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GENETIC VARIATION UNDERLYING COGNITION AND ITS RELATION WITH NEUROLOGICAL OUTCOMES

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DOI
10.1016/j.jalz.2018.06.3017

Publication date
2018

Document Version
Final published version

Published in
Alzheimer's and Dementia: Translational Research and Clinical Interventions

Citation (APA)
Kool, M. J., Cremers, L. G. M., Heshmatollah, A., Ikram, M. K., Uiterlinden, A. G., van Duijn, C. M., Niessen, W., Vernooij, M. W., Arfan Ikram, M., & Adams, H. H. H. (2018). GENETIC VARIATION UNDERLYING COGNITION AND ITS RELATION WITH NEUROLOGICAL OUTCOMES. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*, *14*(7), P1652-P1653. https://doi.org/10.1016/j.jalz.2018.06.3017

Important note
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clinically with progressive memory loss and neuropathologically with neurofibrillary tangles that are indistinguishable from those observed in brains from Alzheimer's disease patients. Yet, the pathogenic events linked to disease remain poorly understood. This study was aimed at identifying genes and pathways that drive to FTLD-tau. **Methods:** To identify the earliest genes and pathways that are dysregulated in FTLD-tau, we identified differentially expressed (DE) genes in RNA-seq data generated from induced pluripotent stem cell (iPSC)–derived cortical neurons carrying *MAPT* R406W and isogenic controls and followed by replication from brain tissue samples. We then identified pathological pathways and drug targets that were enriched among the replicated DE genes. **Results:** We identified 838 genes that were DE in iPSC–derived cortical neurons from *MAPT* R406W carriers compared with isogenic control neurons. We replicated a subset of these genes in brain tissues from *MAPT* R406W carriers. By overlapping the replicated DE genes with genes identified in a GWAS of FTD, we found that five DE genes, *FAM49A*, *NWD2*, *OBSCN*, *PLPPR4* and *SEMA3C*, also harbor SNPs associated with FTD risk ($P < 1 \times 10^{-3}$). These replicated DE genes are enriched in pathways involved in phosphorylation, regulation of phospholipase activity and MAPK signaling. Tyrosine kinase inhibitors targeting some of these replicated DE genes were also identified. **Conclusions:** The results from this study demonstrate that iPSC-derived neurons capture molecular processes that occur in human brains and can be used to model disease. Our results indicate that regulation of phospholipase activity and MAPK signaling are key pathways that lead to disease in *MAPT* R406W carriers. Our analyses also indicate that anti-phosphorylation drugs, such as Sorafenib and Regorafenib, may neutralize some of the pathogenic events that lead to disease.

O5-04-04 CANDIDATE EPIGENETIC MODIFIERS OF TAU PATHOLOGICAL BURDEN IN PRIMARY AGE-RELATED TAUOPATHY

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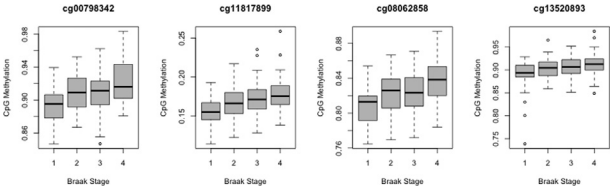
Background: Nearly every adult >50 years of age has neuropathological evidence of tau molecular pathology usually in the form of neurofibrillary tangles. To date, it is unclear why some individuals develop tau and amyloid co-pathology consistent with Alzheimer's disease (AD), while others only develop tau pathology, which was recently termed Primary Age-Related Tauopathy (PART). One hypothesis is that PART represents a spectrum of AD in which individuals with tau pathology will eventually also develop amyloid. Another hypothesis is that these conditions have distinct mechanisms contributing to risk for tau pathology. Recent evidence suggests that epigenetic modifiers may contribute to AD risk, but we are unaware of epigenetic investigations of PART. We evaluated whether epigenetic methylation relates to the severity of tau burden in PART and whether there are distinct epigenetic modifiers across PART and AD. **Methods:** We performed a genome-wide methylation analysis (MWA) of dorsolateral prefrontal cortex tissue obtained from 178 autopsy-confirmed definite PART (Braak Stage I-IV; CERAD=0; Mean Age=85.1±5.6) cases. Samples were collected through the Religious Orders (ROS) and Memory and Aging Project (MAP) studies. Methylation was measured using the Illumina HumanMethylation450 BeadChip and we assessed approximately 420K CpG loci. We used linear regression analyses to relate methylation at each locus to Braak Stage (I-IV) pathological tau burden, covarying for age at death and sex. We report results that survive MWA suggestive significance of p<1e-05. We additionally assessed significant loci in a cohort of 461 autopsy-confirmed AD cases (Braak Stage I-VI; CERAD>2; Mean Age=87.0±4.1) from the ROS/MAP studies. **Results:** We identified 4 CpG loci that were significantly related to tau pathological burden in a dose-dependent manner for PART: cg00798342 (Chr.12; gene unknown), cg11817899 (Chr. 10; *SORCS1*), cg08062858 (Chr. 19; *ARHGEF1*), and cg135520893 (Chr. 9; *RALGDS*; see Figure 1). Each of these loci were not significantly related to tau burden in AD (all p>0.1). **Conclusions:** Our findings are suggestive that there are epigenetic modifiers of tau pathological burden in aging individuals. Moreover, these loci do not appear to modify tau pathological burden in AD and therefore suggest that the underlying mechanisms for risk of tau molecular pathology may differ between AD and PART.



