A rare genetic variant in the PLCG2 gene is associated with a reduced risk of all major types of dementia and an increased risk to reach an extremely old age

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Table 1
DLB v non-DLB diagnostic pathways

	DLB	Non-DLB	Statistic (student's t-test)	p-value
Number of diagnoses before final diagnosis	1.1	0.6	2.97	0.003
Time between first secondary care appointment and final diagnosis (years)	1.2	0.6	2.42	0.017
Number of imaging tests before final diagnosis (including DAT scans)	1.7	1.2	3.09	0.002
Number of clinical assessments at home before final diagnosis	3.9	1.8	2.31	0.02
Number of clinic appointments before final diagnosis	2.6	1.5	1.45	0.15

Table 2
Regional variation in DLB diagnoses

	North East	East Anglia	Statistic	p-value
Core features of DLB at time of diagnosis (mean)	1.5	2.1	-2.78 (student's t-test)	0.007
Suggestive features of DLB at Time of diagnosis, including DAT scans (mean)	0.8	0.4	2.63 (student's t-test)	0.011
Abnormal DAT scans prior to diagnosis	24	1	12.9 (chi squared)	0.001
DAT scans prior to diagnosis (including normal)	31	1	20.6 (chi squared)	<0.001
Total diagnostic features (core and suggestive) of DLB at time of diagnosis	2.4	2.6	-0.80 (student's t-test)	0.42
Time between first secondary care appointment and final diagnosis (years)	1.4	0.9	1.03 (student's t-test)	0.31

Table 3
PDD v PD differences

	PDD	PD	Statistic (chi squared)	p-value
Visual hallucinations	86%	28%	22.9	<0.001
REM sleep behaviour Disorder	53%	33%	2.49	0.12
Cognitive fluctuation	75%	11%	22.8	<0.001
One or more carer stress events	59%	29%	3.00	0.22

O5-03-06 EGOCENTRIC SPATIAL NAVIGATION IMPAIRMENT IS MORE PRONOUNCED IN AMYLOID POSITIVE MCI PATIENTS: PILOT DATA FROM THE CZECH BRAIN AGEING STUDY

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Background: Spatial navigation (SN) is impaired early in the course of Alzheimer's disease, (AD). However, SN studies with biomarker-defined preclinical and prodromal AD are lacking. SN can be divided into two basic components, which depend on different brain structures - navigation using position of the body (egocentric; parietal lobe dependent) and a distant orientation cues (allocentric; medial temporal lobe structures dependent). The aim of the study was to compare differences in these spatial navigation components in biomarker well-defined participants with mild cognitive impairment (MCI). **Methods:** 22 participants with MCI underwent MRI, neuropsychological assessment, flutemetamol PET and computer and real-space versions of the human analog of the Morris Water Maze task (Hidden Goal Task), which allows for measurement of allocentric and egocentric SN components. PET was evaluated visually and the results were used to dichotomize the cohort in two groups: amyloid negative (n=11) and amyloid positive (n=11). Participants with confluent vascular changes were excluded. **Results:** The groups did not differ in age, sex, education or MMSE. In the egocentric SN test, the amyloid negative group had more accurate performance than the amyloid positive group in both computer ($F_{2,75}$=4.49; p=0.047) and real-space ($F_{2,75}$=4.94; p=0.038) versions. In the allocentric SN test, we did not find any differences between the groups. **Conclusions:** Our results show that impairment of the egocentric SN in both computer and real-space versions of the test is more pronounced in amyloid positive MCI patients. The use of biomarkers can elucidate potential of SN as a screening tool for AD.

