A nonsynonymous mutation in PLCG2 reduces the risk of Alzheimer's disease, dementia with Lewy bodies and frontotemporal dementia, and increases the likelihood of longevity.

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Abstract

Background: *PLCG2* plays an important role in immune system signaling, and is expressed in several immune cell types including the microglial cells in the brain. In 2017, the genetic variant rs72824905 (p.Pro522Arg) in the *PLCG2* gene (Phospholipase C Gamma 2) was associated with a reduced risk of Alzheimer's disease (AD). Here we investigated whether the rs72824905 variant had a similar protective effect on six other brain diseases. We further tested if rs72824905 increases the likelihood of longevity, since a reduced risk of neurodegenerative diseases might associate with general survival.

Methods: We investigated the effect of carrying rs72824905 on disease risk in a total of 35,237 patients with one of seven brain diseases. We studied AD (N = 4,985), frontotemporal dementia (FTD) (N = 2,437), Lewy-body dementia (DLB) (N = 1,446), progressive supranuclear palsy (PSP) (N = 882), Parkinson's disease (PD) (N = 10,058) amyotrophic lateral sclerosis (ALS) (N = 10,953) and multiple sclerosis (MS) (N = 4,476) by comparing them with in total 48,315 controls using logistic regression models. Next, we studied the effect of carrying rs72824905 on longevity by comparing individuals who reached at least 90 years (N = 3,516) with individuals who died before age 90 years or were last screened before 90 years (N = 9,677). In addition, we studied the association of rs72824905 with survival after the age of 90 in a subset of long-lived individuals followed until death. Finally, we supported our findings by studying by-proxy phenotypes in the ~450.000 participants of the UK-biobank. We associated the rs72824905 genotypes of UK Biobank participants with parental history of dementia as proxy for dementia and as a proxy for longevity we studied parental age over 90 as well as parental age over 95 years of age. All individuals were from European ancestry.

Results: The rs72824905-G genotype associated with a reduced AD risk (Odds ratio (OR) = 0.57, $p = 4.7.2\times10^{-4}$), a reduced DLB risk (OR = 0.54, $p = 4.5\times10^{-2}$) and reduced FTD risk (OR = 0.61, $p = 1.0\times10^{-2}$). We did not find evidence for association of rs72824905 with the risks of PSP (OR = 1.46, $p = 0.19$), PD (OR = 1.18, $p = 0.10$), ALS (OR = 1.07, $p = 0.26$) and MS (OR = 0.99, $p = 0.95$). The rs72824905-G genotype was associated with a 1.49-fold increased likelihood of reaching >90 years ($p = 6.4\times10^{-3}$): variant carriers lived longer after the age of 90 years, median 4.7 (inter quartile range = 1.9 - 7.4) years compared to non-carriers 3.3 (IQR = 1.4 - 5.8) (Hazard ratio = 0.75, $p = 0.07$). By-proxy analyses supported the associations of rs728824905 with dementia as well as longevity. Variant carriers have a lower likelihood to have a parent with dementia (OR = 0.88, $p = 1.8\times10^{-3}$) and had a

significantly increased likelihood of having a parent aged >95 years (OR = 1.19, $p = 2.1\times10^{-2}$).

Conclusions: Our results show that rs72824905 in *PLCG2* protects from AD, DLB, FTD dementia and increases the likelihood of longevity. Together, our findings highlight a central role for *PLCG2* related immune signaling in the brain, that should be subject of future studies as drug target for multiple brain diseases.

Introduction

The protein product of the phospholipase Cγ2 (*PLCG2*) gene is involved in the transmembrane transduction of immune signals [1-3] that determine the fate and function of various immune cell types, both in the periphery and the brain.[2,3] It is known that gain-of-function mutations in the *PLCG2* gene cause autoimmune disorders [4-7] and resistance to treatment of chronic lymphocytic leukemia.[8]

In 2017, a genome wide association study (GWAS) of Alzheimer's disease (AD) showed that the rare nonsynonymous variant in the *PLCG2* gene (rs72824905; p.Pro522Arg; NC_000016.9:g.81942028C>G) reduced AD risk (OR = 0.68, $p = 5.4\times10^{-10}$).[9] Both in mouse and human brain tissues, *PLCG2* has been shown to be overexpressed >6-log fold in microglia compared to other brain cells.[10] Since microglia are the immune cells in the brain, these findings suggest an important role for *PLCG2* in the brain immune response. Next to *PLCG2,* GWAS studies of AD identified multiple other immune and microglia related genes that associate with AD (e.g. the triggering receptor expressed on myeloid cells 2 (TREM2) gene). Pathway analysis based on these same GWAS studies indicate that the immune system plays a key role in the development of Alzheimer's disease.[9] Likewise, human genetic studies imply the immune system plays a role in other neurodegenerative diseases such as frontotemporal dementia (FTD),[11] Parkinson's disease (PD)[12], and multiple sclerosis (MS).[13-15] We reasoned that next to AD, *PLCG2* related immune signaling may be involved in the etiology of these other neurodegenerative diseases. This led us to question whether the rs72824905 variant in *PLCG2* is also associated with a reduced risk of other neurodegenerative diseases.

Here we tested if rs72824905 protects for other neurodegenerative diseases. We first tested whether rs72824905 associates with reduced risk of AD, FTD, dementia with Lewy-bodies (DLB), progressive supranuclear palsy (PSP), PD, amyotrophic lateral sclerosis (ALS) and MS. Since a reduced risk of neurodegenerative diseases could lead to an increased survival to old age, we tested whether rs72824905 increases the likelihood of longevity.

Methods

Study populations and genotyping

We present a short description of 16 cohorts, often including multiple sites or studies, that contributed to this manuscript in **Supplementary Table 1**. Studies were approved by

corresponding ethics committees and informed consent was obtained for all participants (**Supplementary Table 1**). Study characteristics (age, percentage female, apolipoprotein E (APOE) status and age) are described in **Supplementary Table 2**. We determined rs72824905 genotypes (NC_000016.9:g.81942028C>G, p.Pro522Arg) using direct genotyping with a variety of genotyping arrays or TaqMan genotyping. If direct genotyping was not available we used imputation to 1000 Genomes phase I version 3 [16] or the Haplotype Reference Consortium (HRC) reference panels.[17] Details on genotyping or imputation by study can be found in **Supplementary Table 3**. We only studied participants from European descent.

