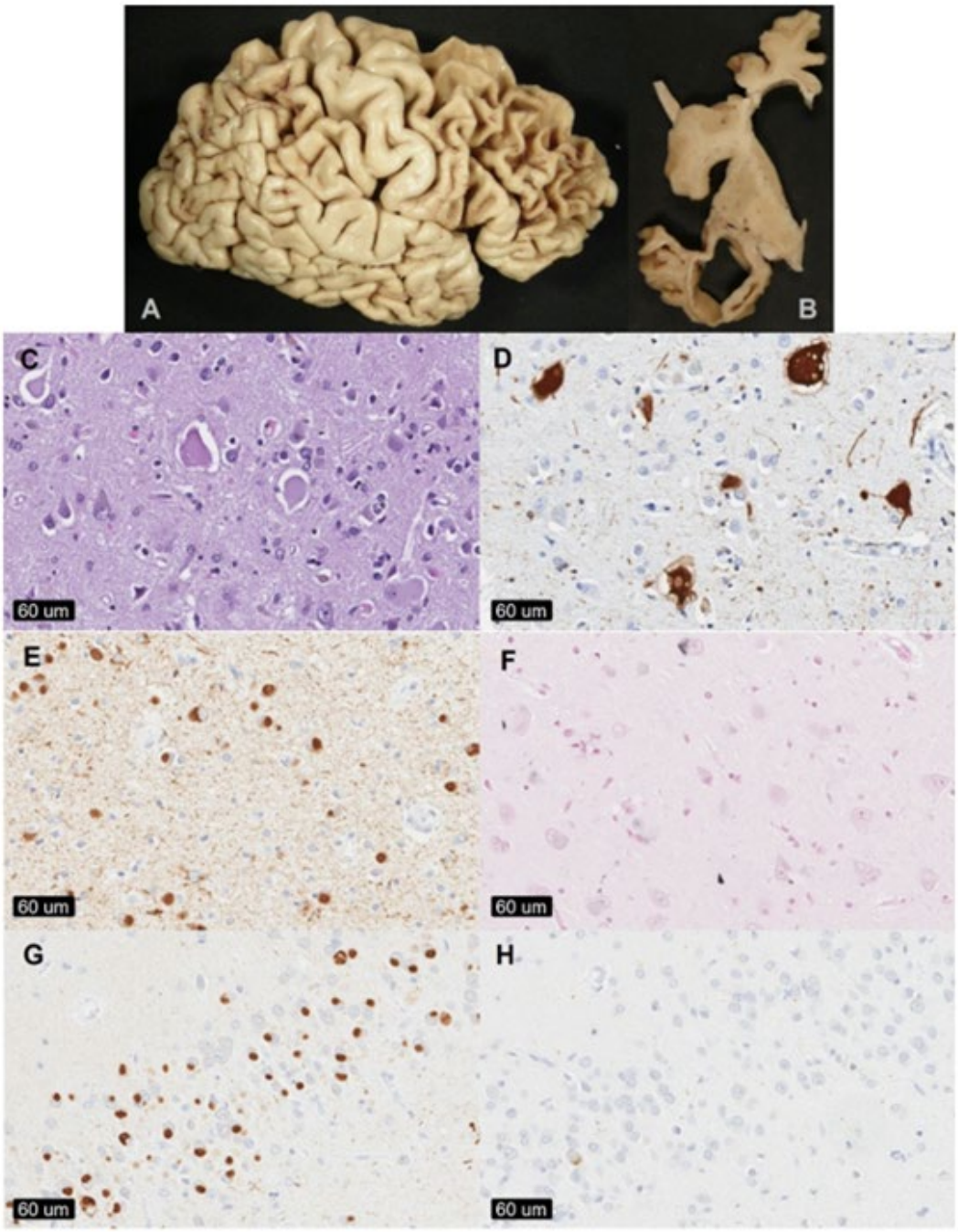


Figure 2: Pathological assessments of Pick's disease brains at Mayo Clinic Brain Bank for Neurodegenerative Diseases in Jacksonville, FL, USA. [A] The superior and dorsolateral surfaces of the frontal cortex and temporal lobe often show severe circumscribed 'knife-edge' edge atrophy. [B] Coronal sections 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 αB-crystallin may highlight ballooned neurons. [E] Phosphorylated tau antibodies highlight spherical cytoplasmic neuronal inclusions and may also show marked neuropil staining, especially in cases with concomitant Alzheimer's type pathology. [F] Gallyas silver stains may stain isolated glial lesions or neurofibrillary tangles; however, Pick bodies do not show any significant degree of silver staining. [G] 3R tau staining of the dentate fascia of the hippocampus show strong immunoreactivity of spherical inclusions. [H] 4R tau staining of the dentate fascia show negative spherical inclusion, although isolated neurofibrillary tangles may stain positive. Images are from Pick cases submitted to MCJ.