ORAL SESSIONS
O5-04
GENETICS FOR ALZHEIMER'S AND OTHER DEMENTIA

O5-04-01 A RARE GENETIC VARIANT IN THE *PLCG2* GENE IS ASSOCIATED WITH A REDUCED RISK OF ALL MAJOR TYPES OF DEMENTIA AND AN INCREASED RISK TO REACH AN EXTREMELY OLD AGE

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Background: The genetic variant rs72824905-G(p.Pro522Arg) in the *PLCG2* gene(Phospholipase C Gamma 2) was previously found to associate with a reduced risk of Alzheimer's disease (AD). We hypothesized that the variant might reduce the risk of other neurodegenerative diseases as *PLCG2* plays an important role in innate immune system signaling, and is expressed in microglial cells in brain. Therefore, we tested if the variant associated with a reduced risk of Fronto-temporal Dementia(FTD), Lewy-body dementia (LBD), Progressive Supranuclear Palsy(PSP), Parkinson's Disease(PD) and Amyotrophic Lateral Sclerosis(ALS). Additionally, we investigated if carriers had an increased risk to reach extreme ages in good cognitive health. **Methods:** We determined rs72824905-G genotypes in 2,129 AD, 2,273 FTD patients, 1,075 LBD patients, 625 PSP patients all from European descent(consortia in author list). We genotyped 464 nonagenarians and 268 self-reported cognitively healthy centenarians. Patients and aged cases were compared with population-matched controls(N_{max}=10,891). Cohorts were analyzed using the score test and if necessary cohorts were meta-analyzed in R with the 'SeqMeta' package. One-sided p-values are reported. Association results were extracted from existing meta-analyses of 6,248 PD patients(6,031 controls) and 10,953 ALS patients(20,673 controls). **Results:** We replicated the protective effect of rs72824905-G on AD(OR=0.49; 95%CI 0.33-0.73, $P=2.5\times10^{-4}$), and we found a similar protective effect on FTD, LBD and PSP(aggregate OR=0.65; 95%CI 0.49-0.86, $P=1.4\times10^{-3}$). The effect was comparable for FTD(OR=0.66, 95%CI 0.48-0.90, $P=4.8\times10^{-3}$), LBD(OR=0.64, 95%CI 0.35-1.19, P=0.08) and PSP(OR=0.71, 95%CI 0.29-1.74, P=0.26). There was no significant effect in the large meta-analysis of PD(OR=0.79, 95%CI 0.56-1.12, P=0.10) or ALS(OR=1.07, 95%CI 0.87-1.33, P=0.26). Lastly, we considered the effect on extreme aging. Carriers of rs72824905-G had 1.65-fold(95%CI 0.91-2.99, $P=4.8\times10^{-2}$) increased chance to become a nonagenarian and 3.2-fold(95% CI 1.49-6.95, $P=1.4\times10^{-3}$) increased chance to become a cognitively healthy centenarian. **Conclusions:** The amino acid substitution Pro522Arg in *PLCG2* reduces the risk of AD and non-AD dementias, as well as increase the risk to reach extreme ages. No evidence of association with PD and ALS was found, despite large sample sizes. We speculate that an improved immune response as consequence of this variant in the *PLCG2* gene makes the brain resilient to neurodegenerative processes leading to dementia.

O5-04-02 RARE CODING MUTATIONS ASSOCIATED WITH ALZHEIMER DISEASE AND OTHER DEMENTIAS

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Background: Much of the unexplained heritability of Alzheimer disease (AD) may be due to rare variants whose effects are not captured in genome-wide association studies. We applied a strategy focused on rare variants occurring only in cases or controls. **Methods:** The AD Sequencing Project performed whole-exome sequencing on non-Hispanic white elders (5617 AD cases, 4594 controls). In 110 genes previously associated with AD or dementia, minor alleles of rare variants occurring only in AD cases or controls were tabulated. Top findings were explored with bioinformatics analyses and protein homology modeling. **Results:** *NOTCH3* rs149307620 had the largest number of minor alleles in only AD cases (n=10). *NOTCH3* has been associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a diagnostically distinct disorder from AD, marked by severe headaches in young adulthood and stroke and dementia later in life. A genetic link between AD and *NOTCH3* has not been established, except for a single report of a distinct *NOTCH3* mutation shared by several AD-affected members of one family. Seven cases with rs149307620 and available clinical or autopsy data displayed classic AD symptoms with progressive memory loss, moderate to severe amyloid and tau pathology at autopsy and no evidence of stroke or severe microvascular disease. The mutation is found in the EGF protein domain near the JAG1-NOTCH3 binding site.