Study populations of AD, FTD, DLB and PSP patients

We compared rs72824905 genotypes of in total 4,958 AD patients and 8,492 controls from eight cohorts. All samples were independent from Sims *et al.*[9]. We compared in total 2,437 FTD patients with 10,647 controls from four studies and two consortia. Further, we studied 1,444 DLB patients with 5,286 controls from five cohorts and 882 PSP patients and with 3,187 controls from five cohorts. Details on sample size by cohort and which cohort contributed to which analysis can be found in **Supplementary table 2**.

Study populations of ALS, PD and MS patients

To study the association of rs72824905 with ALS, PD and MS we obtained summary statistics from existing GWAS meta-analyses, see **Supplementary Table 1, 2 and 3** for study descriptions. We present results of a combined total of 10,058 PD patients that were compared with 8,258 controls: data from 9,205 PD patients and 6,771 controls from the International Parkinson Disease Genomics Consortium (IPDGC)[18] was combined with data from 853 PD patients and 1,487 controls from the MAYO clinic. Furthermore, we studied 10,953 ALS patients and 20,673 controls, which represents the subset of the data presented by van Rheenen *et al.*[19], for which rs72824905 was imputed with sufficient quality (imputation quality >0.3). Last, we studied 4,476 MS patients and 5,714 controls which were previously described by Dankowski *et al.*[20]

Study populations of longevity

We investigated the association of rs72824905 with longevity in 5 different cohorts, in total we compared 3,516 individuals who reached at least 90 years with 9,677 controls individuals who died before age 90 years or were last screened before 90 years (**Supplementary table 1, 2 and 3**). A subset of 1,136 Dutch long-lived individuals there was follow-up data until

death was available.[21] In this subset we compared the survival of carriers of rs72824905-G with non-carriers.

Studies of dementia and longevity by-proxy in the UK biobank

The UK biobank is a study of genetic and health of a half million people from the United Kingdom.[22] Information from parents or first-degree relatives can be used as a proxy-phenotype for the participants.[23] In this study we used maternal and paternal history of Alzheimer's/dementia as proxy for dementia[23,24] and the reported age of the parents (at completing the survey or death) as proxy phenotype for longevity.[25] In the UK biobank the rs72824905 variant was imputed using the available genotyping arrays and the HRC-reference panel as previously described.[26] The maternal and paternal by-proxy phenotypes were analyzed separate using genotypes of the participants and the results were meta-analyzed.

We compared rs72824905 genotypes of 32,262 participants whose mother was reported to have dementia with the genotypes of 346,999 participants whose mothers did not have dementia. Likewise, we compared 16,968 participants whose father had dementia with 358,468 whose fathers did not have dementia. For the analysis of longevity-by-proxy we chose the age of 90 years as a cut-off for the minimum age reached by the parents. By-proxy analyses are prone to dilution of effect,[23,24] therefore a more extreme parental age cut-off of 95 years was studied as well. In this analysis we compared 35,256 UK-biobank participants who had a mother who reached at least 90 years (7,790 mothers reached the age of 95 years) with 342,810 participants whose mother did not reach 90 years of age. Likewise, we compared 17,558 UK-biobank participants with a father who reached at least 90 years (3,043 fathers reached the age of 95 years) with 353,100 participants whose father was under 90 years old.

Statistical analysis

R (version 3.5.1) was used for all analysis.[27] Logistic regression models were fitted within studies to assess the association of rs72824905 with AD, FTD, DLB, PSP patients and long-lived individuals, compared to controls. For each study we calculated the odds ratio's (OR) and 95% confidence intervals (CI). Since covariates that account for population stratification were not available for all studies, we accounted for population substructure by comparing cases and controls from the same study or country of origin. We meta-analyzed the effect estimates (log(OR)) from the studies using inverse-variance fixed-effect meta-analyses (R-package 'rmeta' v3.0). The fraction of variance that is due to heterogeneity was estimated by the I^2 statistic.[28] We visualized survival of rs72824905-G carriers compared to non-carriers

using Kaplan-Meier curves. Differences in survival were tested using a Cox proportional hazards model correcting for (age at inclusion, sex and relatedness).

For MS the results originate from a single study, which used ancestry principal components (PCs) to adjust for population stratification.[20] The statistical methods of the GWAS meta-analyses of ALS and PD were previously described [18,19] In short, individual cohorts calculated logistic regression models and then summary statistics of cohorts were combined using inverse-variance fixed-effect meta-analyses. PCs were used to adjust for population stratification. Analysis in the UK biobank were performed using logistic regression models adjusted for genotyping array and the first 12 PCs. Effect estimates of the paternal and maternal analysis were combined using inverse-variance fixed-effect meta-analysis (R-package 'rmeta' v3.0). We reported two-sided *p*-values and considered *p*-values < 0.05 as significant.

Power analysis

For all diseases studied we performed power analysis using the online tool Genetic Association Study (GAS) power Calculator implementing the methods described in Skol *et al*. [29]. We calculated power of our analysis to attain a *p*-value of 0.05 and used the total number of cases and controls from our analysis. We assumed an additive model, a minor allele frequency of 0.009 and a disease frequency of 0.01 for all diseases (higher disease frequency assumption would lead to higher power estimates). We report the power for an OR between 1 and 2. This corresponds to protective OR (the inverse OR=1/OR) between 0.50 and 1.

