WP 5

Familial disease cohort **Start date: 1 June 2015.**				**Completion date: November 2019**
Overall work package objectives: To establish a familial disease discovery drawn from the UCL FAD (including DIAN), Familial FTD (including GENFI), HD (Track HD) and new LRKK2 cohorts to provide unique biomarker validation identifying disease specific and disease common biomarkers. 1. Access of familial cohorts not currently associated with DPUK will be scoped to clarify opportunities for synergy between familial and population based cohorts. 2. Comparison of familial case (HD, FAD, FTD, LRRK2) close to symptom onset and with premanifest evidence of atrophy, to assess proteomic profiles that may be common to all four diseases – this will link to WP6. This will also be an early study to establish the processes which allow access to the wider bioresources associated with these multi-national studies 3. c. Comparison of premanifest tau mutation carriers using AV1451 together with csf Aβ and tau. Reports of amyloid deposition in apo4 tau mutation cases allow analysis of the interaction of tau deposition with Aβ which can then be compared with familial and sporadic AD depending on emerging data of alternative tau ligands. (We are currently seeking support from Lilly for free access to the AV1451 ligand). 4. Aid recruitment to the nascent LRRK cohort 5. Validation studies of biomarkers identified in population cohort in WP3 (UK Biobank) and WP4 (1946 birth cohort). Validation study details (scientific content and timing) are dependent on the findings of WP3 and WP4. It is envisaged that validation studies will occur in years 4 and 5 of the project and that further funding will be sought.			**Dependencies to and from other work packages, networks and themes** N/A WP6 N/A N/A WP3 &WP4	
Deliverables	**Milestones**	**Milestone deadline**	**Work package dependencies**	**Person(s) responsible**
Objective 1:				
D1.1 Familial cohort access and governance arrangements in place	M1.1.1 Governance review	M1.1.1 Complete	None	Epie
	M1.1.2 Ethics achieved	M1.1.2 Complete		
	M1.1.3 Scoping exercise complete	M1.1.3 Complete		
Objective 2:				
D2.1 Comparison study complete	M2.1.1 Familial cohort sample drawn down for analyses	M2.1.1 Jan 2020	Dependency on WP6 (Biomarkers)	Lovestone, Rossor
	M2.1.2 Analyses finalised	M2.1.2 Jan 2020		Rossor
Objective 3:				
D3.1 Comparison study complete	M3.1.1 First through clinic	M3.1.1 Complete	None	Rossor
	M3.1.2 10 AV1451 scans in tau families complete.	M3.1.2 Complete		
Objective 4:				
D4.1 Increase cohort recruitment	M4.1.1 Individuals recruited	M4.1.1 Complete	None	Wood
Objective 5:				
D5.1 Validation studies complete	M5.1.1 Validation study protocol agreed	M5.1.1 Complete		

	M5.1.2 Study started M5.1.3 Study complete	M5.1.2 Complete M5.1.3 WP4 is achieved but not WP3.	Dependent on biomarker WP for any other assays	Schott, Rossor, Gallacher

Key updates on delivery against milestones since last report

Milestones continuing as planned

Team members <u>funded</u> (full or part-time) by DPUK

Stephanie Deriziotis, Dexter Penn

Team members involved with the project but <u>not</u> funded by DPUK

Martin Rossor, Suzie Barker, Jonathan Rohrer, Nick Fox

Summary of plans for the future

- Awaiting outputs from WP6
- Tau imaging in GENFI using additional external funding

Risks	Mitigation
1) Loss of data	1) A backup server is in place and hard copy backups of data are stored, when possible.
2) Delays in recruitment for longitudinal data collection	2) Regular team meetings to ensure recruitment is on track.
3) Issues with tracer availability for longitudinal data collection	3) We have regular discussions with suppliers to ensure tracer availability.
4) Lack of funding to continue the study to a third wave	4) Applications for funding from DPUK2 not successful

Outcomes

With the exception of (D5.1) all objectives will be met. The validation of biomarkers (Nfl – measurer) in WP4 is achieved but not WP3.