Established methods for the neuropathological diagnosis of Pick's disease

Currently, diagnostic consensus criteria for the neuropathologic diagnosis of PiD do not exist. In many diagnostic centers a neuropathological diagnosis of PiD relies on the presence of argyrophilic, spherical neuronal inclusions using traditional silver staining methods, such as Bielschowsky's or Gallyas-Braak silver staining methods. Both silver staining methods stain Alzheimer's disease (AD) neurofibrillary tangles, yet spherical inclusions in PiD are positive with Bielschowsky and negative on the Gallyas-Braak silver staining method (21). This differentiation in silver staining methods is helpful especially for centers that do rely on immunohistochemistry against phosphorylated tau (p-tau) and do not have isotype specific tau antibodies incorporated in the diagnostic work-up as AD and PiD neuropathologic changes may co-exist in the same patient. Immunohistochemistry against epitope-specific tau antibodies further helps to distinguish between AD and PiD features. Since both spherical inclusions and neurofibrillary tangles stain positive with antibodies against phosphorylated tau (p-tau), epitope-specific antibodies highlight selective 3R tau spherical inclusions in PiD, which is further validated by antibodies to 4R tau where these spherical inclusions stain negative. This distinction is particularly obvious in the granule cell neurons of the hippocampal dentate fascia, which may be used solely to diagnose PiD.

PIC diagnostic algorithm for pathology confirmed Pick's disease

Since a harmonized neuropathologic diagnostic scheme does not exist it became pivotal to the PIC aims to establish a defined set of operational diagnostic criteria within PIC that would ensure that submitted PiD cases reflect a 3R-predominant tauopathy. All cases submitted to the PIC had an archival neuropathologic diagnosis of PiD (i.e. the presence of argyrophilic or p-tau positive spherical inclusions) and underwent neuropathological assessments at their respective brain banks. Due to the multi-site nature of the PIC, each participating center were requested to submit and report respective 3R and 4R tau staining results for each individual PiD case to the PIC. To fulfill PIC criteria all cases had to confirm the presence of Pick bodies and must have had 3R tau positive and 4R tau negative inclusions. The additional presence of ballooned neurons and negative Gallyas staining of inclusions was preferred to confirm diagnosis. If 3R/4R tau immunohistochemistry had not been performed at their respective brain banks, centers submitted routinely cut sections (up to seven microns) of unstained, formalin fixed paraffin embedded tissue from hippocampal, frontal or temporal lobe regions for 3R and 4R tau immunohistochemistry assessments (**Figure 2**). Cases submitted to Mayo Clinic Brain Bank for Neurodegenerative Diseases were evaluated by two PIC neuropathologists (DWD, SFR) and cases submitted to UCL were examined by two PIC investigators (WS, TL) which included a PIC

neuropathologist (TL), all using the PIC diagnostic algorithm. All sections were stained using standard immunohistochemical methods (22) (**Figure 3**).