Results

Association with brain diseases

We replicated the association of rs72824905 in *PLCG2* with a reduced AD risk (OR = 0.57, $p = 4.7\times10^{-4}$, $I^2 = 0\%$). In addition, we found that rs72824905 associated with a reduced risk of both DLB (OR = 0.54, $p = 0.045$, $I^2 = 0\%$) and FTD (OR = 0.66, $p = 0.010$, $I^2 = 0\%$). In contrast, we found no evidence that rs72824905 associated with PSP (OR = 1.46, $p = 0.19$, $I^2 = 0\%$), ALS (OR = 1.07, $p = 0.52$, $I^2 = 0\%$), PD (OR = 1.18, $p = 0.10$, $I^2 = 0$) and MS (OR = 0.99, $p = 0.95$). The association of rs72824905 with these seven brain diseases is shown in **Figure 1**. In **Supplementary Figures 1-6** we show the association estimates for each study separately in the meta-analyses for AD, DLB, FTD, PSP, ALS and PD (The MS study consisted of a single study).

Association with longevity

In line with a reduced risk of neurodegenerative diseases, we found that rs72824905 associated with a 1.49 (95%CI 1.12-1.98) increased likelihood (p = 6.3×10^{-3}, I^2 = 0%) to reach the age of 90 years. Although no heterogeneity was observed between studies, it is of interest that a cohort of centenarians who were selected based on being 100 years old *and* cognitively healthy (description of '100-plus Study' in **Supplementary table 1**) was most enriched with rs72824905 (OR = 2.26-fold, 95%CI 1.29-3.97, p = 4.3×10^{-3}) (**Supplementary figure 7**). Next, we tested whether carrying the rs72824905 variant was associated with longer survival after the age of 90 years in 1,136 Dutch long-lived individuals of which 96.3% were followed until death (median age at inclusion 93.2, IQR 91.6 - 95.0 years, 63% female; mean survival after inclusion was 3.3 years; inter quartile range (IQR) 1.4-5.8 years). We find that 28 carriers survived median of median 4.7 years (IQR = 1.9 - 7.4) while 1108 non-carriers survive a median of 3.3 years (IQR = 1.4 - 5.8) (**Supplementary figure 8**). However, when tested the difference was not significant (HR 0.75, 95%CI 0.51-1.09, p = 0.078), likely due to the low number of rs72824905 carriers in the analysis, as a consequence of variant rareness (MAF ~1%).

Association with by-proxy dementia and longevity

In line with the protection against AD, the by-proxy analysis showed that the risk to have a parent with dementia was OR = 0.88 (0.81-0.95, p = 1.9×10^{-3}) for carriers of the *PLCG2* variant (**Figure 2**). Next, we tested the association of rs72824905 with longevity-by-proxy. The rs72824905 variant did not significantly increase the likelihood of having a parent who reached at least 90 years (OR = 1.05, p = 0.24). However, carriers did have an increased likelihood of having a parent that reached the age of 95 years (OR = 1.19, p = 2.1×10^{-2}).

Power analysis

Power analysis (**Supplementary Figure 9**) showed that the PD, MS and ALS analysis had adequate statistical power (power >0.8) to detect an protective association (p = 0.05) with an OR~0.68 (the OR for AD reported in Sims et al.[9]). The PSP analysis had the lowest statistical power (0.32 if the expected OR=0.67)

Discussion

The p.Pro552Arg (or rs72824905) nonsynonymous amino acid change in PLCG2 was shown to protect from Alzheimer's disease risk. We replicated this protective effect in independent

AD patients and controls and found that the variant also protected from FTD and DLB. In contrast, we found no evidence for an association of rs72824905 with PSP, ALS, PD and MS. In addition, we found that rs72824905 associated with increased likelihood of longevity. This finding fits with the fact that dementia is the leading cause of death at high age[30] and that we found a protective effect of rs72824905 for the major causes of dementia (AD, DLB and FTD). Indeed, the strongest effect of PLCG2 variant was observed in cognitively healthy centenarians, individuals in which the absence of dementia and extreme longevity is combined. Our findings in patient cohorts were supported by analyses of by-proxy phenotypes for dementia and longevity in the UK-Biobank. Taken together the association of the rs72824905 variant with a decreased risk of multiple dementia types and the increased risk of longevity, warrants thorough investigation of the molecular mechanisms underlying this protective effect.

Thus far the *APOE* ε4 allele is the only genetic factor that has a strong effect on the risk of AD, DLB and FTD. [9,31,32] The HLA-locus and the microtubule-associated protein tau (MAPT) loci (not individual variants) also have (suggestive) effects on the risk of AD, FTD and DLB.[11,31-33] The APOE gene has been implied in a multitude of pathways,[34] *HLA* is implicated in regulation of the immune system and *MAPT* encodes the tau protein. Finding multiple genes implicated in AD, DLB and FTD indicates that although these diseases have distinct aetiologies, they also in part overlap. A possible explanation is that *APOE, PLCG2* and *HLA* are involved in the processing, not the production, of age-related accumulation of proteins.[35] In this regard, it is of interest that, like the *PLCG2* variant, *APOE* and the *HLA-DR* locus are also associated with longevity.[36-39] It is well known that having a dementia-associated neurodegenerative disease is associated with shorter life-span.[40] Vice versa, the escape of diseases is associated with a longer lifespan.[41] It is likely that the association of rs72824905 with longevity is due to the protection against dementia-associated neurodegenerative diseases. However, with the available data we cannot exclude that rs72824905 has an independent effect on the risk of longevity and/or the risk of maintaining cognitive health. In line with this observation we anecdote one cognitively healthy centenarian who is homozygous for the *APOE ε4* risk allele, but also carried the rs72824905-G genotype. On MRI-scan and amyloid scan (PiB-PET) this person had some global atrophy and only amyloid-β positivity in the precuneus and in the frontal lobes (**Figure 3**). Carriers of the *APOE* ε4ε4 genotype have an approximately 80% dementia risk by age 90 years[42] and virtually all are amyloid positive by age 90.[43] In literature only a handful of cases of *APOE* ε4ε4 centenarians are reported.[44,45] It is unknown if these individuals were cognitively healthy. This case shows that cognitively healthy aging in

presence of the *APOE* ε4ε4 genotype is possible, likely due to the protective effect of other genetic variants, such as rs72824905 in *PLCG2*.[42,43]