Publications:

1. Longitudinal (18F)AV-1451 PET imaging in a patient with frontotemporal dementia due to a Q351R MAPT mutation. Convery RS, Jiao J, Clarke MTM, Moore KM, Koriath CAM, Woollacott IOC, Weston PSJ, Gunn R, Rabiner I, Cash DM, Rossor MN, Warren JD, Fox NC, Ourselin S, Bocchetta M, Rohrer JD. J Neurol Neurosurg Psychiatry. 2019 Aug 22. [Epub ahead of print]

Mutations in the microtubule associated protein tau (MAPT) gene are a common cause of inherited frontotemporal dementia (FTD) and result in the deposition of pathological tau protein in the brain. Here we describe longitudinal (18F)AV-1451 PET imaging from a patient with FTD due to a Q351R mutation located on exon 12 of the MAPT gene.6

2. Jonathan Vöglein, Soheyl Noachtar, Eric McDade, Kimberly A. Quaid, Stephen Salloway, Bernardino Ghetti, James Noble, Sarah Berman, Jasmeer Chhatwal, Hiroshi Mori, Nick Fox, Ricardo Allegri, Colin L. Masters, Virginia Buckles, John M. Ringman, Martin Rossor, Peter R. Schofield, Reisa Sperling, Mathias Jucker, Christoph Laske, Katrina Paumier, John C. Morris, Randall J. Bateman, Johannes Levin, Adrian Danek. (2019). Seizures as an early symptom of autosomal dominant Alzheimer's disease. *Neurobiology of Aging*, *76*, 18-23. doi:10.1016/j.neurobiolaging.2018.11.022

This paper assessed the reported history of seizures in cognitively asymptomatic mutation carriers for autosomal dominant Alzheimer's disease (ADAD) and the predictive value of seizures for mutation carrier status in cognitively asymptomatic first-degree relatives of ADAD patients. Among cognitively asymptomatic ADAD family members, the occurrence of seizures increases the a priori risk of 50% mutation-positive status to about 80%. This finding suggests that ADAD mutations increase the risk of seizures.

3. Franzmeier, N., Ren, J., Damm, A., Monté-Rubio, G., Boada, M., Ruiz, A., . . . Ewers, M. (2019). The BDNFVal66Met SNP modulates the association between beta-amyloid and hippocampal disconnection in Alzheimer's disease. *Mol Psychiatry*. doi:10.1038/s41380-019-0404-6

This study suggests that $BDNF_{Val66Met}$ is selectively associated with a higher vulnerability of hippocampus-frontal connectivity to primary AD pathology, resulting in greater AD-related cognitive impairment. The effect of $BDNF_{Val66Met}$ on functional networks that may underlie cognitive impairment in AD is poorly understood. Using a cross-validation approach, we first explored in subjects with autosomal dominant AD (ADAD) from the Dominantly Inherited Alzheimer Network (DIAN) the effect of $BDNF_{Val66Met}$ on resting-state fMRI assessed functional networks.

4. Jonathan Vöglein, Katrina Paumier, Mathias Jucker, Oliver Preische, Eric McDade, Jason Hassenstab, Tammie L Benzinger, James M Noble, Sarah B Berman, Neill R Graff-Radford, Bernardino Ghetti, Martin R Farlow, Jasmeer Chhatwal, Stephen Salloway, Chengjie Xiong, Celeste M Karch, Nigel Cairns, Hiroshi Mori, Peter R Schofield, Colin L Masters, Alison Goate, Virginia Buckles, Nick Fox, Martin Rossor, Patricio Chrem, Ricardo Allegri, John M Ringman, Günter Höglinger, Harald Steiner, Marianne Dieterich, Christian Haass, Christoph Laske, John C Morris, Randall J Bateman, Adrian Danek, Johannes Levin. Clinical, pathophysiological and genetic features of motor symptoms in autosomal dominant Alzheimer's disease, *Brain*, , awz050, https://doi.org/10.1093/brain/awz050

This study assessed the prevalence and characteristics of motor signs in autosomal dominant Alzheimer's disease. Motor symptoms were explored with respect to associations with mutation carrier status, mutation site within PSEN1, basal ganglia amyloid-β as measured by Pittsburgh compound B PET, estimated years to symptom onset and Clinical Dementia Rating Scale-Sum of Boxes. With a prevalence of approximately 30% and increasing severity with progression of dementia, motor symptoms are proven as a clinically relevant finding in autosomal dominant Alzheimer's disease, in particular in advanced dementia stages that correlates with deposition of amyloid-β in the basal ganglia.

