Using genetic markers of vascular risk factors as a tool to better understand their relationship with cognitive decline and dementia in the community

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Using genetic markers of vascular risk factors as a tool to better understand their relationship with cognitive decline and dementia in the community

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Research Abstract

With expanding longevity, the number of dementia cases is increasing worldwide and is expected to triple over the next 40 years. Delaying the onset of dementia and Alzheimer disease (AD) by just a few years could have a major impact on their prevalence at the population level.

To date no effective mechanism-based preventive strategies are available. Vascular risk factors (RFs) are modifiable and given the strong relationship between cerebrovascular disease and dementia they may offer an important opportunity for preventive approaches. Gathering evidence for and improving our understanding of associations between vascular risk and dementia is therefore of paramount importance. Several studies have shown that vascular RFs, especially hypertension, diabetes, and obesity, are associated with an increased risk of dementia, but findings are heterogeneous. In older age, measurements of RFs may be biased, due to comorbidities, concurrent medications, competing risk of mortality, etc. Moreover, clinical RF measurements are highly variable, and single measurements can lead to misclassification of an individual's risk.

Recently, genome-wide association studies (GWAS) have enabled the discovery of numerous common genetic variants associated with an increased risk of developing vascular RFs, stroke, and covert cerebrovascular disease. Although the effect of individual SNPs is usually small, their combined effect in a genetic risk score may be important. Genetic risk variants are not exposed to measurement variability; they can be detected early, in advance of clinically evident vascular RFs and disease, and may be better correlated with lifetime exposure to RFs than single late-life measurements of clinical RFs. Hence they could be useful for identifying individuals with a high risk of vascular-related cognitive decline and dementia that could be used in the future as a target population for testing early preventative interventions.

We propose to utilize data from a large, richly phenotyped and densely genotyped ongoing French population-based cohort (3C Study), to explore associations of genetic markers for vascular risk with dementia, cognitive decline and structural brain aging. We suggest the following aims: (1) test associations of vascular genetic risk scores (VGRS) with incident dementia and cognitive decline; (2) test associations of VGRS with MRI-markers of structural brain aging known to be powerful predictors of dementia; (3) examine causality of associations between vascular RFs and dementia, cognitive decline, and structural brain aging using Mendelian randomization; (4) explore the clinical utility of VGRS in predicting dementia risk by testing the potential for risk discrimination and classification. We seek funding for statistical genetic and epidemiological analyses, genotyping of poorly imputed variants, server maintenance, blood measurements of continuous markers of vascular risk, and travels to facilitate collaborations. Extension of our findings will be sought, through independent funding, in the Framingham Heart Study.

While it is evident that treating vascular RFs is necessary to reduce the burden of vascular disease, the impact of vascular RF treatments on dementia risk is unclear, as well as the optimal timing for intervention. If successful, information obtained from this project, combining cutting edge technology with genome-wide genotypes, as well as elaborate and innovative statistical and epidemiological models, could contribute to optimizing the design of future trials testing the impact of vascular RF treatments on dementia risk.

Further information available at:

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