The mechanism that explains the protective effect of rs72824905-G mutation in the *PLCG2* gene is currently unclear. Thus far only one pre-print paper showed functional experiments that tested the variant-effect in-vitro.[46] They confirmed that PLCγ2 is expressed specifically in the microglia in the mouse and human brain.[10] PLCγ2 mRNA co-localized with microglia-specific markers in healthy brain tissue, as well as in microglia near amyloid plaques in an APP mouse model.[46] Furthermore, functional characterization of PLCγ2 with the p.Pro552Arg amino acid substitution revealed a slight increase in activity compared to wild type PLCγ2.[46] While additional functional experiments will need to confirm these findings, these experiments suggest that the functional changes induced by the PLCγ2 p.Pro552Arg genetic variant may be subtle and therefore difficult to pinpoint. This is according to expectations, as impactful changes to the immune system will most likely be harmful. Indeed, known germline mutations in *PLCG2* cause the immune disorders PLAID (*PLCG2*-associated antibody deficiency and immune dysregulation) and APLAID (Autoinflammatory PLAID)[4,5,7] while somatic variants in PLCγ2 are associated with resistance to treatment of leukemia[8] (reviewed in Koss et al.[47]). The mutations that cause PLAID and APLAID leading to a strong hyperactivation of PLCγ2 after a stimulus. In the case of APLAID (caused by a p.Ser707Tyr substitution) the auto-inflammation has been suggested to be partially driven by PLCγ2-dependent activation of the pyrin (PYD)-domain-containing protein 3 (*NLRP3*) inflammasome.[48] The *NLRP3* inflammasome is a crucial signaling node that ultimately controls the maturation of pro-inflammatory interleukin (IL)-1β and IL-18[49] and has been linked to a multitude of neurodegenerative diseases.[50] We speculate that the protective effects of the rs72824905-G genotype may be explained by detailed changes in the NLRP3 inflammasome activation. Functional studies will have to elucidate the exact effects of the rs72824905 on PLCγ2 function and its effect on immune responses in the brain in the context of AD, DLB, FTD and longevity.

Strengths and weaknesses: The most important strength of our study is that we investigated the effect of the rs72824905 variant in seven neurological diseases in over 35,000 patients. Further we studied only AD cases that were independent from the original publication[9]. In this way we firmly replicated the originally reported protective effect on AD. The large numbers under study were necessary as rs72824905 is a relatively rare genetic variant (MAF~1% in European ancestry populations). For PD, ALS and MS our sample had adequate statistical power to detect an effect comparable with the variant

association with AD, making it unlikely that an association between rs72824905 and these three diseases will be observed in larger meta-analyses. Still, despite the adequate sample sizes, it is notoriously difficult to prove a negative association in genetic studies. For PSP larger studies are needed to determine association as numbers of cases were relatively low compared to the other diseases studied. Furthermore, the identified effects need to be replicated in other ethnicities in which rs72824905 occurs (i.e. rs72824905 is not observed in the East Asian populations).[51] A weakness of our study is that we were not able to use ancestry PCs to correct for population stratification in all analyses. We addressed this issue by matching cases and controls by study or country of origin. we acknowledge that cases of the different dementia-subtypes may include misclassified AD cases. However, it is unlikely that the protective effect of rs72824905-G in FTD and DLB depends only on misclassified AD cases, as the overall effect in FTD and DLB is highly similar to the protective effect on AD.

Conclusions

Our study is the first to show a protective effect of the rs72824905-G genotype in *PLCG2* that associates with a decreased risk for AD, FTD, DLB and concurrently with an increased risk of longevity. This protective effect was not observed in PSP, ALS, PD and MS cases, which suggests that PLCG2-associated processes overlap in the etiology of AD, FTD and DLB, but not in the etiologies of PSP, ALS, PD and MS. Explaining the protective effect of the PLCγ2 protein on brain immunity may contribute to the design of successful therapeutic intervention strategies applicable to those at risk for brain diseases.

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Figure 1: Association results of rs72824905 with seven brain diseases and longevity. *P- values <0.05.

Association with:	N-cases	N-controls	Odds-ratio	P-value
Alzheimers disease (AD)	4,985	8,492	0.57 [0.41-0.78]	0.00047*
Lewy-body dementia (LBD)	1,446	5,286	0.54 [0.30-0.99]	0.045*
Frontotemporal dementia (FTD)	2,437	10,647	0.66 [0.41-0.89]	0.011*
Progressive supranuclear palsy (PSP)	882	3,187	1.46 [0.83-2.58]	0.19
Amyotrophic lateral sclerosis (ALS)	10,953	20,673	1.07 [0.87-1.33]	0.52
Parkinsons disease (PD)	10,058	8,258	1.18 [0.97-1.44]	0.10
Multiple sclerosis (MS)	4,476	5,714	0.99 [0.74-1.32]	0.95
Reaching the of age >90 years	3,516	9,677	1.49 [1.12-1.98]	0.0064*

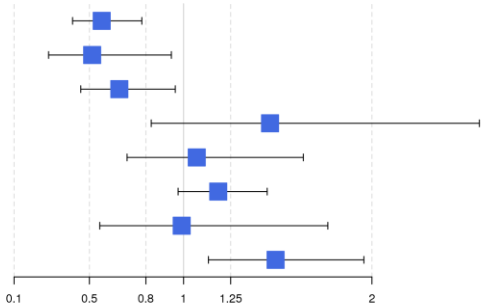


Figure 2: Association results of rs72824905 with dementia by-proxy and longevity by-proxy analysis in the UK Biobank.