5. Oliver Preische, Stephanie A. Schultz, Anja Apel, Jens Kuhle, Stephan A. Kaeser, Christian Barro, Susanne Gräber, Elke Kuder-Buletta, Christian LaFougere, Christoph Laske, Jonathan Vöglein, Johannes Levin, Colin L. Masters, Ralph Martins, Peter R. Schofield, Martin N. Rossor, Neill R. Graff-Radford, Stephen Salloway, Bernardino Ghetti, John M. Ringman, James M. Noble, Jasmeer Chhatwal, Alison M. Goate, Tammie L. S. Benzinger, John C. Morris, Randall J. Bateman, Guoqiao Wang, Anne M. Fagan, Eric M. McDade, Brian A. Gordon, Mathias Jucker, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nature Medicine. 2019 Jan 31; 25:277-283. doi: 10.1038/s41591-018-0304-3

Validates the initial observations that Neurofilament light chain (NfL) is a promising fluid biomarker for disease progression for various cerebral proteopathies. Using the DIAN cohort and an ultrasensitive immunoassay demonstrates that NfL in CSF and serum are elevated in the presymptomatic stages of familial AD. The rate of change in serum NfL is more informative than cross-sectional absolute NfL levels, detecting changes in a timeline of 16.2 years versus 6.8 years before symptom onset. The increased rate of change in NfL was strongly associated with cortical thinning measurements determined by MRI but less with amyloid-β-deposition or glucose metabolism via PET. Overall, this important paper demonstrates that NfL dynamics in serum predict disease progression and neurodegeneration at the early presymptomatic stages of familial AD and is a potentially useful biomarker.

6. Müller, S., Preische, O., Sohrabi, H. R., Gräber, S., Jucker, M., Ringman, J. M., Dominantly Inherited Alzheimer Network (DIAN). (2018). Relationship between physical activity, cognition, and Alzheimer pathology in autosomal dominant Alzheimer's disease. Alzheimers Dement. doi:10.1016/j.jalz.2018.06.3059

Little is known about effects of physical activity (PA) in genetically driven early-onset autosomal dominant Alzheimer's disease (AD). A total of 372 individuals participating at the Dominantly Inherited Alzheimer Network study were examined to evaluate the cross-sectional relationship of PA with cognitive performance, functional status, cognitive decline, and AD biomarkers in cerebrospinal fluid. Mutation carriers were categorized as high or low exercisers according to WHO recommendations. Mutation carriers with high PA showed significantly better cognitive and functional performance and significantly less AD-like pathology in cerebrospinal fluid than individuals with low PA. Mutation carriers with high PA scored 3.4 points better on Mini Mental State Examination at expected symptom onset and fulfilled the diagnosis of very mild dementia 15.1 years later compared with low exercisers. These results support a beneficial effect of PA on cognition and AD pathology even in individuals with genetically driven autosomal dominant AD.

7. Ángel Araque Caballero, M., Suárez-Calvet, M., Duering, M., Franzmeier, N., Benzinger, T., M Fagan, A., Ewers, M. (2018). White matter diffusion alterations precede symptom onset in autosomal dominant Alzheimer's disease. Brain. doi:10.1093/brain/awy229

Here, we assessed mean diffusivity alterations in the white matter in 64 mutation carriers compared to 45 non-carrier family non-carriers. Using tract-based spatial statistics, we mapped the interaction of mutation status by estimated years from symptom onset on mean diffusivity. The earliest increase of mean diffusivity was observed in the forceps major, forceps minor and long projecting fibres-many connecting default mode network regions-between 5 to 10 years before estimated symptom onset. Higher mean diffusivity in fibre tracts was associated with lower grey matter volume in the tracts' projection zones. Results suggest that regionally selective white matter degeneration occurs years before the estimated symptom onset. Such white matter alterations are associated with primary Alzheimer's disease pathology and microglia activity in the brain.

8. McDade, E., Wang, G., Gordon, B. A., Hassenstab, J., Benzinger, T. L. S., Buckles, V, Dominantly Inherited Alzheimer Network. (2018). Longitudinal cognitive and biomarker changes in dominantly inherited Alzheimer disease. Neurology. doi:10.1212/WNL.0000000000006277

To assess the onset, sequence, and rate of progression of comprehensive biomarker and clinical measures across the spectrum of Alzheimer disease (AD) using the Dominantly Inherited Alzheimer Network (DIAN) study and compare these to cross-sectional estimates. We conducted longitudinal clinical, cognitive, CSF, and neuroimaging assessments (mean of 2.7 [±1.1] visits) in 217 DIAN participants. Linear mixed effects models were used to assess changes in each measure relative to individuals' estimated years to symptom onset and to compare mutation carriers and noncarriers. Longitudinal β-amyloid measures changed first (starting 25 years before estimated symptom onset), followed by declines in measures of cortical metabolism (approximately 7-10 years later), then cognition and hippocampal atrophy (approximately 20 years later). There were significant differences in the estimates of CSF p-tau181 and tau, with elevations from cross-sectional estimates preceding longitudinal estimates by over 10 years; further, longitudinal estimates identified a significant decline in CSF p-tau181 near symptom onset as opposed to continued elevations. These longitudinal estimates clarify the sequence and temporal dynamics of presymptomatic pathologic changes in autosomal dominant AD, information critical to a better understanding of the disease. The pattern of biomarker changes identified here also suggests that once β-amyloidosis begins, additional pathologies may begin to develop less than 10 years later, but more than 15 years before symptom onset, an important consideration for interventions meant to alter the disease course.