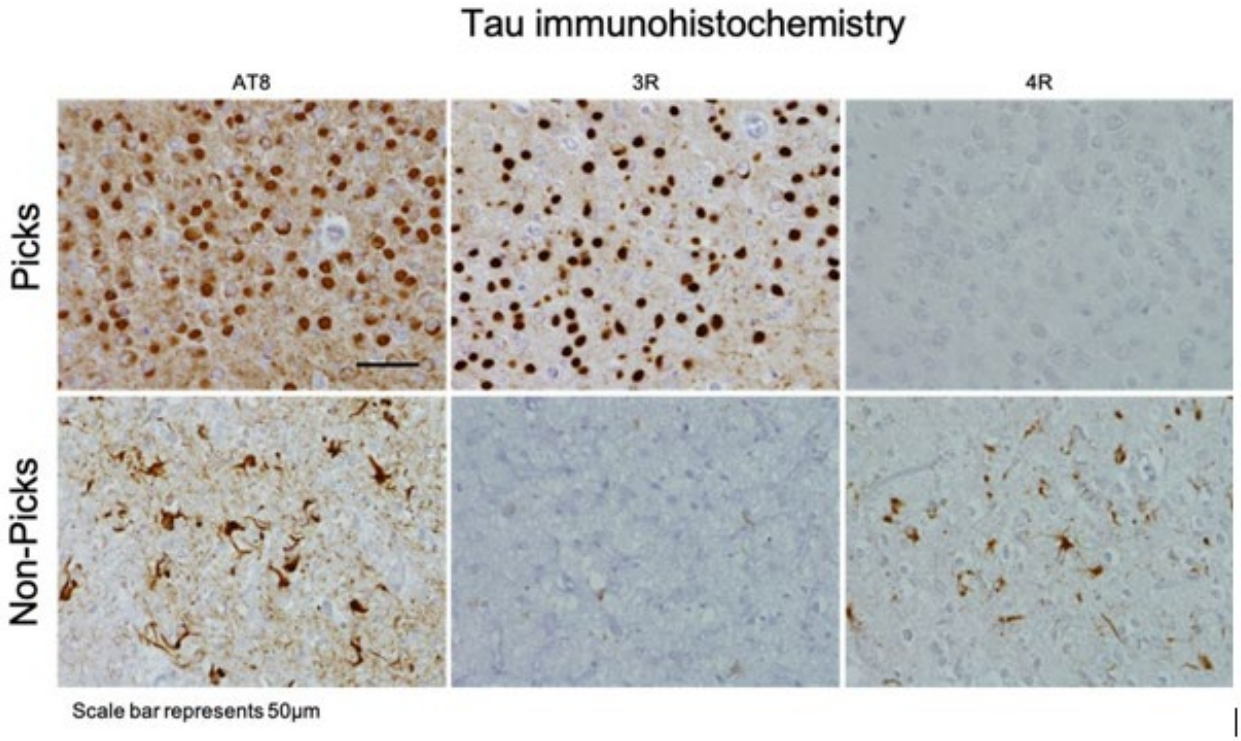


Figure 3: Pathological assessments of Pick's disease brains at Queen Square Brain Bank for Neurological Disorders (QSBB), UCL Queen Square Institute of Neurology, London, UK. The top row shows a Pick's disease case that was positive for AT8 and 3R-tau immunoreactive Pick bodies. The bottom row shows a non-Pick's disease case (that was originally pathologically diagnosed with Pick's disease) that was positive for AT8 and 4R-tau but negative for 3R tau immunoreactive Pick bodies. Images are from Pick cases submitted to UCL.

DNA Preparation

DNA was extracted from each subject at their respective collection site. At MC, genomic DNA was extracted from frozen brain tissue from PiD cases and from peripheral blood lymphocytes from control subjects using an automated or manual method. Automated DNA extractions were carried out using Autogen Tissue Kit reagents according to manufacturer protocols and were processed on the Autogen FlexSTAR+ (both Autogen, Holliston, MA, USA). At QSBB, total genomic DNA was extracted from frozen brain tissue using the Kleargene XL Nucleic Acid Purification kit (LGC, Hoddesdon, Herts, UK). DNA quality was assessed with a NanoDrop 8000 spectrophotometer (ThermoFisher Scientific, USA) and absorbance ratios for 260/280 and 260/230 were between 1.7-2.2 and 2.0-2.2, respectively.

SNP Genotyping

The *MAPT* H2 haplotype-tagging variant rs8070723 was genotyped in all cases and controls. In addition, 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 (23, 24). North American cases and all controls were genotyped using TaqMan SNP genotyping assays on an ABI 7900HT Fast Real-Time PCR system (Applied Bio-systems, Foster City, CA, USA), as previously described (25). *MAPT* variants were genotyped according to manufacturer instructions (primer sequences available upon request). Genotypes were called using TaqMan Genotyper Software v1.3 (Applied Bio-systems, Foster City, CA, USA). European and Australasian cases were genotyped using KASP™ SNP genotyping assays on the Hydrocyler2 system (LGC Genomics, Hoddesdon, Herts, 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, Herts, UK). Genotype call rates for all subjects 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 cases were assessed for population stratification using available whole SNP genotyping data. After standard genotyping data quality control steps, we performed a principal components analysis (PCA), merged all cases with the European (CEU) HapMap reference dataset, and identified any cases of non-white European ancestry which were excluded from further analysis. Allele and genotype frequencies for each variant are detailed in **Supplementary Table 1**.