Association with:	Comparing:	Odds-ratio	P-value
Parental dementia	16,968 father cases vs. 358,468 father controls + 32,262 mother cases vs. 346,999 mothers controls	0.88 [0.81-0.95]	0.0018*
Parental age >90 years	17,558 father's age =90 years vs. 353,100 father age <90 years + 35,256 mother's aged =90 years vs. 342,810 mother's aged <90 years	1.05[0.97-1.13]	0.24
Parental age >95 years	3043 father's age =95 years vs. 353,100 father's age <90 years + 7790 mother's aged =95 years vs. 342,810 mother's aged <90 years	1.19 [1.03-1.38]	0.021*

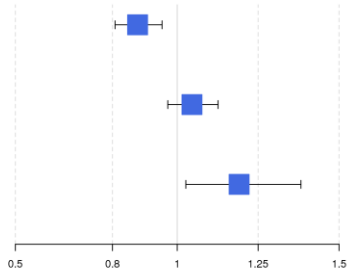
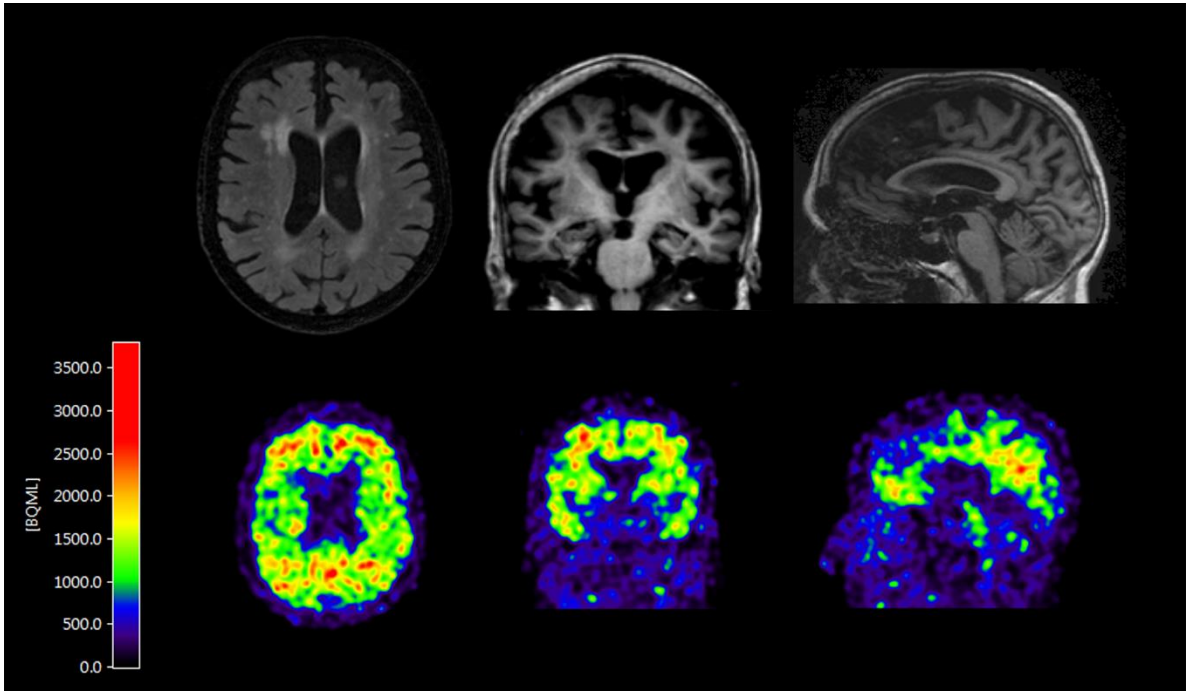
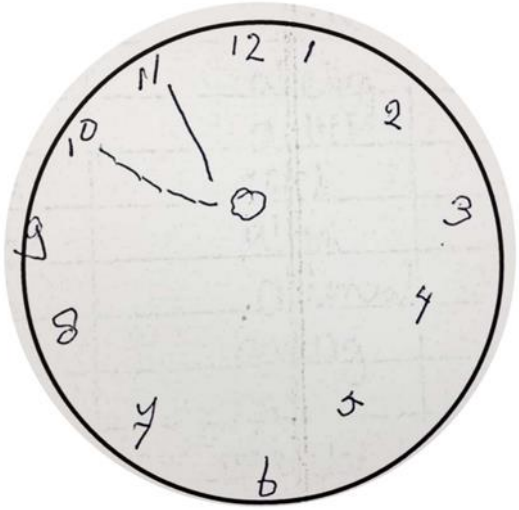


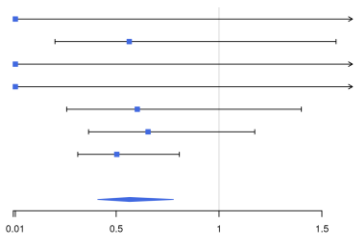
Figure 3: MRI-scan and PiB-PET scan and of 102-year-old centenarian carrying the homozygote APOE ε4 genotype as well as the rs72824905-G genotype in *PLCG2*. MRI-scan (Titan 3T MR scanner) shows some hippocampal atrophy (MTA grade 2), some global cortical atrophy (GCA-scale grade 1), but pronounced posterior cortical atrophy (grade 2), moderate white matter hyperintensities (Fazekas grade 2), no lacunar infarcts or microbleeds. PET-PiB (scan after admission of 396 MBq C-11 PIB)[52]: Positive binding precuneus and some binding in frontal lobes. Neuropsychological testing around time of scanning showed average performance on global cognitive functioning/MMSE, memory, attention, working memory, fluency and visuo-spatial tests compared to a cohort of cognitively healthy centenarians. The result of the clock drawing test is shown. The patient was asked to draw a clock and put the time at ten before eleven.





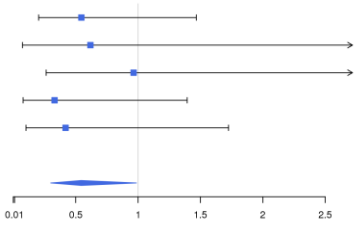
Supplementary Figure 1: Forest plots for the cohort-specific effects of rs72824905 with AD.

