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The importance of genomics in advancing the treatment of dementia

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The incidence and prevalence of Alzheimer's disease and related dementias continues to rise as life expectancy increases worldwide. If these diseases could be diagnosed accurately before symptom onset, strategies could be developed to protect brain neurodegeneration and enable endogenous and exogenous neuroplastic repair mechanisms to continue to maintain a sufficient level of cognitive functioning. However, a major hindrance to improving the diagnosis of Alzheimer's disease is that the etiology is still unclear. Pathological mechanisms of genetic origin have been proposed (eg, involving the ApoE-ε4 allele[1]). However, genetic mutations driving disease in non-hereditary forms of Alzheimer's disease and related dementias (ie, sporadic cases) are rare and diverse in the general population, requiring highly advanced analyses of multiple genetic datasets to link rare variants to clinically confirmed cases. The best method to do this genetic linkage is by genome-wide association studies (GWAS). Previous GWAS in transgenic mice and humans have indicated the involvement of genes associated with inflammation and microglia in Alzheimer's disease and related dementias. However, new loci have now been reported in two studies.[3,4]

In the first study, Bellenguez and colleagues[3] reported the findings of a meta-analysis of GWAS that included genetic data from the European Alzheimer & Dementia Biobank consortium, which comprises people with clinically diagnosed Alzheimer's disease and controls without cognitive decline. The study also included genetic data from a proxy Alzheimer's disease cohort from the UK Biobank dataset, comprising people who did not have a clinical diagnosis but who reported they had a parent with dementia. From 111 326 clinically diagnosed or proxy Alzheimer's disease cases and 677 663 controls, a total of 75 risk loci were identified, consisting of 33 loci that have previously been linked to Alzheimer's disease and 42 totally new loci. No significant genetic overlap was seen between loci known to be associated with other neurodegenerative disorders, such as Parkinson's disease or amyotrophic lateral sclerosis, and the 42 new loci. Molecular

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pathways associated with the 75 loci were related to amyloid β, tau, lipid metabolism, endocytosis, and immunity (ie, high expression of microglial genes). Additionally, a connection to vasculature was noted, via the epidermal growth factor receptor locus. These data were also used to derive a genetic risk score for Alzheimer's disease. Diagnostic accuracy improved when all 75 loci were computed, although the effect size was small. Surprisingly, the accuracy of the genetic risk score was independent from the number of *APOE* ε4 alleles.

In the second study, Yang and colleagues[4] reported the very difficult isolation and molecular characterisation of vascular and perivascular cell types from specimens of frozen human brain tissue, which were obtained from people with Alzheimer's disease and controls with no cognitive impairment. Cells isolated from the hippocampus and superior frontal cortex were representative of the blood–brain barrier and included both vascular cells and astrocytes. Yang and colleagues reported that brain regions have a strong effect on the number of astrocytic genes. They also noted baseline inflammation in hippocampal endothelial cells from the Alzheimer's disease samples. These data suggest that, during the Alzheimer's disease course, some brain vascular cells might undergo dedifferentiation in the functional continuum of the artery-capillary-vein structure, but they do not form novel brain vascular cell types or subclusters. However, the changes in vascular structure and genes were heterogenous across regions in people with Alzheimer's disease, with an overall loss in the number of brain vascular cell nuclei, which could be related to blood–brain barrier structural alterations that are frequently observed in people with Alzheimer's disease and related dementias. Importantly, by performing species comparisons and GWAS, Yang and colleagues noted that 30 of the top 45 risk loci for Alzheimer's disease and related dementias were associated with microglia in transgenic mice, whereas in humans they are shared between microglia and brain vascular cells. This finding suggests that mouse markers are likely to be poorly predictive of human pathology, and transgenic models of Alzheimer's disease are known to develop limited vascular pathology.

These two genetic studies have some limitations. First, most human brain tissues used in GWAS are collected after death, and people with Alzheimer's disease and related dementias will have severe neurodegeneration. Second, comorbidities such as cardiovascular disease are often unknown or not reported, meaning that the molecular pathways identified by GWAS might reflect late rather than early brain pathological mechanisms. Third, nuclear RNA was used in the two studies, which differs in proportion and splicing from cytoplasmic messenger RNA[5] and does not reveal the importance of synthesised proteins and their post-translational modifications in the pathology of Alzheimer's disease and related dementias. This limitation highlights the need for functional validation of risk variants.

Because of the strong links to vascular pathology reported in these genetic studies, it might be of interest to compare genetic data for Alzheimer's disease and related dementias with those for cardiovascular disease, metabolic disorders, and other conditions with a vascular component. In silico analysis could be a useful strategy to identify and subsequently propose the repurposing of existing drugs for these vascular conditions, which might alter genetic risk factors for Alzheimer's disease and related dementias—eg, the diuretic bumetanide and APOE4-related Alzheimer's disease.[6] Similarly, interactions between

genes and environment have not yet been investigated thoroughly. For example, APOE4 homozygotes are associated with a higher risk for developing Alzheimer's disease, but the penetrance is not 100%. Thus, environmental factors might moderate or exacerbate the effect of genetic risks.

Despite the limitations, these two studies on genetic risk factors for Alzheimer's disease and related dementias provide valuable new information for potential clinical applications. First, continued improvements in GWAS and tissue isolation methods allow the identification of rare genetic variants. After functional validation, these new variants could be included in genetic risk scores and diagnostic paradigms that might subsequently translate to clinical practice. Moreover, the new variants represent possible novel therapeutic targets that could be investigated in models of Alzheimer's disease. Second, both studies highlight the importance of inflammation and vascular alterations in Alzheimer's disease and related dementias, which could point to potential new treatments that target these biological processes. The identification of novel and rare genetic risk factors for Alzheimer's disease and related dementias is a robust driver for development of accurate diagnostic tools and protective strategies that, if applied early, could lead to a reduction in the incidence of Alzheimer's disease and related dementias in the near future.

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