Statistical Analysis

Single-variant associations with risk of PiD were evaluated using logistic regression models that were adjusted for age and sex. Odds ratios (Ors) and 95% confidence intervals (Cis) were estimated and correspond to each additional minor allele. Single-variant associations with AAO and DD in PiD patients were examined using linear regression models that were adjusted for sex and series (AAO analysis) or sex, AAO, and series (DD analysis). Regression coefficients (referred to as β) and 95% Cis were estimated and are interpreted as the increase in the mean AAO or DD corresponding to each additional copy of the minor allele. For all single-variant associations, 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.

Associations between six-variant *MAPT* haplotypes and risk of PiD were assessed using score tests for association under a logistic regression framework (26), where tests were adjusted for age and sex. Ors and 95% Cis were estimated and correspond to each additional copy of the given haplotype.

In analysis of PiD patients, associations of six-variant *MAPT* haplotypes with AAO and DD were assessed using score tests for association under a linear regression framework (26), where tests were adjusted for sex and series (AAO analysis) or sex, AAO, and series (DD analysis). B-coefficients and 95% Cis were estimated and are interpreted as the increase in the mean AAO or DD corresponding to each additional copy of the given haplotype. Haplotypes occurring in <1% of subjects in a specific analysis were excluded from that analysis.

We adjusted for multiple testing separately for each outcome measure that was examined (presence of PiD, AAO, or DD). P-values <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 < 0.0028 (18 tests) were considered as statistically significant after Bonferroni correction in the disease-association analysis, and p-values < 0.0031 (16 tests) were considered as statistically significant in the AAO and DD analyses. P-values ≤ 0.05 were considered as significant in all remaining analysis. All statistical tests were two-sided. Statistical analyses were performed using R Statistical Software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

Study sponsors (for individual brain bank collections) had no such involvement with this study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. All authors confirm that they had full access to all the data in this study and accept responsibility of publication submission.

Results

A total of 338 pathologic-defined PiD cases were identified across 39 independent recruitment sites to establish the first PiD consortium (PIC). There was a significant association between the *MAPT* rs8070723 H2 allele and an increased risk of PiD in the overall series (OR: 1.35, 95% CI: 1.12-1.64, P=0.0021), with minor allele frequencies of 29.0% in the 338 PiD patients and 23.0% in the 1,312 controls. *MAPT* rs8070723 was not associated with AAO (β: -0.54, 95% CI: -1.94 to 0.87, P=0.45) or DD (β: 0.25, 95% CI: -0.46 to 0.96, P=0.50). Single-variant associations with PiD, AAO and DD are shown for all six *MAPT* variants used to define *MAPT* haplotypes in **Supplementary Tables 2 and 3**. Of note, there was not a notable association between rs242557 and risk of PiD (OR: 0.94, 95% CI: 0.79-1.12, P=0.51, **Supplementary Table 2**).

In secondary analysis, an evaluation of associations between six-variant *MAPT* haplotypes and risk of PiD is displayed in **Table 2**. As with the single-variant analysis, the H2 haplotype was associated with an increased risk of PiD (OR: 1.34, 95% CI:1.11-1.63, P=0.0028); the slight difference between the two numerical estimates is due to the two different analysis approaches. Additionally, a nominally significant (P<0.05) protective association was noted for the rare H1f haplotype (0.0% in PiD, 1.2% in controls, P=0.049), with a slightly weaker finding noted for H1b (OR: 0.76, 95% CI: 0.58-1.00, P=0.051). There were no other notable associations between *MAPT* haplotypes and risk of PiD (all P≥0.15, **Table 2**).