			AD			
Study	**N-cases**	**N-controls**	**MAF-cases**	**MAF-controls**	**Odds-ratio**	**p-value**
UCLA/UCSF GIFT	224	249	0.00	2.01	0.00 [0.00-Inf]	0.982
NDRU cohort	527	343	0.66	1.17	0.56 [0.20-1.57]	0.272
Brain compendium	277	362	0.00	0.83	0.00 [0.00-Inf]	0.979
Spanish cohorts	23	746	0.00	0.67	0.00 [0.00-Inf]	0.991
Swedish studies	564	3480	0.53	0.88	0.60 [0.26-1.40]	0.239
MAYO	1477	1487	0.64	0.98	0.66 [0.37-1.17]	0.155
Amsterdam UMC	1893	2571	0.63	1.24	0.50 [0.31-0.81]	0.004
Combined OR	**4985**	**9238**	**0.56**	**1.02**	**0.57 [0.41-0.78]**	**0.000**



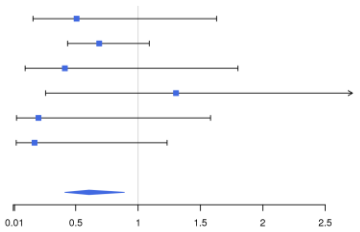
Supplementary Figure 2: Forest plots for the cohort-specific effects of rs72824905 with LBD.

			DLB			
Study	**N-cases**	**N-controls**	**MAF-cases**	**MAF-controls**	**Odds-ratio**	**p-value**
NDRU cohort	622	343	0.64	1.17	0.55 [0.20-1.47]	0.230
Brain compendium	97	362	0.52	0.83	0.62 [0.07-5.20]	0.658
Spanish cohorts	232	746	0.65	0.67	0.96 [0.26-3.53]	0.956
MAYO	306	1487	0.33	0.98	0.33 [0.08-1.39]	0.132
Amsterdam UMC	189	2571	0.53	1.24	0.42 [0.10-1.73]	0.228
Combined OR	**1446**	**5509**	**0.55**	**1.06**	**0.54 [0.30-0.99]**	**0.045**



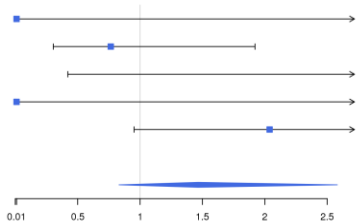
Supplementary Figure 3: Forest plots for the cohort-specific effects of rs72824905 with FTD.

			FTD			
Study	**N-cases**	**N-controls**	**MAF-cases**	**MAF-controls**	**Odds-ratio**	**p-value**
RiMod-FTD	255	1660	0.59	1.17	0.51 [0.16-1.63]	0.254
IGFC	1360	5059	0.81	1.17	0.69 [0.44-1.09]	0.111
UCLA/UCSF GIFT	132	249	0.76	2.01	0.41 [0.09-1.80]	0.239
Brain compendium	93	362	1.08	0.83	1.30 [0.26-6.57]	0.748
Spanish cohorts	366	746	0.14	0.67	0.20 [0.03-1.58]	0.127
Amsterdam UMC	231	2571	0.22	1.24	0.17 [0.02-1.23]	0.080
Combined OR	**2437**	**10647**	**0.64**	**1.16**	**0.61 [0.41-0.89]**	**0.011**



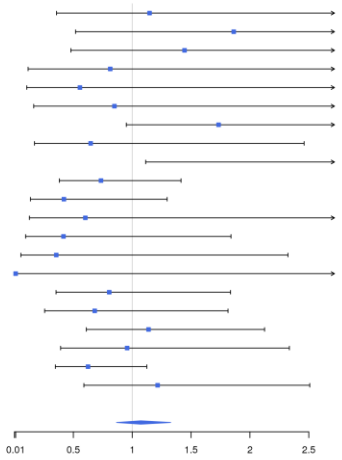
Supplementary Figure 4: Forest plots for the cohort-specific effects of rs72824905 with PSP.

			PSP			
Study	**N-cases**	**N-controls**	**MAF-cases**	**MAF-controls**	**Odds-ratio**	**p-value**
UCLA/UCSF GIFT	12	249	0.00	2.01	0.00 [0.00-Inf]	0.991
NDRU cohort	613	343	0.90	1.17	0.77 [0.30-1.92]	0.569
Brain compendium	17	362	2.94	0.83	3.71 [0.42-32.66]	0.238
Spanish cohorts	9	746	0.00	0.67	0.00 [0.00-Inf]	0.992
MAYO	231	1487	1.95	0.98	2.04 [0.95-4.36]	0.067
Combined OR	**882**	**3187**	**1.19**	**0.99**	**1.46 [0.83-2.58]**	**0.186**



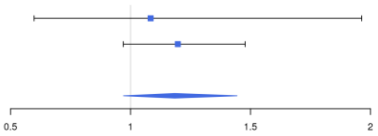
Supplementary Figure 5: Forest plots for the cohort-specific effects of rs72824905 with ALS.

			ALS			
Study	**N-cases**	**N-controls**	**MAF-cases**	**MAF-controls**	**Odds-ratio**	**p-value**
stratum s1	423	420	0.84	0.74	1.15 [0.36-3.68]	0.8170
stratum s2	299	317	1.25	0.76	1.86 [0.52-6.69]	0.3324
stratum s3	145	4882	1.29	1.03	1.44 [0.48-4.36]	0.5347
stratum s4	288	268	0.48	0.41	0.81 [0.12-5.71]	0.8363
stratum s6	168	159	0.81	1.32	0.56 [0.10-2.97]	0.4859
stratum s8	308	331	0.50	0.57	0.85 [0.16-4.41]	0.8452
stratum s9	614	2687	1.34	0.78	1.73 [0.95-3.16]	0.0846
stratum s10	266	513	0.66	0.95	0.65 [0.17-2.46]	0.5102
stratum s11	382	244	1.42	0.28	10.48 [1.11-98.64]	0.0080
stratum s13	952	1829	0.70	0.97	0.73 [0.38-1.41]	0.3465
stratum s14	518	258	0.65	1.39	0.42 [0.14-1.30]	0.1333
stratum s15	290	93	1.04	1.57	0.60 [0.13-2.86]	0.5346
stratum s17	203	221	0.89	1.50	0.42 [0.09-1.84]	0.2379
stratum s18	205	242	0.42	1.04	0.35 [0.05-2.32]	0.2457
stratum s21	264	443	0.02	0.87	0.00 [0.00-550327.04]	0.0034
stratum s22	559	2003	0.71	0.87	0.81 [0.35-1.84]	0.5987
stratum s23	327	1005	0.93	1.21	0.68 [0.26-1.81]	0.4279
stratum s24	1032	2502	0.81	0.73	1.14 [0.61-2.12]	0.6850
stratum s25	1399	648	1.05	0.94	0.96 [0.39-2.34]	0.9229
stratum s26	1715	1075	0.82	1.19	0.62 [0.35-1.12]	0.1184
stratum s27	596	533	1.43	1.18	1.22 [0.59-2.51]	0.5950
Combined OR	**10953**	**20673**	**0.89**	**0.93**	**1.07 [0.87-1.33]**	**0.5187**