9. Franzmeier, N., Düzel, E., Jessen, F., Buerger, K., Levin, J., Duering, M., Ewers, M. (2018). Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease. Brain: a journal of neurology. doi:10.1093/brain/awy008

Patients with Alzheimer's disease vary in their ability to sustain cognitive abilities in the presence of brain pathology. Higher functional MRI-assessed functional connectivity of a hub in the left frontal cortex is a core candidate brain mechanism underlying reserve as it is associated with education (i.e. a protective factor often associated with higher reserve) and attenuated cognitive impairment in prodromal Alzheimer's disease. However, no study has yet assessed whether such hub connectivity of the left frontal cortex supports reserve throughout the evolution of pathological brain changes in Alzheimer's disease, including the presymptomatic stage when cognitive decline is subtle. Our findings suggest that higher resilience against the development of cognitive impairment throughout the early stages of Alzheimer's disease is at least partially attributable to higher left frontal cortex-hub connectivity.

Project narrative

The DPUK team at UCL has been working with small cohorts of people with the rare familial forms of dementia. Detailed studies of disease progression in these cohorts allows scientists new insights that can then be tested in the larger cohorts.

Working with these small familial disease cohorts, the UCL team found that neurofilament concentrations in CSF can function as a useful sign of neurodegeneration. This is now being considered for inclusion in clinical trials of treatment.

The overarching goal of WP5 has been the integration and facilitation of collaborative projects within DPUK familial disease cohorts. WP5 has facilitated contractual arrangements between Swansea and the familial cohort with data transfers to Swansea for Huntington's disease and fronto-temporal dementia cohorts already commenced.

The second objective of the group was to explore proteomic biomarkers of familial dementia cases and neurofilament light (NFL) was identified as a promising unifying feature. A pilot study in familial Alzheimer's disease by the group reported that NFL concentrations differentiated between PSEN1/APP mutation carriers and non-carriers (doi: 10.1212/WNL.0000000000004667). Analysis of 502 NFL samples in the 1946 cohort is underway as well as a consultation with other cohorts on pooling samples for

wider NFL testing. The third objective of the group was to explore tau pathology in pre-manifest tauopathy. Using DPUK funding WP5 has completed 12 tau scans in GENFI and supported tau scanning in FAD (20 cross-sectional and 13 longitudinal) in the 12 scans. Total UK GENFI recruitment is now 115. A fourth goal of WP5 was to support recruitment in the LRRK2 cohort - genotyping is nearly complete on the 436 subjects.

Efforts by the UCL team led by Martin Rossor have succeeded in enhancing the number of familial cohorts associated with DPUK and available for studies. The team have worked across the familial AD (FAD), frontotemporal (FTD) and Huntington's disease (HD) cohorts to show first Neurofilament Light (NfL) measured in CSF was a biomarker of neurodegeneration and then to extend NfL measurements to blood using an ultrasensitive assay. Serum NfL was shown to be increased up to ten years before onset in presymptomatic FAD mutation carriers and to correlate with disease intensity in the FTD cohort. Plasma NfL predicts clinical onset in the HD cohort and correlates with cognitive and brain atrophy measures. NfL is now being considered for inclusion in clinical trials in all these disorders. Further funding has been achieved to extend this biomarker work – with a number of grants and fellowships. [1,2]

In FAD a novel marker of cognitive decline (accelerated forgetting) was shown to detect change in presymptomatic carriers significantly earlier than conventional measures – as a result this test is now being considered for inclusion in a major international study. The group has been productive in their research outputs publishing papers in high profile journals including Lancet Neurology. The team has also been major contributors to GENFI, an international multicentre cohort study investigating genetic forms of FTD. The focus has been the development of biomarkers and batteries of tests with further work on trials of novel therapies planned in conjunction with pharma companies.

A no cost extension also supported the additional study of HSV-1 reactivation in the DIAN cohort. This is to test the hypothesis that HSV reactivation may occur due to Alzheimer's pathology and exacerbate the neurodegeneration. A total of 387 individuals have had HSV titres determined are we are awaiting rates of brain atrophy measures.

[1] "Developing blood based biomarkers to detect preclinical Alzheimer's disease and predict progression" was accepted for funding from the Weston Brain Institute Novel Biomarkers 2017 program – PI J Schott

[2] "DRI-DRC clinical research: from patient to bench and back." - £600K – PI N Fox