	MAPT variant						Haplotype frequency (%)		Association with Pick's disease	
Haplotype	rs1467967	rs242557	rs3785883	rs2471738	rs8070723	rs7521	Pick's disease patients (N=338)	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	N/A[1]	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

Table 2: Associations between MAPT haplotypes and risk of Pick's disease.
ORs, 95% CIs, and p-values result from score tests of association that were adjusted for age and sex. [1]Indicates a haplotype that was not observed in Pick's disease patients, making estimation of an OR impossible. P-values <0.0028 are considered as statistically significant after applying a Bonferroni correction for multiple testing. OR=odds ratio; CI=confidence interval.

Associations of *MAPT* haplotypes with AAO and DD in PiD patients are shown in **Table 3**. None of the six-variant *MAPT* haplotypes were significantly associated with AAO or DD after correcting for multiple testing (P<0.0031 considered significant). However, nominally significant associations were observed with AAO for H1b (β: 2.66, 95% CI: 0.63 to 4.70, P=0.011), H1i (β: -3.66, 95% CI: -6.83 to -0.48, P=0.025) and H1u (β: -5.25, 95% CI: -10.42 to -0.07, P=0.048), and with a shorter DD for H1x (β: -3.73, 95% CI: -6.98 to -0.48, P=0.025).

		Association with age of disease onset		Association with disease duration	
Haplotype	Haplotype frequency (%), N=309	β (95% CI)	P-value	β (95% CI)	P-value
H1b	13.3%	2.66 (0.63, 4.70)	0.011	-0.03 (-1.07, 1.02)	0.96
H1c	10.0%	1.63 (-0.61, 3.86)	0.15	0.08 (-1.05, 1.22)	0.88
H1d	7.2%	0.79 (-1.79, 3.38)	0.55	-0.91 (-2.21, 0.39)	0.17
H1e	9.3%	0.52 (-1.94, 2.98)	0.68	0.52 (-0.72, 1.76)	0.41
H1h	4.0%	2.03 (-1.57, 5.64)	0.27	-0.45 (-2.27, 1.37)	0.63
H1i	4.1%	-3.66 (-6.83, -0.48)	0.025	-0.90 (-2.53, 0.72)	0.28
H1l	3.5%	-1.75 (-5.42, 1.92)	0.35	0.43 (-1.42, 2.28)	0.65
H1m	3.1%	-1.25 (-5.33, 2.84)	0.55	0.94 (-1.11, 3.00)	0.37
H1o	1.2%	0.05 (-6.91, 7.00)	0.99	0.03 (-3.47, 3.52)	0.99
H1p	1.0%	-5.65 (-12.60, 1.30)	0.11	0.17 (-3.36, 3.69)	0.93
H1u	2.2%	-5.25 (-10.42, -0.07)	0.048	-2.40 (-5.03, 0.22)	0.074
H1v	2.1%	-1.74 (-6.61, 3.13)	0.48	1.91 (-0.54, 4.35)	0.13
H1x	1.4%	-5.39 (-11.84, 1.07)	0.10	-3.73 (-6.98, -0.48)	0.025
H1y	1.5%	-0.70 (-6.93, 5.54)	0.83	1.82 (-1.31, 4.95)	0.26
H1z	1.6%	-1.81 (-8.02, 4.40)	0.57	-0.08 (-3.20, 3.05)	0.96
H2	29.4%	-0.62 (-2.03, 0.79)	0.39	0.22 (-0.49, 0.93)	0.54

Table 3: Associations of MAPT haplotype with age of disease onset and disease duration in Pick's disease cases.
β values, 95% CIs, and p-values result from score tests of association that were adjusted for sex and series (age of disease onset analysis) or sex, age of disease onset, and series (disease duration analysis). 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 <0.0031 are considered as statistically significant after applying a Bonferroni correction for multiple testing. β=regression coefficient; CI=confidence interval.

Discussion

PiD is a rare, predominantly sporadic 3R tauopathy that presents primarily as a behavioral or language variant of frontotemporal dementia (1-6). Little is known regarding the etiology or underlying pathobiology of the disease. To date, no genetic variation has been shown to associate with disease risk, although three cases with PiD or PiD-like pathology have been suggested to be caused by rare *MAPT* mutations (11-14). In the present study we have shown that the common *MAPT* H2 haplotype, strongly protective in 4R-tauopathy, is associated with an increased risk of PiD (3R tauopathy). This was only possible by establishing and creating a global consortium (PIC) to increase the number of available pathologically-defined PiD cases. Previous early genetic studies were underpowered with only 34 cases and 33 cases respectively (19, 20); a ten-fold increase in sample size was needed to establish *MAPT* H2 as a risk factor for in PiD.