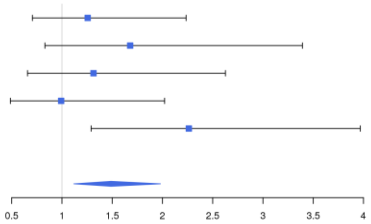
Supplementary Figure 6: Forest plots for the cohort-specific effects of rs72824905 with PD.

			PD			
Study	**N-cases**	**N-controls**	**MAF-cases**	**MAF-controls**	**Odds-ratio**	**p-value**
MAYO clinic PD	853	1487	1.06	0.98	1.08 [0.60-1.96]	0.791
IPDGC	9205	6771			1.20 [0.97-1.48]	0.094
Combined OR	**10058**	**8258**			**1.18 [0.97-1.44]**	**0.095**

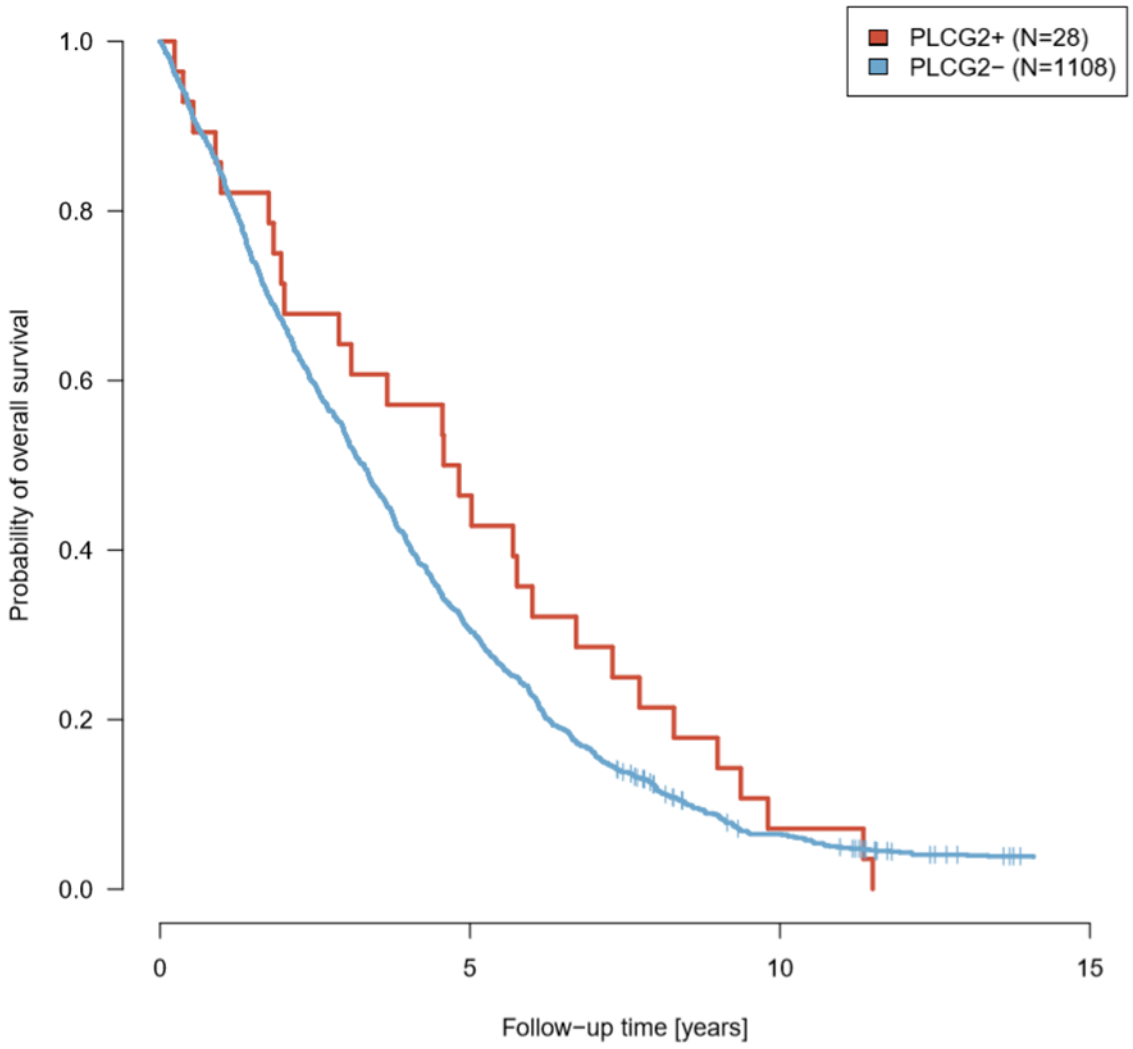


Supplementary Figure 7: Forest plots for the cohort-specific effects of rs72824905 with longevity.