O5-04-05 GENETIC VARIATION UNDERLYING COGNITION AND ITS RELATION WITH NEUROLOGICAL OUTCOMES

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Background: General cognition in adults shows variation due to brain and cognitive reserve, and degenerative components. A recent genome-wide association study identified genetic variants for general cognitive function in ninety-nine independent loci [1]. The relation of these variants with cognitive decline, the incidence of dementia, parkinsonism and stroke, and brain imaging markers is still unknown. In this study, we

aimed to elucidate the pathways underlying these associations. **Methods:** This study was conducted within the population-based Rotterdam Study (mean age 65.3±9.9 years, 58.0% female), with a mean follow-up of 12.2 years for the clinical outcomes and 6.1 years for cognitive decline. We used genome-wide significant genetic variants for general cognitive function to construct a polygenic score (PGS). Additionally, we excluded variants previously associated with educational attainment at multiple significance thresholds to eliminate the cognitive reserve component. These PGSs were subsequently studied in relation to cognitive decline (N=5,229), daily functioning (N=5,229), as well as incidence of dementia (n/N=1,444/11,070), parkinsonism (n/N=258/11,486) and stroke (n/N=1,120/11,391), and brain changes on magnetic resonance imaging (N=3,710). **Results:** A higher PGS including all genome-wide significant variants (N=113) was related to higher educational attainment (p-value=1.1×10^{-6}), less decline in the Mini-Mental State Examination score (p=1.8×10^{-3}), a larger intracranial volume (p-value=5.8×10^{-3}), and better microstructural white matter integrity (lowest p-value=2.6×10^{-4}), although only the first survived all adjustments for multiple testing. No significant associations were found with other measures of cognitive decline, daily functioning, the incidence of dementia, parkinsonism or stroke. Excluding genetic variants associated with educational attainment (p-value<0.05) resulted in a PGS with 29 genetic variants. This PGS caused an attenuation of the associations found, except for an increase in dementia risk (hazard ratio=1.07, p-value=0.015). No single variant was significantly associated with any of the outcomes. **Conclusions:** This study suggests that the genetic variants associated with general cognitive function mainly represent the reserve component of general cognitive function rather than the degenerative component.

[1] Davies; G, Lam; M, Harris; SE, Trampush; JW, Luciano; M, Hill; WD, et al. Ninety-nine independent genetic loci influencing general cognitive function include genes associated with brain health and structure (N = 280,360). BioRxiv. 2017.