Previous research in frontotemporal dementia linked to chromosome 17 with tau pathology (FTDP17t) has clearly demonstrated that mutations in the 5′ splice site of *MAPT* exon 10 can increase the incorporation of the exon into the mRNA and increase 4R isoform production, emphasizing how important exon 10 alternative splicing regulation is as dysregulation influences tangle formation and neurodegeneration outcome (16, 27). Given the association of *MAPT* H2 with a 3R-tauopathy, and its protection in 4R-tauopathy, it is possible that the *MAPT* H1 and H2 haplotypes increase the expression of 4R and 3R tau respectively. Previous studies have attempted to investigate the haplotype 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 (28-30). The genetic predisposition herein described would appear to support the hypothesis that the pathologic effects of the H1-H2 haplotypes is via isoform specific expression differences. This may have implications in the determination of therapeutic strategies that have focused on either overall lowering of tau expression or specifically targeting the lowering of 4R-tau or increasing 3R-tau isoforms. The overall balance of the 3R and 4R forms of tau would appear to be important for the primary tauopathies but does not in itself explain the mixed pathology observed in AD, although it is tempting to suggest an overall increased expression of total tau may be underlying the mixed pathology.

In addition to providing evidence that the *MAPT*-H2 haplotype is associated with an increased risk of PiD, we observed nominally significant associations that were observed with risk of PiD, AAO, and DD, however these will require validation. This study has strengths in the assembled large PiD series of patients and the direct genotyping of the H1-H2 haplotype, but there still remains several limitations which are important to note. The possibility of a type II error (i.e. false-negative finding) is important to consider, and we cannot conclude that there is no true association between a given haplotype and risk of PiD simply due to a non-significant p-value in this study. Additionally, we were

unable to regress out genetic principal components, and so it is possible that population stratification could have had an influence on our results. However, we used the case genetic principal components to exclude any cases of non-European ancestry and our control MAPT H1-H2 frequencies were in keeping with published data and the general population frequency, in fact the highest population control frequency in gnomAD is 23.8% very similar to our 23% (31). Ongoing studies looking at genome-wide disease associations in PiD with available genome-wide SNP data for controls support the current findings (data not shown).

In summary, PiD is a rare and understudied disease with a devastating impact on both patients and their families. Through collaboration and building of the PIC, we have for the first time a rare opportunity to engage in studies that may tease out the underlying pathobiology in PiD. As a primary tauopathy, there is the possibility that the identification of genetic variables, such as *MAPT* H2, involved in PiD pathology will inform on other more common tau-related disorders, PSP, CBD, and potentially AD. Larger scale unbiased studies to explore genome-wide or structural genetic variation in PiD are now warranted. Furthermore, resolving the genetic determinants of PiD may help in establishing diagnostic criteria and elucidating the dysfunctional pathways may direct future therapeutic intervention strategies.

Data sharing

The PIC have built a database that contains detailed demographic, clinical, and pathological information for deidentified participants with Pick's disease. Basic demographic information (e.g. age at onset, age at death, disease duration, sex, and ethnicity), family history, clinical history (e.g. behavioral and language impairments, presence of parkinsonism, upper and lower motor deficits, MMSE, and CDR), and pathological observations (e.g. 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 subject upon request. All requests must be submitted to Owen A. Ross (email: ross.owen@mayo.edu) or Jonathan Rohrer (email: j.rohrer@ucl.ac.uk).

Conflicts of Interest

M.A.N. and D.V.'s participation in this project was part of a competitive contract awarded to Data Tecnica International LLC by the National Institutes of Health to support open science research. M.A.N. also currently serves on the scientific advisory board for Character Bio Inc. and Neuron23 Inc.

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Author Contributions

RRV, WJS, RR, DD, JDR, JAH and OAR were involved in conceptualisation and design of study. RRV, WJS, SFR, TL, MGH and MS carried out the formal analysis including pathology review and statistical analysis. RV, WS and OAR wrote the original draft of manuscript. All authors were involved in funding acquisition, resources, validation, critically reviewing and approving final version of manuscript.

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