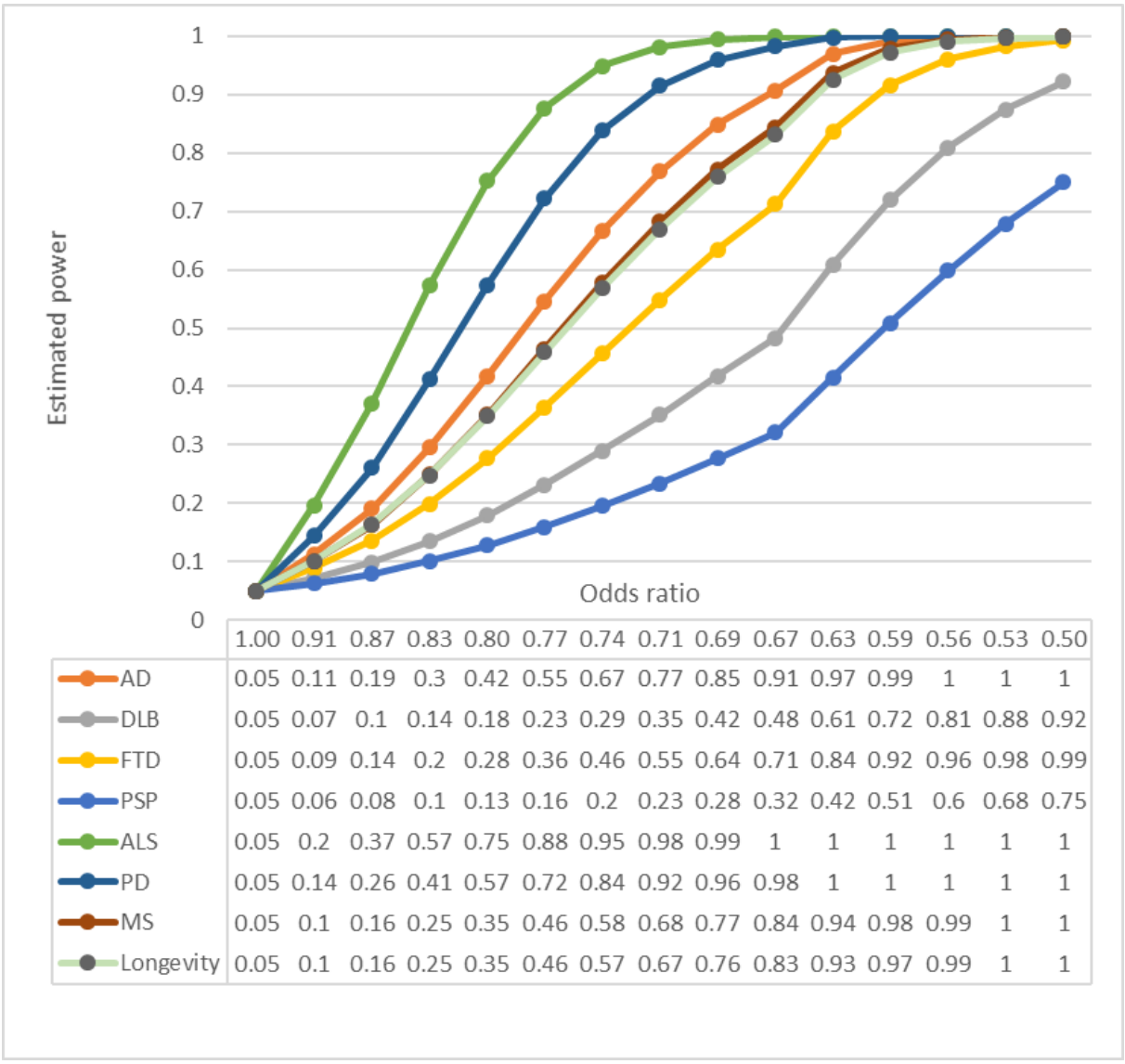
			Longevity			
Study	**N-cases**	**N-controls**	**MAF-cases**	**MAF-controls**	**Odds-ratio**	**p-value**
GBC	770	2709	1.04	0.83	1.26 [0.71-2.24]	0.438
LLS	1138	743	1.23	0.74	1.68 [0.83-3.39]	0.149
AgeCoDe	462	861	1.52	1.16	1.31 [0.66-2.63]	0.440
Danish studies	853	2793	0.59	0.59	0.99 [0.49-2.02]	0.983
Amsterdam UMC	293	2571	2.73	1.24	2.26 [1.29-3.97]	0.004
Combined OR	**3516**	**9677**	**1.19**	**0.89**	**1.49 [1.12-1.98]**	**0.006**



Supplementary Figure 8: Survival after the age of 90 years of rs72824905-G carriers vs. non-carriers.



Supplementary figure 9: Power analysis for Alzheimer's disease (AD), Frontotemporal Dementia (FTD), Lewy-body dementia (DLB), Progressive Supranuclear Palsy (PSP), Parkinson's Disease (PD) Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS). Statistical power of our analysis to attain a *p*-value of 0.05 is shown for the odds ratios (ORs) between 0.50 and 1. We used the total number of cases and controls from our analysis. We assumed an additive model, a minor allele frequency of 0.009 and a disease frequency of 0.01 for all diseases. The table shows the exact estimates of statistical power.



	1.00	0.91	0.87	0.83	0.80	0.77	0.74	0.71	0.69	0.67	0.63	0.59	0.56	0.53	0.50
AD	0.05	0.11	0.19	0.3	0.42	0.55	0.67	0.77	0.85	0.91	0.97	0.99	1	1	1
DLB	0.05	0.07	0.1	0.14	0.18	0.23	0.29	0.35	0.42	0.48	0.61	0.72	0.81	0.88	0.92
FTD	0.05	0.09	0.14	0.2	0.28	0.36	0.46	0.55	0.64	0.71	0.84	0.92	0.96	0.98	0.99
PSP	0.05	0.06	0.08	0.1	0.13	0.16	0.2	0.23	0.28	0.32	0.42	0.51	0.6	0.68	0.75
ALS	0.05	0.2	0.37	0.57	0.75	0.88	0.95	0.98	0.99	1	1	1	1	1	1
PD	0.05	0.14	0.26	0.41	0.57	0.72	0.84	0.92	0.96	0.98	1	1	1	1	1
MS	0.05	0.1	0.16	0.25	0.35	0.46	0.58	0.68	0.77	0.84	0.94	0.98	0.99	1	1
Longevity	0.05	0.1	0.16	0.25	0.35	0.46	0.57	0.67	0.76	0.83	0.93	0.97	0.99	1	1

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