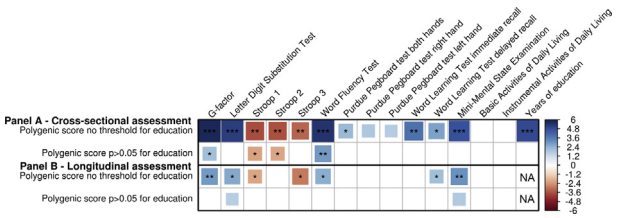

Figure 1. Association between genetic variants for general cognitive function, and cognitive function and daily functioning at one point in time, as well as years of education (panel A), and change in cognitive performance and daily functioning over time (panel B), adjusted for age and sex. Two polygenic scores are presented, one including all independent lead variants (N=113), and one only including variants with a p>0.05 for the association with educational attainment (N=29). Larger blocks indicate higher t-values. Higher scores indicate better performance, except for the Stroop test, the Basic Activities of Daily Living and Instrumental Activities of Daily Living. Significance levels are indicated by asterisks: *p<0.05, nominally significant; **p<0.0038 (panel A) or p<0.0040 (panel B), adjusted for the number of independent traits as calculated through 10,000 permutations; ***p<3.4×10^{-5} (panel A; 0.0038/113) or p<3.5×10^{-5} (panel B; 0.0040/113), additionally adjusted for the number of genetic variants.

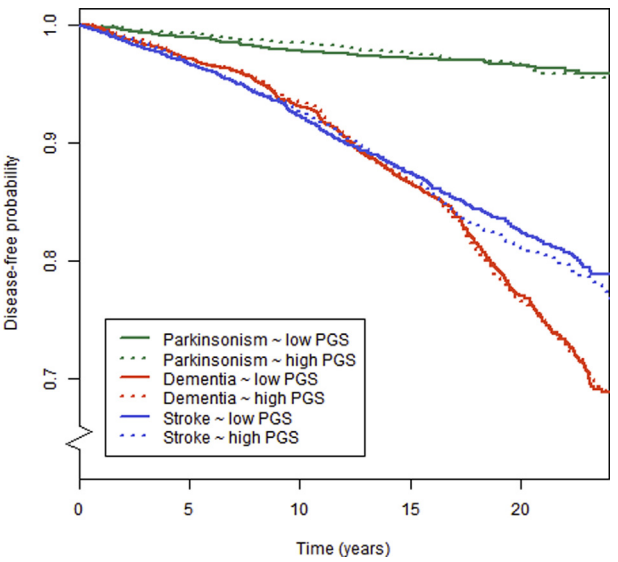

Figure 2. Kaplan-Meier curves presenting the association between low (i.e. below the median; solid lines) and high (i.e. above the median; dotted lines) polygenic scores including all lead variants (N=113), and the disease-free probability over the time for dementia, parkinsonism, and stroke.

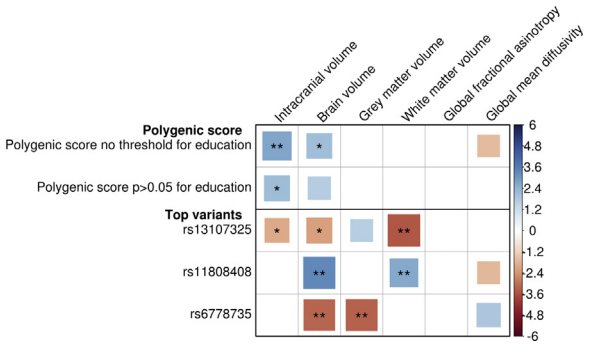

Figure 3. Association between genetic variants for general cognitive function and several brain imaging markers, adjusted for age and sex, and additionally for intracranial volume if the outcome is not intracranial volume.
Two polygenic scores are presented, one including all independent lead variants (N=113), and one only including variants with a p>0.05 for the association with educational attainment (N=29). Larger blocks indicate higher t-values. Positive associations depicted in blue correspond to a larger volume or a better white matter microstructural integrity. Significance levels are indicated by asterisks: *p<0.05, nominally significant; **p<0.0101, adjusted for the number of independent traits as calculated through 10,000 permutations; ***p<8.9×10^{-5} (0.0101/113), additionally adjusted for the number of genetic variants.

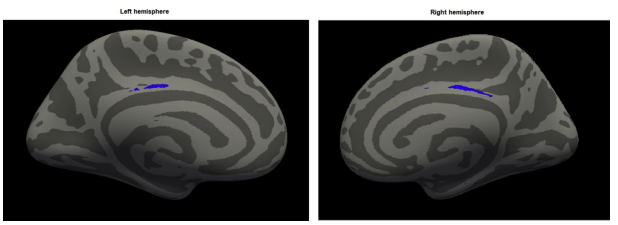

Figure 4. Figure presenting the location of vertices in which genes are differentially expressed after adjusting for multiple testing (p<7.18×10^{-12}, depicted blue). Gyri are depicted in light grey, sulci in dark grey.

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